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Theoretical Issues on Systems Science

Edited by
Gianfranco Minati, Alessandro Giuliani and Andrea Roli

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About the Editors

Gianfranco Minati

Gianfranco Minati, a mathematician and systems scientist, lives in Milano, Italy. He has switched from a position as an executive in a large industrial–financial Italian group (1979–1984) to one in research. He is the founder (1996) and president of the Italian Systems Society (AIRS); a Member of the scientific committee of Conferences and Systems Societies; and a Doctoral lecturer (2000–2017) at the Polytechnic of Milan, Italy. He is also an Editor of the Springer Contemporary Systems Thinking book series, and he is the author of 42 chapters in books; the editor of 12 books; the author or co-author of 17 books; and the author of 76 articles and of academic publications. His current research interests focus on Architecture and Design as social meta-structures that influence the processes of emergence in social systems, Artificial Unconscious in AI, Complex Systems, the Dynamic Usage of Models (DYSAM), Emergence and de-emergence, Logical Openness, Mesoscopic Coherence, meta-structures, Multiple Systems, Quasi-systems, and Theoretical incompleteness.

Alessandro Giuliani

Alessandro Giuliani lives and works in Roma, as a Research Director at Istituto Superiore di Sanità (Italian NIH). He was a visiting professor at Tokio Keio University, Bioinformatics Institute in Kerala, National University of Singapore (NUS), Rush University of Chicago (USA), Trivandrum (Kerala, India) and Tomsk Universities (Russian Federation). He serves as a professor on a contract basis of Computational Biology at Sapienza University of Roma and is a member of the Faculty of the Doctorate in Computational Biology.

The main research goal of Dr. Giuliani is the development of quantitative 'soft' models of complex systems, allowing for an effective exchange between biology and physico/mathematically oriented scientists.

Alessandro Giuliani's most relevant contributions are the following:

1. The development of the Recurrence Quantification Analysis (RQA) technique (together with Joseph Zbilut and Charles Webber), now routinely adopted in fields from theoretical physics to biochemistry and psychology.

2. The development of a network formalization of amino acid contacts inside protein structures, allowing for the prediction of features like the allosteric behaviour and dynamics of studied systems (together with Luisa Di Paola).

3. The definition of a statistical index to locate the 'tipping point' preceding a change in the cell differentiation state from omics data (together with Masa Tsuchiya, Keinichi Yoshikawa and Sui Huang).

4. The definition of a sort of 'Protein Intelligence', adopting IIT (Information Integration Theory) formalism in the study of protein structure and dynamics (together with Timir Tripathi and Vladimir Uversky). He has authored around 450 papers in international peer-reviewed journals and 10 popular science books.

Andrea Roli

Andrea Roli is an assistant professor at Università di Bologna. His research areas are Artificial Intelligence and Complex Systems, with a focus on biological models, biorobotics, and collective intelligence. His main current research activities are gene regulation models for robot control and information theory techniques for the analysis of complex system dynamics. Andrea Roli teaches courses in computer science basics, artificial intelligence, and complex systems. He is a member of the Italian Association for Artificial Intelligence (AI∗IA). He collaborates with IRIDIA (Institut de Recherches Interdisciplinaires et de Développements en Intelligence Artificielle), Université libre de Bruxelles, and the Namur Center for Complex Systems (NAXYS). He is also an ECLT fellow (European Centre for Living Technology, Venice). In February 2025 he was awarded the title of a senior fellow of BrIAS (Brussels Institute for Advance Studies).

Preface

This paper summarizes the aims and results of this Special Issue. Research on complex systems has focused, for example, on models and simulations [1,2], as well as emergence, self-organization, and chaos theory [3,4].

In "Theoretical Issues on Systems Science", we presented examples of theoretical issues to be explored, including theoretical incompleteness, multiplicity, systems as networks and chaos, and game theory. Other less explored research topics include equivalence and tolerance in systems, pending systems, recurrence and self-reflexivity, remote synchronization, and the significance of using complex numbers in system models.

The first group of six contributions addresses theoretical aspects, including (1) the role of noise in complex systems; (2) the potential of general systems theory to serve as a theory of everything; (3) the serious theoretical inadequacy of applying classical axiomatic deductive mathematical approaches to topics such as control evolution by rewriting DNA "instructions"; (4) the near non-existence of purely "theory-free" approaches and the balance between theoretical and empirical contributions; (5) the neglect in the reductionism of the fact that systems acquire properties and the assumption that multiple, variable interactions of complexity can be analytically "zipped"; and (6) tree-based methods for statistical learning, for which the author presents a systems theory-based framework to speed up discrete event system stochastic simulations.

The second group of contributions examines theoretical aspects within specific fields, including (1) human dynamics; (2) human cognition; (3) complex physiological processes; (4) medicine; (5) chemical organization theory; and (6) psychotherapy.

The papers in this Special Issue exemplify possible lines of research on the topic of this issue.

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Gianfranco Minati, Alessandro Giuliani, and Andrea Roli

Guest Editors

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Article

On the Positive Role of Noise and Error in Complex Systems

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Abstract: Noise and error are usually considered to be disturbances negatively affecting the behavior of a system. Nevertheless, from a systemic perspective, taking into account openness and incompleteness of complex systems, noise and error may assume a creative, constructive, and positive role in that they are a source of novelty that can trigger the reorganization of the system, the growth of complexity, and the emergence of new meaning. Examples of this phenomenon can be found in evolutionary phenomena driven by affordances, the formation of new attractors in dynamic systems responding to external perturbations, and improvisation in music. We argue that it is possible to identify general properties that enable the positive effect of noise and errors in complex systems, namely, multilevel organization, redundancy, incompleteness, and criticality. These properties play a major role in living systems and can guide the design of robust and adaptive artificial systems.

Keywords: noise; error; redundancy; incompleteness; multilevel; criticality; affordance; evolution

1. Introduction

Noise and error are usually associated with phenomena that harm or produce detrimental effects to a system. Classical reductionist scientific and engineering approaches try to protect a system from perturbations, reduce internal noise, and provide strict rules and control procedures to constrain the behavior of the system to precise dynamics. Noise is an undesirable perturbation or fluctuation; it is typically treated as a quantity to be minimized, as it might introduce variability and imprecision into the behavior of a system. On the other hand, error is commonly associated with the discrepancy between a desired target behavior and the actual one. Therefore, error typically depends upon an observer [1] in that it is a deviation from what the observer considers the correct, expected behavior of a system. Error functions are indeed used to control a system and keep it within predefined functional ranges or as an objective function in training.

However, noise and error can also have positive and constructive effects. A prominent example is stochastic resonance [2], which exploits random noise to improve signal-to-noise ratio in nonlinear systems. The impact of stochastic resonance on the improvement of the performance of a (nonlinear) system has also been found in biological systems, e.g., in the brain [3]. Also errors can bring benefits; for example, a deviation from the "correct" DNA replication process may introduce beneficial mutations.

While the positive role of noise and error in complex systems (both natural and artificial) has been discussed in detail in specific cases, general theories of these phenomena are still missing. The aim of this work is to contribute to the definition of an abstract and general systemic perspective on this subject. In this paper, we identify general conditions that can make the impact of noise and error positive on the behavior, adaptation, or evolution of a system, including the possibility of generating novel behaviors, meanings, and increases in internal complexity. We will first illustrate three representative examples that provide

the basis for the introduction and discussion of general mechanisms and properties. In the following, we will use the two terms *noise* and *error* as all-encompassing words expressing perturbations, fluctuations, variability, and deviation from a target behavior.

2. Three Examples from Different Realms

We illustrate three examples from different domains that we think provide a characterization of the relevant aspects concerning the positive contribution of noise and error in the dynamics of complex systems. The first case illustrates the advantage of unexpected events in adaptation and evolution in natural systems; conversely, the second one deals with robots that have to learn a given task and adapt their perceptual mechanisms while operating with noisy sensors. Finally, the last example comes from social interaction in the arts and concerns improvisation in music. Starting from the properties identified in these examples, in the subsequent sections, we depict a general view of our argument.

2.1. Adaptation and Evolution through Affordances

The notion of *affordance* was introduced in psychology by Gibson [4]. This concept has been subsequently adopted in other areas, such as biosemiotics [5] and robotics [6]. Affordances refer to what the environment offers to an organism, for good or ill. In this light, an affordance is "a possible use of *A* by an organism to accomplish *B*". For example, a hole in a rock affords a wasp a safe place to build a nest, or a suitable shell affords a shelter for the hermit crab *Pagurus bernhardus*. Notably, affordances can be manifested either as opportunities or as obstacles on the organism's path to achieving a goal. It is important to remark that affordances are not independent features of the environment [7], as a change can be neutral or not depending on the conditions of the organism, its goals, and its repertoire of actions [8–10].

This psychological ("agential" [7,11]) notion of affordance is at the basis of numerous adaptive processes in living organisms. For example, unexpected changes in the environment (i.e., errors with respect to a prediction) can be a source of affordances. Changes in the environment consist of alterations of the portion of the environment that an organism perceives and with which it can interact, including other organisms. In biosemiotic terms, this niche is the *Umwelt* of the organism [12,13]. A change in the environment triggers in the organism a process to detect affordances: the ones useful for the organism are selected. An example from human behavior is jury-rigging: a problem to be solved (e.g., a window accidentally broken by hail) is an opportunity to find a quick and effective solution by using what is currently available (e.g., the cover of a cardboard box and adhesive labels).

Besides the psychological notion just discussed, affordances also play a major role in evolution. Most adaptive steps happen in evolution by means of affordances, which are seized by heritable variations and natural selection (heritable variations include gene mutation and also epigenetic phenomena [14]). In the history of evolution, one can find abundant examples of adaptations that emerged by using the same organ for a new use. These evolutionary phenomena are called Darwinian *pre-adaptations* or exaptations [15]. In these cases, the organ affords a new use for the organism. For example, feathers evolved for thermal insulation but were later co-opted for the new function of flight stabilization [16,17]. Another case in point is that of lens crystallins, which first originated as enzymes [18].

Abstracting, we can view affordances as open possibilities in evolution; heritable variation and selection then seize some of them. Crucially, a possibility can be driven by random events and accidents, such as genetic mutations. For example, noise and errors in protein synthesis produce an increase in variety and diversity of cell behaviors. Again, a change in the environment of organisms triggers an implicit process of affordance detection; the ones useful for the survival of the organisms are seized by selection [19].

Natural systems composed of more than one species are a prominent case of higher-order dynamics, in which the niche of each species is composed of the environment and other species. For example, the waste produced by a species can be exploited by another one, i.e., the waste produced by an entity can be seen as an affordance by another entity. Systems

composed of interacting species have an evolutionary advantage if they can mutually offer each other complementary capabilities [20]. This symbiotic cooperation also produces rich semiotic networks [21], which confer both robustness and plasticity by enabling multiple alternative signaling pathways and diverse mechanisms to act in the environment. This property, also called degeneracy [22], is crucial for complex natural systems.

In summary, both adaption and evolution can take advantage of noise and errors as they trigger a process of affordance detection, i.e., they create the need or the opportunity for a change in either organism behavior or heritable material. This change often introduces novelty, as it expands the actual possibilities of the organisms.

2.2. Adaptation of Robots Controlled by Noisy Sensors

The example we illustrate here comes from the domain of artificial systems, namely robots, and it makes it possible to identify another context in which noise and error can be beneficial. The results we describe show that a robot subject to a simple adaptation mechanism can attain a high performance even in light of sensor damages; furthermore, the robot's performance seems to be improved by a small amount of noise. We first illustrate the experimental setting, then we focus on the effect of noise and error in sensing.

Adaptation in noisy contexts is a typical scenario in nature. We recently explored an analogous case in simulation, where we let robots adapt to performing a simple task under the condition that some of their sensors needed for accomplishing the task were noisy or broken [23]. The experiment involved a robot controlled by a Boolean network [24–26] that has to learn to go towards the light (phototaxis behavior). The behavior of the robot is produced by the dynamics of the Boolean network, which updates the values of its nodes synchronously. Some nodes of the network, called "input nodes", are connected to the light sensors, and some others (the "output nodes") are connected to the motors controlling the wheels of the robot. If a light sensor is connected to a node of the network, the value of this node is set to 1 if the sensor reading is higher than a given threshold. The other nodes assume the values according to their Boolean update function. The value of the output nodes is used to move or halt the wheels (in our experiments, robots have two wheels).

The robot is subject to a simple adaptation process based on the possibility of changing the connections from its light sensors to the network during its life. Note that the structure and the update functions of the network remain unchanged during adaptation. An adaptation step is illustrated in Figure 1. The robot starts with an initial configuration of sensor-to-node connections and undergoes an evaluation phase in which the distance covered towards the light is taken as the evaluation function (to be maximized). After this phase, a random perturbation of the current sensor-to-node connection is exerted, and the robot is evaluated again. If the incumbent configuration provides a better evaluation than the previous one or it does not decrease it, this configuration becomes the current one, and the process proceeds by perturbing the new configuration; otherwise, a new random perturbation of the previous configuration is sampled. This adaptive process is a kind of stochastic adaptive walk in the space of sensor-to-node connections.

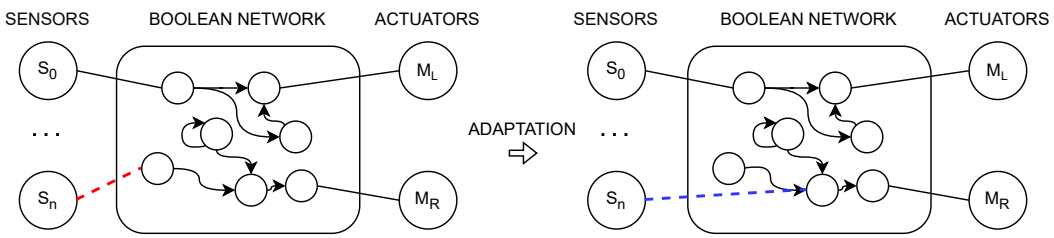

Figure 1. Example of an adaptation step (taken from [23]). A light sensor is connected to a different network node. The adaptation affects only the node to which a sensor connects, leaving the topology of the network unchanged.

The focus of this experiment is on sensors, which can be broken and, therefore, carry incorrect pieces of information to the network. Sensors can simply be detached from input nodes (hence, they do not carry information), can be set to a random constant value, or can produce random signals. The robot is equipped with 24 light sensors evenly distributed along the perimeter of its cylindrical chassis. We consider the case of a varying number of contiguous faulty sensors, from 0 to 24. For each sensor damage amount and for each possible kind of damage, statistics are collected on the performance of the robots, measured as the final distance to the light (details can be found in [23]).

Surprisingly, the overall performance does not monotonically degrade with the number of faulty sensors. Instead, we found that a limited amount of faulty sensors (between 3 and 6) enables the robot to perform better than in the case with all the sensors correctly working. In other words, the addition of errors in sensor readings turns out to be beneficial to the behavior of the robot.

The kind of noise considered in this example apparently differs from the one previously discussed. Nevertheless, in the case of robots, the perturbation exerted by noise and errors in the sensors forces the robot adaptation process to find a configuration that can distinguish between relevant and irrelevant information. To some extent, even in this case, errors generate the need to search a novel model of the environment (namely, a new sensor-to-node configuration) able to deal with a discrepancy between what is expected and what is actually perceived.

2.3. Improvisation in Music

Music is acknowledged to be a universal trait of humans [27], and it traverses and involves all the aspects that characterize our species. Here, we briefly discuss improvisation in music from a systemic perspective, emphasizing its main general mechanisms.

Improvisation is "the creation of a musical work, or the final form of a musical work, as it is being performed. It may involve the work's immediate composition by its performers, or the elaboration or adjustment of an existing framework, or anything in between. To some extent every performance involves elements of improvisation, although its degree varies according to period and place, and to some extent every improvisation rests on a series of conventions or implicit rules. [. . .] One of the typical components of improvisation is that of risk: that is, the need to make musical decisions on the spur of the moment" [28].

While varying across time and culture, independent of the degree of improvisation in a performance, musical improvisation stands as a prototypical case of impromptu creation that requires a fast answer to external stimuli that are not planned and internal decisions that might also be affected by mistakes, which in turn trigger further reactions (by the other musicians or the same performer). In general, improvised musical performances rely on stylistic constraints (e.g., basic chord sequences) as well as musical structures that are dynamically created during the performance (e.g., temporary key changes). When more musicians are involved in the performance, an action a musician takes might not match with the expectations that another musician has. In other words, there may be an error or a discrepancy in the expected behavior observed by the latter musician. A prominent example is jazz: an extemporaneous variation in a chord perturbs the *adjacent possible* [29,30] of future musical decisions, perhaps limiting some options, but also disclosing opportunities that could not be reached without the variation. Errors of this kind, as well as mistakes and accidental events, can trigger novelty. For example, a distraction can cause a mistake in the execution of a note on a trumpet, which might suggest a new melodic direction to the other musicians.

In this third example, the role of noise and error is similar to that illustrated in Section 2.1, as they can be seen as a perturbation that triggers the exploration of a new space of possibilities. Nevertheless, improvisation in music emphasizes a typical (cognitive) mechanism to explore the adjacent possible: breaking some of the rules originating from shared conventions and performance practice (e.g., a response to an error can be the

temporary change of the meter) or from the current structure of the music performed (e.g., a chord change to respond to an error).

2.4. A General Mechanism

The three examples illustrated above share a common, general mechanism: noise or error generates a tension between the expected state and the actual one, and this tension triggers a local exploration process aimed at finding a solution to this tension. This solution consists of a structural change in the system.

Formally, let suppose that the behavior B of a system in general depends on the model of the environment, M_e, the model of itself, M_s, the repertoire of actions, $\mathcal{A}$, and the goals, $\mathcal{G}$. The repertoire of actions $\mathcal{A}$ includes actions that produce the behavior and other "meta-actions" that manipulate the models, the goals, and the actions themselves (these meta-actions are required for executing the adaptation process). In summary, $B = f(M_e, M_s, \mathcal{A}, \mathcal{G}) = f(\mathcal{U})$, where $\mathcal{U} = \langle\, M_e, M_s, \mathcal{A}, \mathcal{G} \,\rangle$. For the sake of readability, we omit the dependence on time. Whenever noise or error intervenes, $\mathcal{U}$ is likely to require a change to enable the agent to reach its goals (which also includes maintaining a specific behavior). A schematic representation of this process is as follows:

i. The system's behavior is determined by $\mathcal{U}$. The space of possible variations and extensions of $\mathcal{U}$ is, in principle, "unprestatable" [31].
ii. A perturbation in the form of noise or error takes place.
iii. A process for revising or extending $\mathcal{U}$ is triggered. The *adjacent possible* of the system depends on the perturbation received, the goals, and the repertoire of actions.
iv. A new configuration $\mathcal{U}'$ is seized.

The processes for changing $\mathcal{U}$ are multiple and depend on the kind of system and adaptive process involved. We can identify necessary properties a system needs so as to exploit noise and error in a positive, constructive way. This is discussed in the next section.

3. Positive Effects of Noise and Error as Well as Conditions Enabling Them

One of the main effects of noise and error is that they can be sources of novelty. Obviously, the generation of novel behaviors or structures is not simply produced by random and accidental events. Genetic mutations do not correspond to novel useful phenotypic traits per se; the accidental appearance of a new species in an ecosystem is not guaranteed to produce changes in the environment; a fault in a robot sensor is very often detrimental rather than producing novel opportunities; and a mistake in playing a chord on a guitar might simply introduce an unpleasant and distracting dissonance. Therefore, the question arises as to what the conditions are that enable noise and errors to generate novelty and have a positive impact on the system.

3.1. Multilevel Organization

The starting point of our discussion is the work by Atlan [32], who points out that one main effect of noise on biological systems is that it enables them to create meaning. The first step of his argument is that, in the usual Shannon approach, noise acts as a disturbance on a communication channel between a source X and a destination Y. Noise introduces ambiguity in the destination message; it leads to an augmentation of $H(Y/X)$. However, still according to the Shannon theory, the entropy (now intended as the complexity) of the compound system that contains both X and Y is $H(X, Y) = H(X) + H(Y/X)$. Noise increases $H(Y/X)$: the higher the amount of noise, the higher the conditional entropy between Y and X, because higher is the chance that the destination receives a different symbol than the one sent by the source. While, from the communication channel perspective, this is detrimental for accurate signal transmission, the diversity or complexity of the system as a whole clearly increases. In other words, a richer diversification of the intra-system causal pathways occurs because of more complex relationships between X and Y. As Atlan remarks, it is always possible to consider this increase in the entropy of the compound system as an increase in its complexity (i.e., reduction of its redundancy; see

below) because the Shannon entropy functions cannot distinguish meaningful complexity from mere disorder (i.e., meaningful from meaningless messages).

This entropic complexity growth is the very source of change under the condition that the compound system (source plus destination) is just one level of the system, i.e., if the transmission of information from X to Y is a lower-level mechanism in a multilevel system. This is the case for biological systems; for example, variance in the synthesis of proteins makes it possible to explore novel protein variants and so create affordances and, hence, new possibilities for adaptation. Here, a crucial step takes place: among the new affordances that are available, the ones that carry a specific advantage for the system are seized. This newly established advantage is the origin of the creation of meaning. For example, take a new protein that works as a receptor for a molecule providing elements that boost cell metabolism. Once this new receptor stably enters the system dynamics, the detected molecule assumes a meaning because it "matters" to the system. Before the appearance of the new receptor, the molecule was in fact invisible and nonexistent in the system. Analogous considerations hold for evolution by selection and heritable variations. Meaningless noise produced by random mutations generates affordances that are then seized by higher-level interpretation (i.e., selection) as useful new phenotypic traits [8]. One can easily identify the same mechanism in improvisation. Not all variations produced by a musician trigger a specific reaction from the others, just the ones that are recognized by another musician as opportunities and assume meaning (this is, of course, subjective).

Tomasello [33] points out that the higher the amount of unpredictability in the environmental niche of an agent, the more complex its behavior mechanisms have to be. A simple negative feedback loop is sufficient for a constant and predictable environment, but it is largely ineffective in dynamic and varying environments.

A minimal example is provided by a simple threshold response behavior mechanism equipped with the possibility of adjusting the threshold. This mechanism can work if noise is limited and its intensity is not subject to quick changes. In the frame of the formalization introduced in Section 2.4, the behavior of the agent can be expressed as an action $a \in \mathcal{A}$ taken if the sensor percept $s \in M_e$ is greater than a threshold $t \in M_s$. An action $\hat{a}$ can be triggered to adjust the threshold t so as to dampen the effect of a constant noise; however, such a mechanism is ineffective if the intensity of noise is wide and quickly changes over time.

Complex behavior mechanisms imply multiple and complex internal structures. As a consequence, we identify a first necessary condition for enabling noise to produce positive effects: the **multilevel organization** of a system.

We observe that a multilevel organization in artificial systems, such as robots, permits the reconfiguration of sensors, the emergence of new sensors [34], and even the use of *metasensors* [35] that make it possible to reconfigure and rearrange the system so as to reduce the discrepancy between the environment and the *Umwelt* of the robot.

3.2. Redundancy

A second necessary property is **redundancy**, which can also manifest as *degeneracy* [22]. An interpretation of redundancy in terms of syntactic information (*à la* Shannon) sheds light on the connections with the previous argument.

Rephrasing Atlan [32], redundancy is the reduction of entropy due to limits, constraints, and stable structures in the system. In terms of information theory, for a system composed of two variables X and Y, the redundancy R is defined as: $1 - \frac{H(X,Y)}{H(X)+H(Y)} = \frac{H(Y)-H(Y/X)}{H(X)+H(Y)}$. In general, $R = 1 - \frac{H}{H_{\max}}$, where $H_{\max}$ is the maximum entropy of the system, attained when its parts are totally independent.

As previously noted, noise augments the ambiguity function $H(Y/X)$; hence, the lower the amount of noise, the higher the redundancy. A non-negligible degree of redundancy is therefore initially needed for being converted into meaningful complexity by a noise-induced increase of $H(Y/X)$. This process is equivalent to the reduction of (parts of the) redundant or constrained causal relations between the elements of the systems that

concur with the overall X,Y correlation. Indeed, a system working at maximal entropy (no internal constraints, i.e., X and Y are free to vary independently) has no resources to rearrange to make sense of new stimuli. It is then able to reshape redundant structures and processes so that a complex system is able to create new meanings (as Atlan dubbed it, following von Foerster [36], to generate "complexity from noise").

As in Section 2.4, redundancy makes it possible to change $\mathcal{U}$ by reusing, rearranging, and recombining the objects already contained in $\mathcal{U}$. For example, let us consider a robot controlled by an artificial neural network. An unexpected external condition requires a weight update (which in general corresponds to a change in M_e and M_s). If the entropy of the network is not maximal, i.e., if its maximal classification capacity has not been reached, there is a possibility of weight adjustments such that the new situation can be considered in the responses of the network, hence the behavior of the robot. No redundancy would mean no possibility of keeping the current abilities and adding new ones.

3.3. Incompleteness

The modifications of $\mathcal{U}$ can also introduce new degrees of freedom, i.e., new relevant variables, because redundancy and degeneracy open the possibility of evolutionary adaptations and exaptations happening because "each molecule and structure in evolving cells and organisms in the biosphere stands ever-available to be co-opted and selected, alone or with other things, for indefinite adaptive new uses such that myriad new adaptations [...]" [37].

In general, creation of meaning and complexity growth in a system take place through the act of seizing affordances or, in general, of choosing one among several options that have "appeared". We remark that options appear because the system is triggered to look at its adjacent possible because of a change or a stimulus. As this process depends on the current structure of the system, its goals, and its repertoire of actions, the path that the system can take for a self-rearrangement to make sense of a new stimulus is in general open and "unprestatable" [31]. For example, in evolution, new interactions may arise over time, either by the emergence of new organs or by new ways for using the current ones. Analogously, a new melody produced by mistake by a musician can be subsequently used as a pattern by other musicians (as is often said among musicians: "It's not the note you play that's the wrong note: it's the note you play afterwards that makes it right or wrong" [38]). *En passant*, we observe that this interpretation of "enabling error" has strong similarities with MacKay's notion of information as "the distinction that makes the difference" [39].

This *incompleteness* plays a fundamental role in the evolution and adaptation of complex systems because it makes it possible to provide new interpretations of external and internal stimuli. Incompleteness is of course also a consequence of the fact that the processes in the system are not univocally specified and can be executed by following alternative, non-equivalent paths. Such a property is called *logical openness* [40–42], which characterizes living organisms as well as biological and social organizations. Artificial systems lack logical openness because they can be articulated in precise functional parts, each designed for a precise function, while the structure and behavior of evolved complex systems emerge through a dialectic interaction with the environment [38,43–46]. Finally, we observe that the steps involving the modification of $\mathcal{U}$ as a consequence of noise and error are in general path-dependent [47].

3.4. Criticality

The ability of a system to change itself to make sense of a stimulus possibly originating from noise or errors also requires the ability to balance robustness and flexibility because only the stimuli that can assume meaning in the system should trigger an adaptation process. A case in point is the ability of living organisms to properly balance robustness against mutations and phenotypic innovation. In general, the property of achieving a good balance between a coherent response to external stimuli and the ability to classify inputs into a sufficient number of classes is achieved by systems characterized by dynamic

criticality, i.e., systems poised at the edge between order and disorder [25,48,49]. There is evidence that many natural and artificial systems are critical: from cells [50–52] and brains [53] to robots [54]. Remarkably, the property of dynamical criticality nicely fits into the framework of multilevel, open, and redundant systems that can undergo processes of self-configuration, adaptation, and creation of meaning to cope with and exploit noise and errors.

Lastly, we discuss a final aspect of noise and errors, shown in the example of adaptive robots with faulty sensors discussed above, which requires further elaboration. In abstract terms, this case is characterized by the fact that the inputs of the system are noisy and can carry incorrect information (i.e., not coherent with the state of the environment). According to Shannon's theory of information, this is the typical situation with a noisy communication channel, which is exactly the same setting we discussed at the beginning of this section. In the scenario of robots with faulty sensors, the effect of noise and errors is to help the system focus on relevant parts of the external stimuli and optimize its internal resources to properly and reliably respond to external inputs. This kind of noise lessens the redundancy of sensors, enabling the internal control mechanism of the system to achieve a higher efficiency in interpreting the inputs coming from the sensors and computing the actions to take. Notably, works in criticality and parallelism in optimization by means of stochastic local search [55] provide evidence that the relaxation of some constraints of a problem or a reduction in information make it possible to obtain better results than the ones that could be achieved with the complete and correct description of the problem [56–58].

4. Conclusions

We have discussed some general properties and conditions that enable complex systems to profit from noise and error to improve their performance, increase their complexity (in terms of structure or behavior), and create meaning. These properties are: multilevel organization, redundancy, incompleteness, and dynamical criticality. Further steps are aimed at the formalization of these properties and conditions in the various scenarios in which they play a role, both natural and artificial. Regarding artificial systems, it is important to remark that the dynamics and the adaptive abilities of artificial systems strongly depend on their substrate. While robots controlled by typical programs are subject to the limitations of computation based on Turing machines, therefore not considered to be truly logically open [40,59,60], different substrates make it possible to overcome these limits. A case in point is that of molecular robots built on the basis of chemical networks. Indeed, molecules and reactions are not just computing nodes and connections belonging to a computational domain. Rather, molecules have access to a potentially unbounded space of interactions, whose dimensions are not restricted and can unpredictably evolve as a result of previous interactions [61].

The connection between these processes of creation of meaning and complexity growth with Shannon information theory may provide a basis for establishing a formal link between information theory based on syntax (i.e., without semantics) and semantic information [62–64] and the way organisms and complex systems in general can make sense of their experiences.

Finally, we observe that the process of self-adaptation triggered by errors and unexpected percepts can be suitably described inside the theory of active inference [65], which can also provide a grounded probabilistic framework for the topics discussed in this paper.

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systems

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Review

Universal Complexity Science and Theory of Everything: Challenges and Prospects

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Abstract: This article argues that complexity scientists have been searching for a universal complexity in the form of a "theory of everything" since some important theoretical breakthroughs such as Bertalanffy's general systems theory, Wiener's cybernetics, chaos theory, synergetics, self-organization, self-organized criticality and complex adaptive systems, which brought the study of complex systems into mainstream science. In this respect, much attention has been paid to the importance of a "reductionist complexity science" or a "reductionist theory of everything". Alternatively, many scholars strongly argue for a holistic or emergentist "theory of everything". The unifying characteristic of both attempts to account for complexity is an insistence on one robust explanatory framework to describe almost all natural and socio-technical phenomena. Nevertheless, researchers need to understand the conceptual historical background of "complexity science" in order to understand these longstanding efforts to develop a single all-inclusive theory. In this theoretical overview, I address this underappreciated problem and argue that both accounts of the "theory of everything" seem problematic, as they do not seem to be able to capture the whole of reality. This realization could mean that the idea of a single omnipotent theory falls flat. However, the prospects for a "holistic theory of everything" are much better than a "reductionist theory of everything". Nonetheless, various forms of contemporary systems thinking and conceptual tools could make the path to the "theory of everything" much more accessible. These new advances in thinking about complexity, such as "Bohr's complementarity", Morin's Complex thinking, and Cabrera's DSRP theory, might allow the theorists to abandon the EITHER/OR logical operators and start thinking about BOTH/AND operators to seek reconciliation between reductionism and holism, which might lead them to a new "theory of everything".

Keywords: reductionism; holism; emergence; theory of everything; complexity science; systems theory; cybernetics

1. Introduction

The search for a single, all-encompassing systems theory goes back at least as far as the first half of the 20th century (e.g., Bertalanffy's General Systems Theory (GST), Wiener's cybernetics) (see [1–8]). Later theories dealing with complex systems, such as chaos theory [6], synergetics [9–11], self-organization [12,13], self-organized criticality [14], and complex adaptive systems [15,16], also followed this monistic way of thinking. Admittedly, much of the relevant work on complexity follows the ethos of rejecting the Newtonian paradigm built on Cartesian reductionism and turning to holism [17–19]. In this regard, some authors sought to end "reductionist complexity science" (RCS) and, with it, perhaps, efforts to create a "reductionist theory of everything" [20,21]. Despite this severe setback for RCS, many reductionist-oriented scientists have not lost faith in a universal theory for all complex systems.

On the other hand, holism and the theory of emergence have been integral to systems theory and "complexity science", at least since von Bertalanffy's GST. However, some authors hold that emergence has made it possible to extend the narrow scope

of systems theory beyond the natural sciences to the field of social and socio-technical sciences [8,22–26].

This paper generally defends the view that the founders and advocates of the significant theories of complex systems uninterruptedly insisted on a single "theory of everything". This search in itself entails reductionism–monism, a doctrine(s) that reflects the logical empiricism's search for linguistic or nomological unity through a "theory of everything" [27,28]. Reductionism generally states, "One can explain some object by reducing it to a different, usually simpler object or a thing" [29] (p. 5). According to the reductionists, therefore, all specific theories dealing with various complex systems should be replaced by a set of powerful algebraic expressions or a few computer models that predict the whole system's behavior based on the behavior of the components that lie at a lower level.

The problem is that these reductionist attempts fail to recognize the emergence-related hierarchies often observed in complex systems. But even those who accept ontological holism and emergence in natural and social realities believe that the theory of emergence can somewhat explain the gap between the micro and macro worlds. Yet even in their efforts to explain all kinds of world phenomena, there is a trace of the reductionist–monistic notion of a single theory or explanatory framework that unites most, if not all, sciences. Paradoxical as it may sound, this holistic-oriented theory is also reductionist–monist to a certain extent, as it is consistent with the belief that there is a single overarching theory that can replace other, more specific theories of particular sciences such as biology, psychology, economics, etc. However, it seems that the theory of emergence cannot explain the transition from the micro-world of physics to the macroscopic phenomena of the higher sciences, at least not for now. Therefore, it cannot be straightforwardly appreciated as a "theory of everything". At least, that is what I suggest in this paper. However, based on current empirical and philosophical knowledge, the "holistic theory of everything" has much more potential to take precedence in the search for a theory of everything than the reductionist theory.

The thesis of two theories of "everything" in "complexity science" and their same reductionist–monistic denominator is not new. However, I offer a fresh argumentation for it. Unfortunately, the discussion of the conceptual framework underlying systems or complexity-related "theory of everything" is somehow ignored and not discussed as it should be. It is noteworthy that this paper does not discuss other field-related attempts to establish a "theory of everything", such as the one advocated by Steven Hawking [30] in physics or psychology, such as the semantic general theory of everything discussed by Samsonovich et al. [31] or the algorithmic "theory of everything" in computer science discussed by Schmidhuber [32].

This article is structured as follows. First, Section 2 briefly overviews GST and cybernetics as precursor theories of contemporary "complexity science". It also discusses the holistic and reductionist threads that run through these theories. Section 3 briefly discusses chaos theory, synergetics, self-organization, and complex adaptive systems. Section 4 then sets out the convergence between systems theory, cybernetics, and complexity and shows how this convergence supports the notion of "complexity science", which promotes either reductionist or holist "theory of everything". Then, Section 5 examines the viability of the reductionist "theory of everything" in the era of holism and emergence and the limitations of the holist "theory of everything". A critical analysis of the arguments in these sections will ultimately help us recognize the perils and promises of the "theory of everything" inspired by complexity and, in the concluding section, point out possible new paths toward it.

2. The Doctrinal Aspects of General Systems Theory, Cybernetics, and Chaos Theory

Many authors, inspired by the results of a paper by Naomi Oreskes and colleagues (1994), perhaps consider reductionism and RCS dead or at least banished from current research practice. Of course, this assumption could be valid because it is becoming increasingly clear that reductionism fails when confronted with emergent phenomena in complex

systems [18,33–35]. However, as I will discuss, reductionism in some forms was never excluded from systems and complexity research efforts to create a "theory of everything". In this context, the hypothesis I wish to discuss, and test here is that the long-stated scientific goal has been, and continues to be, to provide a general framework for a unified or integrative explanation of various complex systems (e.g., natural, social, or engineering systems). In other words, I am sympathetic to the idea that efforts to develop a complexity-inspired "theory of everything" based on either reductionism or holism have survived to this day. Does the history of systems and complexity theory support this contention?

First, GST, which is one of the direct roots of these theories [36], was developed initially in biology by the Austrian biologist Karl Ludwig von Bertalanffy, who emphasized the central importance of "systems" to biology and other sciences [1–3,37,38]. However, it is debatable whether he is the only one responsible for the origin of systems theory. As Gunter [8] suggests, some authors cite the biologist Paul Weiss and his dissertation published in 1912 and even R. I. Williams as significant figures in the development of systems theory. However, von Bertalanffy made the most important conceptual and mathematical contributions to the further development of systems theory or what he called "systems science".

Von Bertalanffy [3] recognized the disadvantages and limitations of the mechano-reductionist approach and the advantages of holism in investigating the incredible complexity of the living world. This doctrinal shift helped establish the paradigm of biological systems as "ultimate realizations of complex systems" [39] and "probably the most complex entities to study in their natural environment" with multiple chains of interacting causalities [40] (p. 546). Von Bertalanffy also sharply criticized the unscientific character of 19th- and 20th-century neovitalism advocated by Driesch, Bergson, and others [3]. Instead, he proposed holism as a promising scientific alternative to vitalism [41]. He vividly maintained that life appeared to contradict the fundamental law of thermodynamics because living organisms, as open, dynamic systems of matter in a steady state and not in equilibrium as their change over time, can absorb and release material and energy from and to the environment to maintain their particular organization [2,41] (p. 248).

Nevertheless, acquiring the biological organization, in principle, cannot contradict the fundamental laws of physics. As von Bertalanffy stated in his book The Problems of Life [37], systems science is not about contradicting the laws of physics but about using them to analyze individual parts and processes in living things on the basis of which we can understand the relationship between the individual components that produce the organism as a whole [41]. He [3] (p. 409) even praised Descartes' comparison between man-made machines and life (Descrates' bete machine and the homme machine of Lamettrie) and Darwin's idea of natural selection as a crucial mechano-reductionist contribution to the understanding of order and organization in the biological domain. Clearly, GST or systems science owes much to centuries-old Cartesian reductionism, which modern complexity theorists are unfortunately quick to reject. Paradoxically, one might rhetorically ask if we would even understand the meaning of holism if it were not for such mechanistic attempts to understand life. However, what is holism in the context of systems theory?

Historically, "holism" can be traced back to the ancient Greeks and Aristotle's principle that "the whole is greater than the sum of its parts", which refers to the unity of the whole or "wholeness", but the South African Jan Smuts coined this term in 1926 [42]. It can be viewed from at least three philosophical perspectives: epistemological; methodological; and ontological. Epistemological or confirmation holism (Duhem–Quine thesis) is the view that a single model, theory, or hypothesis cannot be tested in isolation [43]. For example, it is essential for understanding the explanatory value of complex and global climate simulation models [44]. On the other hand, methodological holism, which goes hand in hand with epistemological holism, underscores that "Systems have to be studied by considering the things that are their parts in the context of the whole" [45] (p. 110). This is an appropriate heuristic approach to studying other non-complex systems as well. It is worth noticing that methodological and epistemological holism coincide in many

aspects. For example, in social sciences, methodological individualists and methodological holists debate whether individualist explanations can do holist explanations' explanatory job [46]. In other words, the disagreement is whether individual actions can account for the explanation of social phenomena or whether we need explanations of the social whole and their actions.

On the other hand, ontological holism runs profoundly through the heart of complexity and its predecessor theories, such as GST. It states [45] (p. 110), "Holistic systems are such that their constituent parts have some of the properties that are characteristic of these things only if they are organized in such a way that they constitute a whole of the kind in question". Nevertheless, many ideas and concepts that have emerged over the centuries have contributed to the development of systems science, "In a sense, one can say that the term "system" is as old as European philosophy" [3] (p. 407).

Although von Bertalanffy openly advocated holism, I believe he was a reductionist–monist in terms of his ideas about the transformative and revolutionary impact of GST on the advancement of science. In his numerous texts and books, he argued that GST had already proved its superiority over other scientific theories by enabling the scientific and mathematical formalization of many on-first-sight unscientific concepts such as whole, wholeness mechanization, centralization, hierarchical order, stable and stationary states, equifinality, and shows their applicability to various systems [1–3]. Although he did not directly engage with logical positivism or other perspectives on science, to my knowledge, he pretty much agreed with the positivists' search for a "theory of everything", albeit under the conditions imposed by his theory. Positivists often regarded physics as a fundamental science that should be admired and aspired to by all other sciences. In von Bertalanffy's view, GST, which builds on physics, is a "new science" that explains the living, non-living, social, and technical realms and man's place in the universe. In an early formulation of GST, expressed orally in the 1930s and later printed in 1947 and reprinted in 1955, 1968, and 1972, von Bertalanffy writes [3] (p. 411),

"There exist models, principles, and laws that apply to generalized systems or their subclasses irrespective of their particular kind, the nature of the component elements, and the relations or "forces" between them. We postulated a new discipline called General Systems Theory. General Systems Theory is a logico-mathematical field whose task is the formulation and derivation of those general principles that are applicable to "systems" in general".

It seems that he envisioned GST as a "theory of everything", which he called systems science. Systems science is the "Scientific exploration and theory of "systems" in various sciences (e.g., physics, biology, psychology, and social sciences) [3] (p. 414). Not only did he hold that interdisciplinary GST aimed to explain complex phenomena in nature and society, but in his 1972 paper [3], he openly discussed the possibility of establishing a systems technology, a systems philosophy, and a systems ontology. Thus, by proposing a new philosophical paradigm based on the "systems" concept and a "model of certain general aspects of reality", GST aims to provide a transdisciplinary synthesis of knowledge. Here, it becomes clear that von Bertalanffy, instead of physics, demands GST as a unifying force that would replace the role of physics as a fundamental and paramount science. Obviously, GST would become a sort of "new philosophy" anticipating the further progress of civilization.

All these suggest that von Bertalanffy was a kind of reductionist or monist who paved the way for the "theory of everything" and a figure who simultaneously wholeheartedly accepted the matters of holism in his long life's work. This shared vision and mission of systems-complexity-oriented "theory of everything" was later reiterated and emphasized by Richardson and Cilliers [21] (p. 6) when they said that RCS aspired to take over the role of the physical sciences by attempting to reduce and explain all of reality through "A handful of powerful, all-encompassing algebraic expressions". Unfortunately, instead of interdisciplinarity and transdisciplinarity, GST took the path of specialization [47].

However, von Bertalanffy is not the only one among the great names of science to advocate a single theory capable of explaining diverse and complex natural and social

phenomena. Inspired by messaging in the technical field, mathematician and philosopher Norbert Wiener, America's second Leibniz, invented the inter-scientific discipline of cybernetics that studies the theory of communication and control in the animal and the machine [4,5,48]. He writes on this general scope of cybernetics, which will later be called first-order cybernetics [5] (p. 267):

"As a means of controlling machinery and society, the development of computing machines and other such automata, certain reflections upon psychology and the nervous system, and a tentative new theory of scientific method".

First-order cybernetics, which deals with the complex entity (innate complexity) (see [49]), was systematically introduced into many sciences, including biology (biocybernetics), thanks to Norbert Wiener [4], Ross Ashby [50,51], Hans Drischel [52] and some philosophical reflection on it [53]. Later, in the 1960s, Heinz von Foerster [54] proposed second-order cybernetics, which focused on cognitive complexity (the term used by Fereidunian et al. [49]) and emphasized the cognitive limits of the observer when observing complex or simple systems [55].

3. The Progress in the Systems Theories from the Mid-20th Century Onward

In the second half of the 20th century, chaos theory, synergetics, self-organized criticality, and complex adaptive systems further carved the landscape of today's systems theory and "complexity science". These theories furthermore expanded the classic range of systems and cybernetic thinking. Nonetheless, they cemented the search for a "theory of everything" to erase the boundaries between the various sciences and explain processes and structures as diverse as cells and the stock market. I will briefly outline these theories in order to understand the seeds of the "theory of everything" that lie within them.

The chaos theory, which, in addition to quantum theory, challenges determinism, emerged relatively later than GST and cybernetics [7]. Although its roots can be traced back to Henri Poincaré [56] and Andreï Nicolaïevitch Kolmogorov [57], Edward Lorenz [6] is considered the official father of chaos theory [58]. Lorenz discovered and described the chaotic behavior of a non-linear system and attractors. Worth noticing here is that the term "chaos theory" was later coined by mathematician James A. Yorke in 1975—chaos theory itself underwent a significant change after the introduction of the concept of "fractal analysis" by Benoît Mandelbrot proposed in 1973 [58]. The invention and mathematical formulation of strange attractors by the Belgian physicist David Ruelle, which states that trajectories in phase space never intersect but form cycles that are not exactly concentric, also contributed to the rapid development of chaos theory in the last quarter of the 20th century [58] (pp. 283–290).

From the 1980s onwards, chaos theory, in its various formulations, particularly fractal analysis, permeated many specific research areas, including geology, climatology, and neuroscience [59–63]. The attractors and equations of fractal analysis are capable mathematical formulations that explain chaotic and non-chaotic behavior in natural and sociotechnical systems. A simple process can become complex because of repeating in time "https://fractalfoundation.org/resources/what-are-fractals/ (accessed on 20 November 2023)". In principle, the behavior of complex systems constituting components might be known (predictable or deterministic) or unknown (unpredictable or stochastic) [49]. This observation holds for creating macroscopic complexity, but biological systems require antichaos; as Lansing [64] pointed out, both self-organization and complex adaptive systems are, in some sense, reactionary to chaos theory since both focus on antichaotic behavior and nontrivial interactions between lower-level constituents that produce system as a whole. In this considerable effort by chaos theorists to explain, model, and predict various phenomena in nature, society, technology, and economy, one can recognize an apparent reductionist–monistic aspiration for the "theory of everything".

As an interdisciplinary field of research, synergetics attempts to decipher general principles that regulate the self-organized formation of macroscopic structures through cooperation between individual parts of a system. It was founded in 1969 by Herman

Haken [9–11]. Basically, synergetics assumes that every complex system is a multi-agent system with synergetic effects that can lead to chaotic and disorderly behavior or to orderly and predictable behavior. Synergetics can facilitate the transition from chaotic to orderly, antichaotic behavior to understand the inner workings of life and its evolution. Indeed, a wide range of biological phenomena, such as morphogenesis, qualitative macroscopic changes in animal and human behavior, population dynamics, evolution, neural networks, and electroencephalographic (EEG) signals, can be successfully studied by synergetics [10]. Recent neuroscience research further supports synergism and synergetics' relevance in explaining complex systems' spatio-temporal dynamical behavior. For instance, Varley et al. [65] recently reported that highly synergistic subsystems widely distributed in the human brain might play an integrative role in the brain's functioning.

Furthermore, it seems that scientists and philosophers consider the concept of "complexity" as particularly relevant in relation to "self-organization", "emergence", and "nonlinearity", all of which are typical features of complex systems [66]. While nonlinearity, which is essential to chaos theory, states that minor influences on the system can significantly change the state of the system on a large spatial scale [67,68], self-organization refers to an evolutionary process in which new, complex structures occur primarily within and by the system itself [69]. In other words, scientists recognize that self-organized systems exchange matter, energy, and information with their environment but achieve their organization without environmental instructions thanks to many components whose non-trivial interactions produce structural and dynamical order [12,70,71]. In terms of emergence, self-organization refers to the results of the collective interactions of the constituent components that produce ordered emergent behavior, such as the spontaneous formation of patterns, nonlinear coupling of reactions, bistable switches, waves, and oscillations in time and space of a given system—and it may well be true that it is a fundament of cell biology [71].

Self-organization entered the scientific arena within first-order cybernetics in the 1940s–1950s and was later extended to physics, biology, and neuroscience [50,54,72]. Additionally, it can be defined by the notions of system autonomy. Whether as a stand-alone theory explaining complex patterns in the world (see below self-organizing criticality) or as part of other theories, such as the autopoiesis theory of Varela and Maturana, self-organization points to the autonomous systems that are "Organizationally closed, so that the network of processes is recursively interdependent in the generation and realization of the processes themselves" [72], (p. 2), [73] This closure in production and space, the two premises of autopoiesis, seriously challenges reductionist efforts to explain the higher organization of matter in biological systems solely in terms of component interactions with lower levels. Why?

Both self-organization and autopoiesis hold that the organization and production of these lower-level components depend on the system's higher levels. This general observation implies that the phenomena of the lower level cannot be explained without taking into account the phenomena of the higher level(s) because higher levels help produce and maintain lower-level components. This understanding is a joker card for antireductionism and holism in biology. In other words, two-way causality (reciprocal causality) or interactions between "top–down" and "bottom–up" causalities plays a central role in explaining the inner workings of complex biological systems [35,74,75]. Some, like Pete A.Y. Gunter [8], Fritjof Capra, and Pier Luigi Luisi [76], claim that systems theories should be reframed to include autopoiesis because it has been now extended beyond the boundaries of biology and delve deep into social sciences. A particular extension of autopoiesis had already occurred when it was applied to computer science and the study of artificial life [77].

Furthermore, Wendy Brandts in 1997 [39] also referred to Horgan [78] and Bak et al.'s self-organized criticality [14] to suggest that research on complex systems is fueling enthusiasm for a unified theory of complexity from nature to society [21]. Self-organized criticality is a particular computational model introduced by Pearl Bak in 1987. This mathematically excellent attempt to formulate self-organization considers an attractor that arises by moving far from equilibrium to create a footprint of the complexity of 1/f noise and

fractal structures that are prevalent in nature [14,79]. The central claim of self-organized criticality is that all observed natural dynamic objects can reach a self-organized critical point, which is necessary to generate complex (self-similar) fractal-like structures in space and time if the condition of spatial degrees of freedom is met [14]. However, SOC has some limitations. The most recognizable is that it only recognizes two-time activity scales and interactivity across local spatial connectivities or captures only a single fractal or "monofractal" pattern [79]. In contrast, general cascade computational models inspired by Alan Turing's cascading instability, among others, can explain the perceptive-action system's multifractal nonlinear behavior (multifractal nonlinearity) [79]. For these reasons, self-organized criticality should be considered outdated, superseded, or perhaps updated by other theories, including complex adaptive systems (CAS) theory, which has gained traction in the social and natural sciences.

CAS is one of the most recent, but not the last, of the theories that have developed on the wings of GST, cybernetics, and chaos theory. CAS, a subgroup of nonlinear dynamical systems, assumes that a large number of interacting adaptive agents perform a simple task individually but that their mutual interactions result in complex collective behavior in natural or socio-technical systems [15,16,80–82]. These nonlinear dynamical systems share commonalities and general principles, even if they appear very different to observers [64,83]. Holland [16] (pp. 1–2) enlisted four major features of complex systems applicable to research areas as diverse as encouraging innovation in dynamic economies, providing for sustainable human growth, predicting changes in global trade, preserving ecosystems, controlling the internet, strengthening the immune system, etc. The first is parallelism, which suggests that many agents interact simultaneously by sending and receiving simultaneous signals (protein-related positive and negative feedback cascades in cells). The second feature is the principle of conditional action, which states that the agent's actions usually depend on the signals they receive. The third feature of modularity suggests that group rules can be combined as "subroutines" to deal with each new situation. For example, eight proteins forming a loop are essential for the citric acid cycle (Krebs), a fundamental component of all aerobic organisms, from bacteria to elephants. The final feature is adaptation and evolution, which illustrates that the players in a CAS change over time regarding adaptations that improve the system's performance.

These later theories of complex systems seemingly shared the same undivided vision of Bertalanffy and Wiener's universal "theory of everything" that can successfully deal with many natural and socio-technical macroscopic phenomena. They contributed significantly to strengthening the reductionist and monistic stream within complexity research without, however, abandoning the idea of holism. For this reason, Gunter's [8] list of shared assumptions of all systems theories, which are emergence, holism, hierarchical organization, and "bottom–up" and "top–down" causality, should be updated to include a reductionist–monistic search for all-inclusive systems theory or universal "complexity science". It is worth noting that, unlike GST, these later theories could better deal with all kinds of complex and non-linear phenomena in nature, society, and technology, bringing them much closer to today's understanding of "complexity science". This conclusion is in line with the conclusions of Gunter [8], Turner, and Baker [26] about the failure of Bertalanffy's theory to deal with complexity and nonlinearity and especially Turner's and Baker's arguments about why we should distinguish complexity theory or "complexity science" from systems theory. However, this in no way diminishes the historical importance of GST for developing holistically-based systems thinking, which inspired further scientific advancements.

The search for one all-powerful theory for complex systems has never ceased and continues to permeate research practice and meta-scientific reflection on it today. Even if this is not clearly emphasized in some of the new mathematical and computational formulations of the new generation of systems theory, the beliefs and actions of many scientists support this claim. For example, Ochoa [84] points out that different systems can be modeled based on the exact mathematical framework that current systems science provides. Similarly, Hipólito et al. [85] (p. 7) define complexity science as "Composed of an

array of different techniques, which together aim to capture the unifying common features of the behavior of multi-system interactions".

Also, in a recent topical article by Wong et al. [86] (p. 1), which is already resonating beyond the scientific community, the authors propose a unifying evolutionary framework for the development of living and nonliving complex systems based on three remarkable features: (1) the existence of many components that can adopt a large number of different configurations; (2) the existence of processes that can drive these different configurations; and (3) the selection process that can choose these different configurations based on their function. According to these authors, the "law of increasing functional information" suggests that "universal concepts of selection—static persistence, dynamic persistence, and novelty generation—drive systems to evolve through the exchange of information between the environment and the system". These recent attempts to formulate unifying "laws" that drive complexity in the universe are pretty much in line with what early systems and complexity theorists were trying to achieve.

We should look at the following example as further proof that the reductionist "theory of everything" inspired by systems and complexity theory is taken seriously across sciences, including physics. Lukyanenko et al. [38] (p. 5) nicely illustrated this point:

"Stephen Hawking treats "system" as a fundamental constituent of reality. . . Hence, both in Feynman's formulation, as well as in the rendition by Hawking and Mlodinow, everything in the universe, from elementary particles to the entire universe, is a system, and furthermore, it is the objective of modern physics to predict the properties of these systems".

Furthermore, a fresh article by Poudel et al. [87] published as part of the theme issue "Thermodynamics 2.0: Bridging the natural and social sciences" in Philosophical Transactions A uses an area of physics called thermodynamics, a universal and unifying science, to bridge the sciences of matter (natural science) and of life (social science). In the same thematic issue, Swenson [88] has argued that the fourth law of thermodynamics (the law of maximum entropy production), alongside the first law of time-translation symmetry and the self-referencing circularity of the relational ontology of autocatakinetic systems, are the critical ingredients for a grand unified theory unifying physics, life, information, and cognition (mind). These more recent efforts to explain the complex world in terms of the fundamental laws of physics are an offshoot of the long-standing positivist reductionist tradition that saw physics as the only fundamental science that should replace the other sciences. They also support the assertion that the positivist way of thinking in science is still very much present in today's postmodern age. Whether it is complexity research or physics research in question, all of these reductionist-tinged accounts follow and rely on the offerings of reductionism and monism to legitimize the quest for the "theory of everything".

4. On the Convergence between Systems Theory, Cybernetics, and Complexity

What is complexity? What is "complexity science"? How does "complexity science" relate to systems theory and cybernetics? More importantly, why should we waste our time asking these questions? At least I have a prompt answer to the last question, "The natural world can be generalized to a complex system, and a "science of complexity" would provide us with the knowledge to control just about everything" [21] (p. 10). To be able to provide at least partial answers to these other questions, we should first discuss the relationship between GST, later theories of complex systems, and cybernetics.

From the 1950s on, there was a tendency to merge von Bertalanffy's GST and Wiener's cybernetics [89]. However, as Heylighen and Joslyn [89] (p. 156) aptly put it, "GST studies systems at all levels of generality, whereas cybernetics focuses more specifically on goal-directed, functional systems that have some form of control relationship". Cybernetics also have a specific relationship with the postmodern understanding of knowledge's contextual and subjective nature. In this context, second-order cybernetics, which takes the strict view

that knowledge about complex systems must include the relevant role of an observer who observes the system as such, showed that knowledge is intrinsically subjective [7,54,90–95].

This realization further suggests that the scientific knowledge of "mind-independent" complexity does not directly represent an external or "mind-independent" reality; the subject who perceives complexity actively interprets and adds to its true meaning. In this Kantian-inspired epistemology, our scientific descriptions of the complex world, obtained through various methods, measures, explanations, and representations, should be viewed as "world versions", even if the "world itself" exists independently of our existence.

On the other hand, first-order cybernetics focuses on universal phenomena of control and communication, learning and adaptation, self-organization, and evolution [95–97]. The rough classification of cybernetics into first-order and second-order cybernetics would look like this. Today, however, at the latest, this subdivision is perhaps artificial, as researchers are increasingly pushing for the unification of objective and subjective components in treating complex systems. For example, physicists increasingly use entropy to approach the interplay of subjective and objective components in studying complexity. In this regard, Fagerholm et al. [98] argue that entropy is a property of both a system and an observer, as it can measure hidden information in a system that arises due to the constraints of an observer.

What are the differences between systems theory and broader complexity theory, sometimes called "complexity science"? There is no straightforward answer to this question. However, there are some valuable pushes in this direction. For example, Turner and Baker argue that systems theory, as conceptualized by Bertalanffy, does not account for the nonlinear dynamics of complex systems [8]. However, we must admit that nonlinearity emerged later within chaos theory and has now been incorporated into the new generation of systems theory. It seems that GST, together with cybernetics, chaos theory, synergetics, self-organized criticality, and complex adaptive systems, enabled the development of what we now call "complexity science" and the second generation of general systems theory recently presented by Minati, Pessa, and Licata [99]. Gunter, on the other hand, argues that systems theory and complexity theory share the same foundations and conceptual apparatus [8] (p. 15):

"The terms used by complexity theorists are identical with those used by proponents of biological systems theory: nonlinearity, emergence, uncertainties in prediction, self-organization, bottom-up causality, chaos. Equally significant, complexity theorists attack the mechanistic standpoint in exactly the same way as systems theorists".

In contrast to Gunter, I, along with other authors, see another critical point of difference between systems theory and complexity theory or "complexity science". Unlike the latter, which seeks to explain the emergence and emergent patterns in systems, early cybernetics, and systems theory focused on "positive and negative feedback loops" [22,25]. Indeed, complexity theory, which has changed considerably in light of recent scientific discoveries, particularly in the biomedical field, now focuses on the "leveled ontology" central to 19th and 20th-century British emergentism [18,100]. "Leveled ontology" assumes that the levels in question are not only levels of description or explanation but "levels of reality or ontological levels" [100] (p. 853). These ontological levels are instances of strong emergence or, namely, the understanding that "A high-level phenomenon is strongly emergent with respect to a low-level domain when the high-level phenomenon arises from the low-level domain, but truths concerning that phenomenon are not deducible even in principle from truths in the low-level domain" [101] (p. 244). Besides being focused on the emergence, today's "complexity science" tries to understand the relationship between the micro and macro properties of complex systems and the practical importance of emergence and holism for science (see [102]). However, I agree with Gunter [8] and many others, such as Medd [21,24], in their advocacy of complexity theory or "complexity science" as a comprehensive systems theory that deals with natural socio-technical and organizational systems.

The critical question is, what is "complexity science"? Does it follow the idea of the "theory of everything"? In the special issue of A Journal of Complexity Issues in Organizations and Management, a publication of the Institute for the Study of Coherence and Emergence (Volume 3, Issue 1, 2001), edited by guest editors Kurt Richardson and Paul Cilliers, a group of renowned philosophers and scientists or "gurus" in the field of complexity set themselves the task of answering the thorny question of what complexity is. Is complexity perhaps a science or a narrative? If it is a science, is it postmodern or postpositivist? As expected, they all give unique answers to the same question, and each gives us clues for further attempts to define the complexity and its science. Moreover, I find their answers still relevant more than 20 years later. I will not go into all the works on this topic but only mention a few relevant to this paper.

In the introductory article, Richardson and Cilliers classify complexity, or "complexity science", into hard, soft, and somewhere between. Reductionism plays an integral part in this division. Hard complexity science (reductionist complexity science, RCS) "Mimics the aim of the physical sciences in trying to reduce the wide richness of reality to a handful of powerful, all-embracing algebraic expressions" [21] (p. 6). Unfortunately, RCS seems to rely on a seductive syllogism that Naomi Oreskes and her collaborators refuted in a 1994 article in which they warn us of the impossibility of validating and verifying numerical models of natural systems [21,78].

On the other hand, soft complexity science recognizes that the complexity inherent in socio-technical organizations, characterized by language and meaning, differs from the natural world [21]. Therefore, some believe that theories of complexity developed in the natural sciences are not directly applicable to social systems but can provide some insight and illumination into the behavior of these systems. Hard complexity science, which promises a universal language and principles applicable to any natural and perhaps social context, unlike soft science, is a real science. The social sciences are considered soft complexity sciences because physical theories such as quantum mechanics have no value to the social sciences [21,103]. To worsen the situation, some hold soft complexity sciences as pseudoscience. For example, Phelan [103] thinks that pseudoscience includes soft complexity sciences (resemblance thinking). Similarly, Edgar Morin [104] distinguishes between "generalized complexity", which refers to the human condition, and "constrained complexity", which enables fundamental advances in formalization and modeling in science.

Nevertheless, both "hard" or "soft" complexity aims at contextual, "non-objective", and "non-static" knowledge. Stated differently, our knowledge of reality is limited, subjective, and context-dependent [55,105,106]. It depends on the subject matter's stability and requires stable boundaries, which do not exist in complex nonlinear dynamical systems. By changing the context, we change the understanding and, thus, problematize the learning process as an essential aspect of complexity [21] (p. 13), "We can never have complete knowledge of a complex system; we can take advantage of the various alternative representations (including our own subjective models) and synthesize more robust approximations allowing more informed decision-making". Even informational–functional approaches to evolving complexity suggest that the context of a system alters the outcome of a calculation in systems with increased functional information defined by static persistence, dynamic persistence, and novelty generation [86].

Considering that there could be scientific appropriations of complexity, the question is what constitutes this "science" more precisely. No uniform definitions of "complexity science" or "complex" exist. Even the RCS with some of its proposed laws, e.g., that complex systems are incompressible (principle of incompressibility), i.e., that "Any description claiming to be complete must be as complex as the system itself", does not seem to be very helpful in the search for a unified definition of complexity science [21] (p. 9). However, Richardson and Cilliers [21] make a point that researchers' personal preferences are critical in determining which definitions of complexity are considered. Likely, these subjective preferences undermine efforts to elevate "complexity science" to the status of a science.

One such definition of complex systems, "Complex systems are comprised of a large number of entities that display a high level of nonlinear interactivity", is pushed forward by Richardson and Cilliers. In defense of the vagueness of attempts to crown complexity as science, we must not forget that the definition of science and scientific knowledge is a centuries-old, still elusive problem of which Richardson and Cilliers are well aware. Indeed, apart from the difficulty of defining a novelty like "complexity science", there is surprisingly no universally accepted definition of what science is.

Scientists and philosophers informed and raised in the positivist tradition assume that an absolute reality exists, regardless of the observer's role in acquiring knowledge about that world [21]. They also believe in mathematically expressed "laws of nature", in the nonsubjective nature of knowledge generated by the scientific method(s), and in reductionist methodology, which asserts that knowledge of the whole can be gained by analyzing the parts of the system and putting them together to understand the whole (the whole is equal to the sum of its parts) [21]. All these criteria are often used to distinguish science from pseudoscience. However, as we have seen above, "complexity science" does not meet these formal requirements. If we strictly adhere to them, there can be no "complexity science". Or is a positivist understanding of what makes science a science perhaps too narrow, Richardson and Cilliers ask? Opinions on this issue are divided. For example, Morçöl [107] holds that "complexity science", while rejecting the Newtonian notion of universal laws, nevertheless uses generalizations often abhorred by postmodernism.

On the other hand, "complexity science" is postpositivist because postpositivism represents a "Compromise between the extremes of positivism and radical postmodernism, in which the contextuality of (local) knowledge is recognized as well as the existence of universal principles (scientific knowledge)" [21] (p. 18) [107]. It seems that complexity science is a "grey" science for the "stuff in between", which, on the wings of postmodernism, warns us to be cautious when uncritically adopting any "black and white" theoretical position [108]. Phelan [103] is critical of Morçoel and others who deny "complexity science" the ability to distinguish science from other types of knowledge. In other words, scientific inquiry is inconceivable without the notion that science is the "supreme arbiter of truth, objectivity, and rationality". Examination of the disciplinary and/or interdisciplinary scientific status of complexity will continue to challenge our ability to distinguish between science and non-science and between different paradigms of scientific rationality (e.g., Newtonian, quantum-mechanical, etc.).

Another valuable line of argumentation about the scientific status of complexity comes from the theory of emergence and self-organization. For example, some authors, such as Medd [24], argue that "complexity science" should emphasize "emergent and self-organized phenomena" from a social science perspective, which are seen as central to defining complexity and overcoming "theoretical complexity science" through a "top–down" and "bottom–up" analysis. In this context, scientists must explain the gap between microscopic diversity and macroscopic order using the theory of emergence and "complexity science". This science deals with order, which is often mistakenly characterized by a relative end state and complexity [23]. In other words, in addition to laws of physics, such as motion, gravity, electromagnetism, and thermodynamics, we need an additional unarticulated law to describe the macroscopic phenomena of our complex, evolving universe [86]. Gunter [8], Turner, and Baker [26] seem right when arguing that complexity theory or the "complexity science" goes beyond the scope of GST and contemporary systems theory, which is closely related to biology. In other words, "complexity science" aspires to the pedestal of theory or science about almost everything, from the atom to the dynamics of ecosystems to society and the stock market.

5. Reductionism, Holism, Emergence, and Theory of Everything

In the previous chapters, we have given some indication of holism and emergence. Here, we will say more about ontological holism and reductionism and their relation to the emergence in the context of systems theory and "complexity science".

First, I will discuss Elder-Vass's version of an influential argument supporting ontological holism that builds upon ontological emergence. This argument, which was put forward by Elder-Vass in 2010 [109], was discussed and reconsidered by Julie Zahle in 2014 [110]. Elder-Vass [109], similar to Robert Rosen [111,112], considers natural or socio-technical systems ontologically or "inherently" complex. To digress, Robert Rosen, a renowned systems thinker, theoretical biologist, and biology's Newton (see [17]), most clearly and forcefully articulated the idea of complexity as a system property, reflecting the need for many different methods to study and representation to describe such systems [111,112]. However, what is whole? Is this concept easy to define, or is it susceptible to relativization?

Any system of interest or entity "Is a relatively enduring whole composed of parts standing in certain relations to each other" [109] (p. 17). As Zahle noticed, "These parts may be entities too, and hence they may themselves be persistent wholes made up of parts standing in certain relations to each other, and so on" [110] (p. 179). Elder-Vass and Zahle see biological reality as "Containing various entities, both combining and dissolving into yet other entities". As expressed by Mario Bunge [113], emergence leads to new entities, while submergence leads to their disappearance. Indeed, Elder-Vass and Zahle are talking about the vertical multilevel stratification of things in nature, for instance, in a living world. Every "whole entity" possesses specific "intrinsic" ontic properties, but the parts also may have their own properties, and in the end, we have numerous properties to deal with.

This line of reasoning quickly leads Elder-Vass to consider what properties have whole that the parts do not have. He gave many examples, and one is very simple: the physicochemical differences between water, hydrogen, and oxygen. In isolation, a prominent property of water is to be a liquid at certain temperatures not possessed by its parts(hydrogen and oxygen atoms). Zahle calls these emergent properties of wholes proper. She cites Elder-Vass and writes [110] (p. 180), "The emergent properties of a whole are ones it has in virtue of, or because of, its parts standing, at that moment, in certain relations to each other". Here, "at that moment" is meant to signal that the relationship between the emergent properties of a whole and its parts is synchronic and non-causal rather than diachronic and causal". By contrast, the emergent properties of the parts Zahle and Elder-Vass hold "Are really a property of the whole that happens to be localized in some respect within the part" [109] (p. 27).

Famous Robert Rosen's distinction between living organisms and machines can demonstrate "whole" and "wholeness" anticipated by ontological holism. The argument, recently restated by De Bari et al. [114] (p. 3), is as follows: while there is an isomorphism between the structure of a machine and the function of its components (the idea that machines are fractionable), organisms are so far not fractionable. In other words, machines comprise man-made and assembled parts or components, each performing a specific function. These assembled machine parts are allopoietic, meaning that they are not self-produced but engineered by humans and other machines. In contrast to machines, there are no clear boundaries between the components of biological organisms. De Bari et al. [114] give examples of the integration of the nervous and vascular systems and of the dependence of the functional role of a particular component on a changing internal and/or external context (e.g., the function of a muscle in different postures or in the context of different activities). This difference between machine and biological systems suggests that analysis in the engineering domain leads to synthesis. This means we can take apart machines to figure out how they work and then learn how to build them, according to De Bari et al. [114]. However, although we know a lot about cell biochemistry and molecular biology, we still do not know how to make cells (synthesis), which underscores the uniqueness of the self-organization of living matter. Now, let us discuss reductionism more specifically.

In his seminal book, published in 1974, Francisco Ayala [115] explained the differences between philosophical modalities of reductionism. Respectively, ontological reductionism questions whether physical–chemical processes are responsible for phenomena on a higher level, e.g., in biology. It rejects non-material principles, such as life force, entelechy, radical energy, etc., as unscientific. Epistemological reductionism is concerned with whether

theories formulated in one branch of science are exceptional cases of theories and laws of another branch of science. Epistemological reductionists may claim, for example, that the theory of evolution is a particular case of some physical theories, which is difficult to prove.

On the other hand, methodological reductionism refers to the issue of research strategies, methods, and methodologies that scientists use in research. In this context, for example, it is interesting whether living processes are best studied at the molecular or higher levels of organization or whether both are necessary to unravel the complexity of life processes. Today, many scientists and philosophers consider both "bottom–up" and "top–down" research strategies equally appropriate for capturing interacting causalities coming from both directions, thus highlighting the fact that there is no privileged level of causation in biology [35]. For instance, it appears that genetic information (bottom–up) intermingles with epigenetic information (top–down) in generating quantitative and qualitative phenotypes, suggesting that both research strategies are needed to define genes and to reflect on the role of genetic processes in physiology and evolution [74]. This argumentation makes physiology again a central field of research within biology, as recently argued by Noble [116].

In my opinion, the reductionist's main line of attack is to refute strong emergence and ontological holism or to show that they are an illusion created by the limited cognitive capacity of our brain when confronted with complex systems. In other words, to win the battle against antireductionism, reductionists focus their attack on criticizing the scientific soundness of strong (ontological) emergence. In this direction, it is worth noting that most philosophers today agree with most scientists in rejecting ontological emergence and accepting ontological reductionism [102]. Indeed, the ontological antireduction is questionable because to defend strong emergence scientifically requires a successful computational and mathematical formalization and characterization of emergent phenomena, about which there is still considerable dispute in the scientific community (see [102,117]).

Some authors, such as Forestiero [118], hold that the low effectiveness of mathematics in solving biological problems in situations when the effects of the whole on the parts are taken into account. This "whole-parts" causality is essential in proving the validity of the autopoietic closure of production assumption. For the success of empirically motivated ontological emergence, scientists must prove that computational systems biology can answer the question of how emergent collective behavior appears on the biological macroscale [119]. On the conceptual level, however, emergence and computability align pretty much [120].

Furthermore, many ontological reductionists, in principle, do not support epistemological and methodological reductionism. However, some go one step further, aiming at epistemological and methodological reduction in specific sciences such as biology to physics as their ultimate goal. Their aim is not only to refute strong emergence but also to show that the theoretical–epistemological–semantic elements of specific sciences (e.g., Nagel's special sciences, Rosenberg's instrumental sciences, or Mayr's provincial sciences) are reducible to theories of physics. These are eliminativists [121]. However, their quest is doomed from the start. Why? Eliminativism fails simply because it does not recognize the uniqueness of the language of higher strata sciences, conceptual frameworks, generalizations, methodological settings, etc. Stated differently, even metaphysical reductionists, such as Alexander Rosenberg [121,122], do not take the idea that biology and psychology's methods, specific theoretical frameworks, such as the theory of evolution, and language biologists and psychologists use daily should be reduced or replaced by physics. The reductionists merely claim that biologists must come to terms with the fact that biology "needs a systematic and complete anchoring in the physical" without disallowing its conceptual and methodological settings, as noticed by Rosenberg [122] (pp. 124–125):

"Of course, the reductionist must recognize the indispensability of the theory of natural selection to biology. Anything else would turn reductionism into an untenable eliminativism".

Incidentally, Rosenberg's understanding of sciences dealing with complex systems is consistent with Richardson and Cillier's notion of the reductionist principle of incom-

pressibility we mentioned in the previous section. This principle is more than crucial to understanding the limited cognitive capacity of humans to explain and investigate complex systems holistically. It also raises concerns about the success and scope of epistemological and methodological holism in complexity research. Unfortunately, some examples from practice also speak for epistemological holism's failure. For example, Lenhard and Winsberg's [44] fear of climate model pluralism suggests skepticism about the value of confirmation holism in real-life science settings. At least the epistemological holism seems to be in an empirical and perhaps intellectual crisis. Any failure to describe or explain complex phenomena holistically through synthesis or integration of system components is equivalent to reductionism [123] or a reductionist, mechanistic view of science à la Newton [17]. Therefore, not only does complexity in biology and other higher-strata sciences challenge the limits of reductionism and determinism, as Mazzocchi (2008) prophetically noted, but the scope and promise of holism also may reach its limits in science these days.

Why do eliminativists fail in the case of epistemological and methodological reductionism? To put it another way, why cannot epistemological emergence die so quickly? Let us discuss the following example. Rosenberg [121] considers the sciences dealing with complex matter, such as biology, to be instrumental sciences. Metaphysically–nomologically speaking, these sciences have no laws of their own and rely on the fundamental laws of physics, but we often mistakenly perceive them as having their laws. In other words, we view the behavior of natural and social systems as if they defy the fundamental laws of physics or are subject to other "emergent laws" because our cognitive limits have been reached in studying, modeling, and explaining complex systems by experimental, computational, and mathematical means. Perhaps this imperfection in our minds leads us wrongly to account for the strong emergence and claim that biology deals with laws and processes that physics cannot explain. Pigliucci [102] (p. 263) summarizes the essence of epistemological or weak emergence accepted by most philosophers and scientists of our time,

"There are no true emergent phenomena, only phenomena that cannot currently (or even ever) be described or understood in terms of fundamental physics, and yet are, in fact, only complex manifestations of the microscopic world as understood by fundamental physics".

Because of the intricate "inherent" complexity of life and the limited cognitive ability of humans to deal with it, we perceive or confuse, for example, weak emergence with its ontological counterparts. Therefore, given the complexity of matter assigned to biology, reductionists are forced to admit, at least in the short term, the impossibility of rejecting epistemological antireductionism and weak emergence. Overall, given the fact that eliminativism is untenable, most reductionists are unwilling to refute the heuristic and pragmatic significance of both epistemological and methodological antireductionism in sciences dealing with higher layer "realities" whose theories are formed conceptually and experimentally in a way quite different from the physical. In this way, they are, in my opinion, in some ways on the same line as the anti-reductionists. As nicely summarized by Nagel [124] (p. 3):

"Epistemological antireductionism holds that, given our finite mental capacities, we would not be able to grasp the ultimate physical explanation of many complex phenomena even if we knew the laws governing their ultimate constituents. Therefore, we will always need special sciences like biology, which use more manageable descriptions".

This rise in epistemological antireductionism coincidence with the fall of eliminative reductionism or the abandoning of some forms of epistemological reductionism in the post-genomic era of biology [125] (p. 359):

"All we can say for sure at the present time is that a specific form of reductionism is starting to disappear from biology, a form in which complex structures and functions could directly be explained by the properties of a limited number of gene products".

Of course, there are other ways to argue in favor of antireductionism and the theory of emergence in "special" sciences, such as the multiple realizability argument (see [126,127],

Maturana and Varela's autopoiesis (biological autonomy) [91,93,94] Whitehead-inspired process ontological view of life [128], etc. Of these mentioned theories, special attention has recently been paid to the process-based ontological view of life, which emphasizes the dynamic rather than the stationary dimension of life functioning. This promising perspective, which is difficult to interpret, "derives" at least in part from ideas such as Bohm's "holomovement" concept of "unbroken and undivided totality" [129] (p. 575). By taking into account the self-organization of an autopoietic system and process-based ontology, emergence can be explained very simply, with minimal assumptions about the properties of the underlying physical processes. This idea is elaborated in recent essays by Heylighen [130,131].

The arguments from the system-related revolutions in the "special" or "instrumental" sciences can also benefit the anti-reductionist efforts. The revolutionary orientation of genetics and genomics toward systems holistic research at the beginning of the 21st century is seen by many as a solid foundation for the justification of anti-reductionism [36,125,132,133]. Echoing François Jacob's book Logic of Life, Michel Morange [125] argues that reductionism cloaked in molecular biological garb seemed to win the battle against holism at the end of the 20th century by explaining the properties of life and genetic control of life's functions in terms of the molecular structural properties and enzymatic capabilities of macromolecules. However, this joy lasted only briefly as holistic models of what life is and how it works emerged on the eve of the 21st century on the wings of what is known today as the post-genomic era.

Now, is it possible to understand the meaning of the expressions "science is holistic" or "science is reductionist" without assuming the relativity of these positions? In other words, is the determination of these scientific perspectives problematic, and if so, are the concepts of reductionist or holistic "theories of everything" also relative? In the book Holism and Reductionism in Biology and Ecology, Rick C. Looijen [134] argued for a relativistic understanding of scientific fields and subfields' holistic or reductionist character and mutual dependence between holism and reductionism. Basically, he claims that a scientific theory, a research program, or even an entire science or sub-discipline can be holistic in relation to a lower level of organization but reductionist in relation to a higher level. He provides illustrative examples to support this idea [134] (p. 121). For example, ecology is holistic compared to physiology, genetics, or molecular biology. Physiology is also holistic compared to molecular biology. Ecology can be considered holistic and reductionist, depending on its sub-disciplinary structure. Population ecology, which studies the relationships between groups of organisms of the same or different species, is holistic compared to auto-ecology, which studies the relationships between individual organisms and the environment.

Above these subfields are systems ecology and landscape ecology, which deal with the complex interactions between all organisms and their environment in a given geographical area and the influences of different landscapes on the diversity and richness of species and communities. Global ecology is holistic concerning all of the above research areas, as it examines global energy and material flows, the influence of global hydrology, atmosphere, and lithosphere on the biosphere and, conversely, the biosphere on these other earth spheres. Although this relativism forces us to be cautious in determining the theoretical perspective we adopt in certain areas of scientific research, the emergence that leads to hierarchies and the hierarchical organization of the sciences and forms the basis of a holistic "theory of everything" holds well as long as we are at the macroscopic level of insights. Whatever level we look at is holistic until we reach the elementary particles, for which other laws seem to apply. With the help of "top–down" and "bottom–up" causality, the same emergence theory should explain the structure and dynamics of the organizational levels of different systems across time and space. In the case of the reductionist "theory of everything", it all boils down to the essential structural components of physical reality and the laws that govern them. For it, there is no fear of relativization. The following

discussion will help us more closely understand the relationship between reductionism and emergence (holism) across sciences.

By finding their way into systems and complexity research, holism and emergence gave a new meaning to the attempts to reduce theories, research programs, and sciences. They may have shifted this discussion into the realm of ontology. For example, referring to famous Anderson's paper [135], Elena Castellani [33] gives a much clearer picture of the relationship between reductionism and emergence when reflecting on the connections of these concepts with the scientific understanding of current quantum field theories as effective field theories. Accordingly, Castellani argues that Anderson opposed the reduction or supremacy of "high-energy physics" over "low-energy physics" (solid-state physics or condensed matter physics) by postulating basic anti-reductionist notions, which I will interpret briefly here [33] (p. 255):

(a) The way down/way up distinction or "top–down"/"bottom–up" distinction, which basically says that research should start with a "top–down" reduction in everything to fundamental laws (reductionist hypothesis) and then use those laws to reconstruct the entire universe (constructionist hypothesis).

However, this thesis actually accounts for and supports reductionist causes since it does not assume emergence and emergent properties and the hierarchical structure of science. Therefore, Anderson [135] (p. 393) and Castellani [33] (p. 255) introduced two other theses, which I find relevant to our cause;

(b) The fact of emergence. The constructionist hypothesis is rejected because of the emergence of new properties, "At each new level of complexity entirely new properties appear, and the understanding of the new behaviors requires research, which I think is as fundamental in its nature as any other";
(c) The hierarchical structure of science. The entities of X are emergent in the sense that, although obedient to the laws of the more primitive level Y (according to the reductionist hypothesis), they are not conceptually consequent from that level (contrary to the constructionist hypothesis).

Having described these notions, let us draw the consequences of this understanding to reach a "theory of everything". It is now worth noting that, with respect to (b) and (c), antireductionists claim that the higher-level phenomena are irreducible to low-level strata. Reductionists, on the other hand, argue that they are reducible. As indicated earlier, antireductionists firmly believe in stratified (layered) ontology in which a higher stratum or layer presupposes lower strata but not vice versa. This reasoning has substantial implications for the disciplinary organization of sciences, as discussed by Sayer [29] (p. 5):

"The strata usually cited are the physical, the chemical, the biological, and the social, but further strata may be invoked within each of these. The plausibility of the idea that the world is stratified arguably provides a warrant for the existence of different disciplines: the physical, the biological, and the social deal with different strata of reality".

Sayer's powerful claim is straightforward: we have different disciplines for the different parts of reality. For example, molecular biology deals with DNA and proteins, while autecology deals with the relationships between individual organisms and the environment. Psychology studies the mental life of humans.

Having said all these about reductionism in light of holism and emergence, the prospects for one all-encompassing reductionist systems theory or complexity theory capable of explaining phenomena across vertical levels of organization of complex systems are not so bright. Simply stated, scientists and philosophers involved in complexity studies must refute ontological emergence to defend one reductionist theory for all systems successfully. Otherwise, their idea of explaining all hierarchies with the laws of the atomic and molecular world would have to be reformulated to include some new macroscopic laws, if not laws, then at least exceptional cases of the same physical laws that govern molecular interactions. As far as the reductionist/antireductionist dispute is concerned, if

reductionists fail to refute emergence, then they must admit their defeat and accept new metaphysics [102].

Even if reductionists are correct and there is no strong emergence in nature, or that emergence is an epistemic phenomenon, scientists should take it seriously because it shows us "Current methodological or theoretical deficiencies that make straightforward reductionist accounts unfeasible in practice, if not in principle" [102] (p. 265). Surprisingly or not, as I already discussed, it is much more difficult for them to justify epistemological and methodological reductionism. It seems neither practical nor pragmatic, for example, to reduce biology's concepts and research programs to physics, systems theory, or "complexity science". This does not exclude that many concepts from systems theory or physics, such as "synergetics", "nonlinearity", and "self-organization", help search for the explanation of evolutionary changes in living organisms. Alternatively, ontological antireductionists rely on strong emergence to build one "holistic theory of everything". They are not convinced that these emergent laws are special cases of fundamental laws of physics.

Whatever path one chooses, the consequences are the same: a theory of everything hits the walls, at least for now. In the first scenario, if one proves that strong emergence is real, one would find it difficult to describe it by mathematical or computational characterization of the interactions of lower-level components, except in sporadic cases [35,117]. This is because current mathematical modeling tools and computational power are limited in describing, modeling, and predicting strong emergent phenomena in the "bottom–up" and "top–down" directions, as philosophical and scientific studies on biological complexity suggest [117,118,121,122,136,137]. Even if one can somehow prove that there is no strong emergence, contemporary science must accept that it has not succeeded in providing a reduction model in which weak or epistemological emergence disappears from the table, either for pragmatic or substantive reasons. This conclusion is supported by the above discussion of Rosenberg's notions of reductionism and eliminativism. A reductionist "theory of everything", at least in its eliminative form, has, thus, come to a standstill because scientists or philosophers have not succeeded in formally proving strong emergence by applying the known mathematically expressed laws of physics on the one hand and disproving weak or epistemological emergence on the other.

In the second scenario, if we show and prove that strong emergence and theory of emergence holds once forever, then the question arises whether it is possible to apply the same theory developed for the macroscopic world to the microscopic world of physics and chemistry. This would be a challenging task whatsoever. But why do both scenarios end with skepticism? Or better say, does one of the above theories of everything take precedence when confronted with the existing scientific and philosophical knowledge?

Let us perform a thought experiment here. As said in a few lines above, the "theory of everything" can be based either on physicochemical laws or the theory of emergence. In the first case, it is reductionist; in the second, it is anti-reductionist. We have already demonstrated skepticism in explaining emergent phenomena utilizing physicochemical macromolecular interactions on more than one occasion. To elaborate on this matter, I will discuss the following example further. Focusing on non-technical ontological emergence in the biosphere suggests that life and its science are built upon the functional integration of parts (e.g., proteins) as part of a broader "Kantian whole upon which selection acts" or better say, "Living things are Kantian wholes where the parts exist for and by means of the whole. Humans are Kantian wholes" [19] (p. 2). In other words, as Kauffman and Roli [19] (pp. 1–2) explain, the Pythagorean dream that "all is a number", taken up by Newtonian physics, suggests that evolving biospheres and ecology lie outside the Newtonian paradigm, thus ending the search for a "reductionist theory of everything" as part of what these authors call the "third major transition in science" that follows the first transition inspired by Newton and the second led by quantum physics.

Nevertheless, Kauffman and Roli's skepticism poses a significant challenge to the idea of the "theory of everything" in the realm of complexity, forcing researchers to abandon their dream of a mathematically expressed "reductionist theory of everything" [19] (p. 6):

"The diachronic evolution of our or any biosphere is beyond entailing law and beyond any mathematics based on set theory". The troubles with the mathematization of biology and biomedicine, applications of analytical and statistical mathematical methods, and atomic and energetic physical models to explain structural and functional properties across multiple levels are long-lasting, even traced back to Edmund Husserl and without to be resolved soon [136,137]

Therefore, we are left with the theory of emergence. Besides the fact that this theory is not clearly mathematically or computationally articulated, the problem is that it cannot be applied in a "top–down" direction to all levels of organization of matter. In living systems, perhaps by means of closure of production, it is possible to argue that higher levels or higher emergent phenomena affect those on lower levels.

It is hard to make such a claim in an inorganic world. In other words, if we use this theory to explain the properties of water that emerge from the fusion of hydrogen and oxygen, we can hardly explain the properties of hydrogen and oxygen with the theory of emergence. Thus, the "holistic theory of everything" would only partially explain the world; primarily, it will be suitable for life sciences, psychology, and social sciences. From this reasoning, we would need other theories to explain the physical and chemical properties of elements such as oxygen and hydrogen and their microstructural organization and interactions unless someone successfully applies the theory of emergence to the subatomic world. Whether this will happen and when I am not sure. One might object that we need a plurality of theories, at least two, to account for the vertical nomological structure of the universe, as thought experiment suggests.

Moreover, a theory of emergence that focuses on the vertical hierarchical structure of the world would not solve the problems of horizontal nomological pluralism that Nancy Cartwright [138] discusses, namely, that there are no universally valid laws of physics in the universe. The early conclusion here is that both attempts to formulate the "theory of everything" have shortcomings. However, this conclusion does not mean we cannot draw new lessons from their shortcomings, direct our intellectual efforts to reconcile them, and arrive at a new promising "theory of everything".

Perhaps the skepticism about both "theory of everything" I have expressed seems premature in light of new trends in systems thinking. Indeed, some new moments in developing the universal complexity theory challenge my skepticism. There are already some signs in this direction. In recent years, systems scientists and thinkers have developed theoretical positions based on solid empirical evidence to explain the universal denominators underlying complexity in mind, nature, and society [81,86,139–141]. In this connection, "complexity science" began to recognize that different systems have similar ways of generating complexity that concretize uniquely across space and time. This is an important step forward toward the "theory of everything" in the field of complexity. Chu et al. [81] (p. 22) mention the following contributors of complexity:

1. Internal inhomogeneity of the system (i.e., it consists of many classes of autonomous agents);
2. Adaptivity of agents in the system;
3. Nonlinear interactions between parts of the system;
4. Net-like causal structure of the system (high connectivity).

The following example demonstrates some of these generators, such as nonlinear interactions and high connectivity. In neuroscience, brain complexity is associated with dynamic instabilities as a precursor for pattern formation and self-organization. No less critical is the homostatic balancing between "the dialectic dynamics of regional functional segregation and global coherent integration" [142]. Although this example concerns the brain, I believe that homeostatic balance, dialectics, and integration can also be found in other organs, organ systems, and entire ecosystems, no more and no less. Homeostasis and integration are, thus, at least features of the biological domain and perhaps also drive other complex inorganic systems, such as the atmosphere, the hydrosphere, the lithosphere, and

socio-technical systems. So, these are some characteristics of organized systems that are more or less universally distributed on different scales.

Nonetheless, there have been significant developments in the search for structural and dynamic universals in nature and mind in the last 25 years in the form of DSRP Theory (DSRP stands for Distinctions, Systems, Relationships, Perspectives), which describes four patterns and their underlying elements [139–141]. In a series of papers, Cabrera and his collaborators hold that universality is structural and dynamic, not informational. Despite the fact that the superficial details of the two systems differ, it does not mean that their fundamental structure or dynamics differ. These empirically supported structural and dynamic universals can be predicted and modeled. DSRP Theory, which highlights how thinking and knowledge evolve, identifies four patterns and their underlying elements—identity (i) and other (o) for Distinctions (D), part (p) and whole (w) for Systems (S), action (a) and reaction (r) for Relationships (R), and point (ρ) and view (v) for Perspectives (P) [141]. These are universal existing in both cognitive complexity (mind) and material complexity (nature), making them grasp between mind and nature (systems thinking or cognitive complexity and material complexity (systems science)) [141]. At some point, if the "theory of everything" becomes a reality, scientists will better understand how these universals drive the domain-specific complexity.

6. Discussion and Conclusions

This paper concludes that reductionism and holism have their share in the search for the "theory of everything". In this context, at least two forms of theories of "everything" appear at the outskirts of systems and complexity research. One is reductionist, the other is holistic. Both ways of explaining phenomena and processes, from atoms to cells, societies, and stock markets, have shortcomings, at least if we carefully analyze mathematical, computational, and philosophical attempts to capture strong emergence and apply the theory of emergence to the subatomic world. One falls short when it comes to recognizing a "leveled ontology" based on emergence. At the same time, the other could, in principle, be successful in better understanding macroscopic physical, biological, psychological, and social phenomena. It is hard to tell whether the "holistic theory of everything" might account for physical forces operating on a subatomic level. The theory of emergence in the subatomic realm does not sound implausible because even subatomic particles have their hierarchical vertical structure, from the Higgs boson to electrons, protons, and neutrons. Particles such as bozon, meson, quarks, etc., which comprise electrons, protons, and neutrons, have different physical properties such as mass, charge, etc. However, the atomic world functions according to the laws of quantum mechanics, and the perceptibility of quantum mechanical effects decreases as the complexity of macroscopic systems increases [113]. Thus, macroscopic and emergence driving subatomic world probably could not align for this reason.

Despite this uncertainty, many other authors are becoming more optimistic that a "holistic theory of everything" is possible after all. I share their empirically grounded optimism. For example, based on everything discussed in this paper, one of the reviewers is very optimistic in this direction and states that "Such a theory, of course, would not be able to explain every single property of every single system, but it may allow for explaining even the laws governing physical particles. The last reflections of Stephen Hawking with his collaborator Thomas Hertog [143] go in this direction, proposing that the properties of the different particles and fields are the result of a historical process of cosmological evolution in which particular values for the physical constants emerged as "frozen accidents", resulting from the symmetry breaking that is characteristic of self-organization". However, we must be cautious here because, as Cabrera and Cabrera noticed [144], what physicists call "theories of everything" refer to the attempt to unify the fundamental physical forces and important theories within physics, such as String Theory or M-Theory. However, this "theory of everything" does not apply across all disciplines and cannot strive for the "unity of all knowledge" [144]. Therefore, the "theory of everything" inspired and led by

"complexity science" and "systems science" has much more credentials to call itself "theory of everything" than those conceived and nourished by physicists.

In the meantime, until a complexity-inspired "theory of everything" emerges, scientists and philosophers should instead focus on scientific pluralism, which is epistemologically and perhaps ontologically compatible with complexity, to advance research practice further [39,145,146]. "Pluralism reflects complexity", Sandra D. Mitchell famously said [146] when discussing and justifying different scientific approaches to studying the same complex phenomenon.

An adequate understanding of the complex world built on pluralistic assumptions would require complementary theories, explanations, and research programs coordinated jointly. Above all, "complexity science" should find ways to reconcile reductionism and holism. Biology can serve as an example and inspiration here. Some philosophers and scientists, such as Walker and Cloete [147], openly discuss and advocate biology as a two-faced science: reductionist and holistic. This dualism is not only some theoretical or speculative things from the pencils of armchair philosophers and scientists. The very research practice supports it. For example, a more experimental systems approach to biological complexity inspired by the post-genomic revolution in biology, the so-called "pragmatic systems biology" adopted and practiced by "molecular systems biologists", contains in a hidden way the remnants of a reductionist methodology and epistemology [18,117,125,132]. On this behalf, Morange [125] has pinpointed that biologists in the post-genomic era, unlike philosophers of science, remain committed to reductionism but with some hints of holism.

On the other hand, systems-theoretical biological thinking, with its applications to biology and medicine (systems biology and systems medicine), tends to build on variants of holism, including ontological holism, holistic modeling, and explanations [18,132,133]. However, this division is somewhat artificial, as molecular and systems biology are interdependent and complementary [148]. Perhaps Morin's Complex Thinking, Bohr's complementarity, and Cabrera's DSRP theory can help reconcile reductionist and holistic "theories of everything". Bohr's complementarity, for example, has already proved helpful in mediating between opposing views or doctrines in physics and neurobiology [149,150] and is quite promising when applied to biological complexity to link theoretical and practical problems both at the local level (organism) and at the global ecological/economic level [151]. All these enlisted conceptual tools could guide and advise the future "theory of everything" in terms of BOTH-AND and not EITHER-OR logical operators. The ideas discussed in this paper certainly need further discussion and theoretical-empirical support to confirm or, in the latter case, reject them.

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Opinion

The Systemic Unity in Mathematics and Science: Beyond Techno-Science Myths †

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† This paper is an extended and largely revised summary of the preface, in Italian, to "Il Liceo matematico: un approccio storico e interdisciplinare all'insegnamento delle scienze e della matematica" di A. Nigrelli e F. S. Tortoriello (Mimesis, to appear, 2025).

Abstract: Dualistic views in mathematics and natural sciences are severely reducing the scope of science. It began by claiming, more than one century ago, that, in mathematical theories, "a formal list of signs" (the axioms and rules of inference, independent from meaning) could allow one to consistently and completely deduce all "true" theorems. It continues today by claiming that "we can control evolution by re-writing the instructions of life written in the four signs of DNA" or mimicking completely human cognition in "sequences of 0 and 1s", independently of our biological body and brain and their historicity. The damages of and the alternatives to these views will be briefly hinted.

Keywords: mathematics; philosophy; history; techno-science; geometry

1. Introduction

The strict separation between "syntax" and "semantics", "intuition" and "logical reasoning" in mathematics and, more broadly, in science has been severely affecting their epistemology. Federigo Enriques (1871–1946), one of the most prominent representatives of the Italian school of algebraic geometry, can be considered a precursor of the conceptual framework set forth in this contribution. According to Enriques, mathematics cannot be fully understood without reference to philosophy and its history, and vice versa; philosophy always had to deal with the developments of mathematics and science in general. Enriques was publicly and violently criticized by Benedetto Croce (the most influential Italian philosopher of the first decades of the last century) for having dared to organize a philosophy conference in Bologna in 1911: he, a mathematician, therefore a "technician without knowledge", opened a lively polemic with Croce and, then, with Gentile. A key issue in Enriques' perspective is the above-mentioned inseparability of intuition and logic, sense and formal deduction,

> [...] *the usual question, whether mathematics should educate intuition or logic, is flawed by an imperfect vision of the value of teaching. In fact, the presupposition of this question is that logic and intuition can be separated as distinct faculties of the intelligence, whereas they are rather two inseparable aspects of the same active process, which refer to each other*.
>
> F. Enriques, Scienza e razionalismo, Zanichelli, Bologna 1912

Why is the role attributed by Enriques to "*intuition*" in this quotation? Because it is by means of intuition (a strict relative of Pascal's 'esprit de finesse') that it becomes possible to see the 'mathematical objects'. Intuition generates the 'insight' (Weyl) essential to invention and proof in mathematics. It is grounded in our human bodily gestures, which organize space by our actions in it.

2. Mathematical Invention

I dare to think that a very ancient gesture, of an eminently mathematical nature, was made by our ancestors many tens of thousands of years ago, when they interpolated the stars with lines that do not exist and gave contours and names to constellations, thus giving meaning, probably mythical, to those meaningless bright points in the sky. That is, they "*imagined configurations of meaning*". Then, at Lascaux and Altamira, over 15,000 years before our era, humans drew lines and edges, on the walls of caves: the edge of a horse or a bison. Objects have no edges: it starts from the primary visual cortex that the brain, in many vertebrates, builds around objects [1,2]; then, we humans, and only we, as far as I know, manage to transform this trace in neurons, this "physiological invention" of the animal brain, into a form of pictorial-mathematical communication between humans, to draw figures as pure edges on the walls of a cave, probably rich in mythical symbolism. Until we get to the splendid definition of beta in Euclid's books, the line is a length without thickness. Then, tracing is combined with language: the student will understand what a continuous line is only when he sees the gesture, the trajectory of the hand, the line traced on the blackboard by the teacher; but only in language will he be able to add, like Euclid: the line I draw is without thickness—at the same time an absurdity and the invention of the mathematical notion of edge, very profound—Euclid's geometric figures are nothing but edges [3]. And this is performing mathematics, an intertwining of geometric gesture, an invariant of action on the plane or in space, and language: paradigmatic examples of proposals for concepts and structures, not arbitrary, because rich in meaning. All mathematics is a permanent invention of new concepts and structures: there is no profound and original proof of a relevant theorem that does not require the invention of new ones. This is the primary incompleteness of every formal-deductive formalism: only in a second phase can we make explicit the notions, the principles, which are always new, and not always applicable according to formal-mechanical rules, even in proof of theorems in Formal Number Theory (Arithmetic) [4].

Mathematical idealities are deeply rooted in the world, even if we tend to place them outside the world. It is not, as Galileo says, nature that is written in the language of mathematics, but mathematics that is written in natural and historical practices and language. In this way we can build a "*dialogue between humanistic culture and scientific culture*", as the authors hope, to "*recover the inseparable link between science and philosophy through a method capable of bringing out the meaning of science for the life of man*" [5,6] and from human life.

3. All Is Code and Computation

Let us now move from a philosophical/scientific debate to techno-science, where the absence of philosophical vision (or its poverty) causes very serious distortions. The Theory of Computability, to which I have long contributed as a mathematician, born in mathematical logic in the 30s (Gödel, Church, Turing, etc.), is a beautiful theory of the discrete: it is given on integer numbers. Then, a lot of work was performed for computability in the "continuum" (or quasi-continuum) and to interpret it in continuous geometric structures (part of the work of the author). But the machine that implements it, the contemporary computer, is a "discrete state machine", as its founder, Alan Turing, defines it. Even the recent Deep Learning concept at the forefront of the new Artificial Intelligence (AI), which uses and develops very powerful mathematical methods in *continua* [7], often coming from mathematical physics (e.g., wavelets, re-normalization), must necessarily be implemented in the discrete state machine in sequences of 0 and 1. Even if some "shapes" that emerge in the mathematical dynamics described with Deep Learning resemble brain dynamics (in language recognition, it is possible to reproduce dynamics that can be glimpsed in the

cerebral cortex—or the same mathematics can be used to describe them), the animal brain does not have "behind" or "under" a discrete state machine that does the calculations, like in the case of Deep Learning. That is, the image of the "thought" that AI sends back to us is always that of a computation on integers. Thus, as some philosophers say, "what cannot be calculated, cannot be thought" [8]. Sequences of 0/1 and calculations in the discrete, algorithms, this is their world. And Pearl and Valiant, both Turing Award winners (the Nobel Prize of Computer Science), explain to us that the laws of physics and biology are algorithms (enriched by statistical correlations between numerical data, for Pearl; "echo-rhythms", says Valiant to highlight the interaction between programs) [9,10]. Excellent technicians in their discipline, they project onto the world what they know how to do, without any critical reflection.

Therefore, in an algorithmic world, a stone falls because it is "programmed to fall" (see also Stephen Wolfram's "A New Kind of Science", Wolfram Media, Champaign, Ill., 2002), just as it happens on a computer screen. Fortunately, Einstein explained to us that a stone falls "for reasons of symmetry" [11], and physics goes on ignoring such nonsense. This is not the case for biology, where in the absence of a "Theory of the Organism" (ontogenesis), despite the rich theoretical debate in the Theory of Evolution (phylogenesis), from Darwin onwards, vague computer metaphors continue to be evoked to talk about the living. So it is said that "we can control evolution", by reprogramming organisms [12–14]. Difficult techniques justify this arrogance (*hybris*), with very modest consequences, especially compared to the promises. After human genome sequencing, as for promise, the title of von Eschenbach suffices: "NCI [Nat. Cancer Inst.] sets goal of eliminating suffering and death due to cancer by 2015" [15], jointly with the promise that within two and three years cancer diagnosis and prognosis should have been made by analyzing DNA. Instead, DNA sequencing does not help distinguish a primary tumor from a metastatic one, benign from malignant [16]; in fact, "*63 to 69% of all somatic mutations [are] not detectable across every tumor region*. . . *Gene-expression signatures of good and poor prognosis were detected in different regions of the same tumor*" [17], and tumors without mutations are observed [18]. And even today, only the histologist, looking at the tissue and the shape of the cells under the light microscope, can tell whether the tumor is malignant, benign, primary, or metastatic. Then, consider the GWA (Genome-Wide Association), a project funded for 10 years with USD 8 billion (!) for the purpose of associating diseases of all sorts with "genes": a mountain (of money) that has produced a few mice [19,20]. In biology, there is no privileged causal level, and even gene expression, which is very important, is a network of genes activated in interaction [21], whose network dynamics are channeled by epigenetic constraints, ranging from the proteome to the structure/position of the cell in the tissue, to the organism, to the ecosystem [22,23].

It is then fair to say that we are dealing with two technosciences united by a new *Imperative Pythagoreanism.* Let me explain. Not only would the essence of the world be in the integer numbers, as the Pythagoreans said (or in sequences of letters, DNA, which is the same thing) or in any case codified in them, but, excluding physical causality, as Einstein and Bohr had understood, the world is made to function like a digital computer: by giving orders. In fact, even functional or "object-oriented" programming languages, widely used in AI, must still be reduced to sequences of orders ("formal reductions", Church-Rosser theorems [24], and normalization theorems [25]); furthermore, their management in the computer with compilers and operating systems are based on orders; it is *imperative* (it is implemented in languages called imperative). And a black stone falls on the screen because the pixels implement orders that make them become black and white in succession. The world and cognition would also be the same: they follow orders—the causal world of

physics, framed by symmetries (conservation properties), is replaced by sets of instructions to be obeyed.

4. Geometry's Sensitivity to Coding

Furthermore, in addition to causality, the geometric notion of dimension is also lost. In fact, what is geometric is "*sensitive* to coding". Continuous spaces, from Descartes to Riemann, of multiple dimensions and with "natural" topologies, cannot be coded in a single dimension: what counts is lost, continuity, and with it, as we said, classical and relativistic causality. Consider that to represent three dimensions in two, with the Italian perspective in Renaissance painting, the first symbolic representation of the "actual" infinity had to be invented: the point of convergence of parallel lines, the projective point, the result of over 1000 years of debate on the infinity of God (in potential, in act?) [26,27]. In the discrete, instead, any number of spatial dimensions can be encoded in a computer's one-dimensional sequence of 0s and 1s: the discrete is *insensitive* to encoding. And this is the common watchword of AI and dominant molecular biology: encoding, encoding... "all is code", everything is (reducible to) linear, alphanumeric code. A conceptual catastrophe, if extended to the world: 2500 years of its mathematical and physical intelligibility, of its causal and spatial structuring, are erased, replacing it with orders coded with four letters in the DNA, or 0 and 1 aligned in a computer. This last one is an excellent technology, based moreover on a radical dualism, the distinction between hardware and software: a splendid idea of Turing for constructing machines (1936), a cognitive and knowledge disaster if projected onto inert and living matter.

My long and repeated American experience suggests to me a reason for the success of such visions in Silicon Valley and elsewhere. For many years, American high schools have taught only computational mathematics, directly programmable in the discrete state machine. If the brilliant student then continues his studies in computer science or engineering, he will never see the continuum of Euclid's gestures, who writes: draw a line from one point to another (axiom 1), extend a segment continuously in a line (axiom 2), draw a circle around a point (axiom 3), etc., continuous trajectories, edges, it was said. She will never truly grasp the importance of the continuous deformations of Riemann spaces to understand Einstein's relativity, which is the dynamics of metric spaces. Nor the fluctuations in the continuum, below the physical measure, therefore non-measurable causes of the unpredictability of deterministic systems. Thus, the world, as Pearl says, is "laplacian", i.e., it is deterministic and predictable, like computational dynamics (except for quantum phenomena in the discrete, says he).

As a consequence, in the dominant molecular biology (fortunately, there are some heroic dissidents), data are collected, and all the possible "-omics" (genomics, proteomics, transcriptomics, glycomics, lipidomics, etc.) hoping to receive answers from the observation of regularities in the data, without a theory of the organism, replaced by vague imperative numerical metaphors: "*we have decoded the instructions written by God in the DNA of every organism*", as Collins declared in 2001, in the presence of Clinton and Blair [28]. Among the dissidents, Sydney Brenner (molecular biologist, Nobel Prize, 2002) observes, "*This science of '-omics' has corrupted us. It has created the idea that if you collect a lot of data, everything is solved*" [29]. And so powerful data extraction and processing technologies are developed in AI and molecular biology, of great engineering intelligence, without theoretical, critical thinking, to be applied without asking questions: a "proletarization" of scientific work [30].

5. Reversing Prometheus' Nightmare

In order to struggle against the cultural degradation of scientific work, we need a "*reversal of the myth of Prometheus*"; that myth which has become a "nightmare" for which

"*we self-transform for the love of our machines, because we take our machines as a model for our alterations*: *we therefore renounce assuming ourselves as units of measurement and with this we limit our freedom or we renounce it*". To get out of what "*Anders defines as Promethean shame*" [5,31], philosophy and science must dialog intensely. It is good that those who do science or teach it, on the one hand, grasp the meaning of their work also thanks to philosophical criticism. On the other hand, philosophy must also subsume in its critical framework the characteristics of science as "substained, collective, critical enquire" [32], with its techniques, of course, but always to be distinguished from technoscience. The scientistic vision of knowledge, based only on the accumulation of techniques, from "problem solving" to "techno-fix", is incompatible with the negative, limiting results that science can also propose; moreover, it was said, that these have always opened up new points of view. Even in AI, thanks to the relative solidity and rigor of some mathematical methods in the continuum, the search for "optimal" paths or values of geodesics in immense phase spaces, we are starting to see some limited results. Recently, it has been demonstrated that the existence of such optima, necessary to find solutions to the problem in question, is equivalent to the Continuum Hypothesis in Set Theory [33]. This hypothesis is undecidable; consequently, there cannot be a "uniform and effective" method to find said optima. That is, and this is also the reality of the facts, in the face of every problem, it will take human work to build mathematics and programming environments and techniques that can deal with it. A minimal change (the passage from 19 squares to 17 in the game of Go) and... the machine stops. Each time, talented technicians must build an ad hoc software, which can also do very well and be very useful.

AI is anything but "plastic", the great property of the animal brain, which makes it "generalist". The latter not only learns to hunt, to look for mushrooms, to play with the owner's son... but above all, it modifies its internal structures. The layered mathematical structure of Deep Learning vaguely resembles the stratification of the visual cortex. But hearing, smell, touch, etc., from what little we know, work thanks to profoundly different brain connectivity structures. However, in the case of cognitive deficit, one can replace the other, modifying itself structurally to perform the new function [34].

These observations, outside of myths, can also help to construct better machines, which, as humans, we certainly need, "*for Heidegger technology is co-determining of knowing*" [5]. And of being in the world: our humanity is also "technological", since the time of the invention of stone worked for a purpose. But as soon as we get to propose even a partial theoretical framework, science knows how to understand its limits and, if possible, identify other ways. Some recent theoretical AIs allow, in addition to remarkable techniques, also some limiting results, as we said. While, in the absence of a rigorous theoretical frame, it is not possible to prove a vague theory false, as Feynman claims, nor provide negative/limitation results, a good way to propose new ideas. This is the case for the "genetic program theory", from Monod to Doudna (mentioned), with his phantom "exact editing" of DNA, thanks to the CRISPR-cas9 technique [12,13]. However, between the most important books of the two authors, a difference must be underlined. Monod's book from 1970 is certainly scientistic, but it tells of great observations and extraordinary laboratory work—in an erroneous theoretical framework. It can happen; it also happened to Ibn Yunus (Egypt, 10th century), a great astronomer and mathematician, co-inventor of spherical trigonometry and a very fine observer of the sky, in the frame of the Ptolemaic, geo-centric theoretical framework [35,36]. But is theoretical and critical thinking so important? As Boltzmann says, "*there is nothing more practical, in science, than a good theory*". With the principle of inertia, Galileo definitively demolishes the Ptolemaic framework (the "retrograde movements" of the planetary epicycles become impossible) and opens the way to Newton. The Theory of Evolution allowed us to make good use of DNA sequencing,

which has contributed to identifying evolutionary correlations of great interest—DNA, for us, is a chemical-physical trace of all evolution, of extraordinary importance, a "constraint" to the molecular dynamics, largely stochastic, channeled by the cell, in interaction with the organism, in its evolutionary history, in an ecosystem [37,38]. The principles, explicit and rigorous, from Galileo (inertia) to Heisenberg (indeterminacy) or to Darwin, whose first principle, "reproduction with variation" (and motility), is at the heart of the production of biological diversity, allow the theoretical construction and that critical step aside. This critical attitude is a fundamental bridge with philosophy and eventually helps to change direction, to invent something new, as happened after the negative results of the Pythagoreans, Poincaré, and Gödel. Major examples in this direction are given by the result of the 1930s on "undecidability" and "incomputability": in order to prove the existence of unprovable assertions, of functions that cannot be computed, Gödel, Church, and Turing, between 1931 and 1936, gave different notions of algorithm, later proved equivalent, and, therefore, of computable function, which will be at the heart of the numerical-algorithmic machine that is changing the world. And changing it for the better, if one develops more critical thinking and less hybris, if one does not project it onto the world, saying that brain and cell, the world, are instances of that alphanumeric machine [31,39]. This is impossible in biology, as long as its "theoretical" framework is dominated by vague digital and alphabetic metaphors (such as the "exact editing" of DNA, as if it were a written text—against the same practice in the laboratory, which is stochastic) and in which the relationship between results and investments (and promises), from human health to GMOs, is very low (see notes and references on the GWA and new GMOs). But the cascade of failures, after the promises to eliminate world hunger with GMOs (2000) [40,41] and cancer (von Eschenbach, 2003, cited), and empirical evidence are not enough. As noted in the book, in reference to Lakatos: "*falsification cannot be the immediate result of an experimental procedure. In his view, no basic assertion can by itself induce a scientist to reject a theory*: "*nature can shout its NO, but human ingenuity can always shout louder; with enough ingenuity and a bit of luck any theory can be defended 'progressively' for a long time even if it is false*"". This is especially true when financial interests clearly outweigh theoretical content; as a courageous biologist colleague says, "the geno-centric enterprise is "too big to fail"" [42–44].

6. Theory Building

Let it be clear that the critical look that we have briefly developed on two very powerful and dominant techno-sciences today is intended to contribute to their better development: the digital computer and its networks, such as molecular analyses of DNA in particular, and their role in the dynamics of the organism are of great importance. But they must be immersed in a critical reflection, both scientific and philosophical. Mathematics plays a crucial role, given it is continuously used and invoked in current technologies, both in a specific and metaphorical way. Furthermore, together with physics, it has been able to propose limits and, therefore, new theoretical inventions. As for its teaching, it must be stressed that an important part of the work of those who do research consists of tackling problems by changing the point of view, trying to formulate them differently, and transporting them from one context to another. Science is not so much "problem solving", as techno-science claims, but rather "theory building": changing the point of view requires criticism and theoretical construction and is also a way to solve problems, "*immersing them in a sea of new concepts and structures*", as Grothendieck, an immense mathematician, used to say.

7. Conclusions: Back to Intuition

We started with a reference to Enriques and the interplay he stressed between logic and intuition in mathematics. Then, we mentioned the understanding of continua "by

intuition" of the "gesture", by our "mathematical seeing" of a trajectory. Brouwer, the founder of the "intuitionist school" in logic, refers to the intuition of the discrete flow of time. The insight by "subitizing" (immediate counting of a small number of objects), which we share with some animals, constitutes another "intuitive practice" of the discrete. The junction of the two experiences of discreteness sets the condition of possibility for the mathematical invariant that we propose as the infinite discrete sequence of integer numbers, the paradigm of a discrete structure (for work and references to "continuous gestures", "subitizing" and Brouwer on discrete counting, see [45]). Then, along history, by discrete vs. continuous mathematics, we provided two different organizations of "reality", which yield a different understanding of causality, as we stressed. Discrete State Machines (DSM), as Turing soundly called it in the 1950s his 1936 invention of the "Logic Computing Machine", opened the way to our fantastic achievements in computing. Turing understood the role of the interplay between continua and discrete by the difference he makes between *imitation* and *modeling* (see [46]): his DSM may imitate a process (human thinking in the 1950 paper, see [46]), with no causal commitment to its "causal structure"; while his model of morphogenesis (the 1952 paper, see [46]) proposes the mathematical description of an action that causes a reaction that causes a diffusion in continua. As a matter of fact, causes are framed by conservation properties in physics that correspond to "*continuous* symmetries" in equations [11,47]. In summary, by the use of continuous vs. discrete mathematics, we provide different understandings of "reality". Intuition and logic may underlie both, but they radically differ in the way we "look" at the world. In particular, because of the lack of an analysis of causality, the description and understanding of phenomena by discrete tools suggest either the intrinsic randomness proper to quantum measurement (assumed by Bohr in the Bohr-Einstein debate, see [5]) or the *Imperative Pythagorism*, mentioned above: mind, biological organisms, inert matter, etc., function by "following the orders". Thus, we can control and reprogram them at will, like on the screen of our digital machines. Our analysis aims at the proposal of alternatives, from biology [22] to cognition [45].

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systems

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Opinion

System Science Can Relax the Tension Between Data and Theory

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Abstract: The actual hype around machine learning (ML) methods has pushed the old epistemic struggle between data-driven and theory-driven scientific styles well beyond the academic realm. The potential consequences of the widespread adoption of ML in scientific work have fueled a harsh debate between opponents predicting the decay of basic curiosity-driven science and enthusiasts hoping for the advent of a 'theory-free' objective science. In this work, I suggest how the system science style of reasoning could drastically de-potentiate this (sometimes deceptive) opposition through the generation of multi-purpose relational theoretical frames stemming from the network paradigm. The recognition of the virtual non-existence of purely 'theoryfree' approaches and the need for a careful balancing of theoretical and empirical contributions is the main claim of the present work.

Keywords: machine learning; data science; complexity; relational systems theory; Hopfield networks; deep learning

1. Introduction

As aptly stressed by Sui Huang in [1], the last decade witnessed a deep epistemic shift from 'theory-driven' to 'data-driven' science. This shift began in the field of biomedical sciences with the rapid onset of 'omics' sciences. The term 'omics' designates different high-throughput techniques allowing the measurement of thousands of different variables in a single sample (e.g., different gene expression levels and metabolite or protein concentrations) [2]. This fact, together with unprecedented and cheap computational power, turned upside down the time-honored basis of the classical statistical approach, in which statistical units (samples) are supposed to outnumber their descriptors (variables).

In the classical case, the choice of variables to analyze is strictly hypothesis-driven: the information content of an experiment stems from a scientific question stated in terms of the relations between a few empirical observables.

Until some years ago, students were discouraged from pursuing projects seeking broad data analyses without the support of a strong hypothesis or question. The 'broad approaches' were considered 'fishing expeditions', producing a plethora of chance correlations [1]. This caveat stems from the mathematical definition of statistical significance. Actually, obtaining a p-value of < 0.05 as a result of an empirical study corresponds to an estimated 5% probability (under certain distributional assumptions) that the results are due to pure chance. If we take into account a dozen variables and we can build a credible narrative, even by a single significant result, the probability of chance correlation is unbearably high. This problem is common in any mathematical modeling of experimental data [3] and pushes scientists to focus on the (few) descriptors predicted to have the maximal information content for the problem at hand.

The overlooking of this caveat provoked a recognized knowledge crisis in biomedical sciences [4,5]. It is totally out of scope to apply a classical inferential approach (despite any smart statistical correction procedure) to face a data set made up of fifty thousand variables attached to ten to thirty samples, as occurs in high-throughput gene expression (transcriptomic) experiments. Notwithstanding this, students are no longer discouraged

but encouraged to undertake largely hypothesis-free CConfirmmics projects that are by far the most popular (and fund-attracting) types of research in biomedicine [1] that now (thanks to a different statistical approach with respect to the classical inferential paradigm) no longer have the stigma of 'fishing expeditions'.

There are two main possible ways to get rid of the curse of high dimensionality. The first one originates from machine learning (ML) and implies a drastic change in the kind of 'scientific question': delving deeper into causative mechanisms and/or testing a general theory, with the focus shifting toward 'directly applicable' goals like clinical diagnosis [6] or the elucidation of the structures of biopolymers [7]. In these cases, high dimensionality is no longer a source of chance correlations, provided a scientist can rely upon both a training set from which to generate a prediction model and one (or more) independent test set to check its accuracy.

The other approach to very-high-dimensional data is related to statistical physics and can turn the curse of dimensionality into a blessing [8] for basic research. This approach implements a change in the scale of the scientific questions. Instead of pursuing the impossible dream of a deterministic model allowing one to climb up the different layers of an organization from the bottom (e.g., molecules) to the top (e.g., an entire organism), the focus shifts toward the mesoscopic scale, maximizing the correlations linking different organizational levels [9]. In the example of transcriptomes mentioned above, this corresponds to forgetting the identity and idiosyncratic roles of single genes and focusing on the trajectories of the entire genome, considering it as an integrated dynamical system [10]. Along this pathway, many different data analysis techniques come into play, ranging from time-honored multidimensional statistical techniques, like principal component analysis, to complex network and non-linear dynamics-inspired approaches [11,12], with all these methodologies redounding around the same concept of correlation.

In the following, I will describe the main philosophical–methodological premises of ML and statistical physics-inspired approaches and how the system science style can help reconstruct the useful synthesis between data and theory that has inspired centuries of modern science and is now showing some signs of increasing tension.

The main goal of this work is to describe the nature of this (apparently inescapable) polarization and how a systemic style of conducting science can reconcile data-driven and theory-driven attitudes. This reconciliation can take place by the recognition of the coding/decoding dynamics by which the correlation structure between variables, naturally emerging from data (the formal system) with no need for strong a priori hypotheses, can be 'decoded' in terms of the actual interactions structuring the investigated phenomenon (the real system).

Section 2 gives a proof-of-concept of the epistemological impossibility of a 'theory-free' scientific investigation by means of a coarse-grain description of computational approaches endowed with different levels of transparency (explainability). Some basic tenets of the scientific method are briefly described to demonstrate how any data structure encompasses more or less explicit theoretical choices.

Section 3 deals with the coding/decoding process inspired by relational systems theory and the link between this theory and network thermodynamics. The clarification of this link passes through a brief description of Hopfield networks, physics-inspired computational tools in which the stored memories (the formal system) correspond to dynamical attractors (the real system).

Section 4 describes a case study in which the network paradigm (the main ingredient of relational systems theory), in the form of the configuration of pairwise contacts between amino acid residues of a protein molecule, allows us to explain, in the language of biochemistry, the recognition of amino acid residues responsible for allosteric effects. This chapter is, thus, a practical example of the coding/decoding process.

Section 5 (the conclusion) summarizes the motivations of the 'data' and 'theory' reconciliation proposal set forth by this opinion paper. The need to re-state the time-

honored principle of the complementary roles played by data and theory originates from the somewhat exaggerated hype surrounding so-called 'artificial intelligence'.

2. Machine Learning and the Dream of a 'Theory-Free' Science

A recent monograph by the UK Royal Society [13] details the avenues of the impact of ML on all fronts of scientific research, from epidemiology to materials science. The basic claim of the 108-page monograph is that the adoption of ML in the scientific workflow will deeply transform knowledge generation in the way it automatically extracts and learns features from raw data [14].

Before critically analyzing the hype around 'ML disruptiveness' in science, it is worth going in-depth into the nature of ML, taking as a paradigm the 'deep learning' algorithms that are at the forefront of machine learning research.

In a broad sense, any fitting procedure that is able to reproduce, with sufficient accuracy, a given property of interest (a dependent variable in statistical jargon, usually denoted by the letter Y) by means of the knowledge of a set of descriptors (independent variables, usually denoted by the letter X) can be considered an ML approach.

ML methods can be ordered based on their degree of 'explainability' [15] from 'black-box' (e.g., multi-layer neural networks) to transparent (e.g., linear discriminant analysis) approaches. The concept of 'explainability' is crucial to understanding the nature of the tension between data and theory; thus, in order to correctly set the problem, let us restrict Y to the case of class prediction, with Y being a binary variable (with only two possible outcomes). As the first step, the machine learner must be trained with a data set (the training set) in which the class labels of the samples are known (the golden standard). The goal is to identify (by suitable metrics of error minimization) rules and feature sets that allow the differentiation of the class labels. For example, if the goal is to predict biological gender, then the class labels (Y variable) could be 'Male' and 'Female', and the feature set (X variables) may comprise both quantitative (e.g., height) and qualitative variables (e.g., 'presence of beard'). If the samples and variables of the training set are both sufficiently representative and informative, then the classifier's predictions in new samples not present in the original training set (test set) will be (almost always) correct [15]. In a 'content-agnostic' situation in which it is out of scope to go in-depth into the nature of between-class differences, prediction accuracy is the only relevant metric for judging an ML tool. While limiting prediction accuracy is perfectly legitimate in many practical situations, e.g., think of the detection of a weapon in the baggage of a traveler, it is a largely defective strategy in scientific work.

In the case of science, limiting the focus to prediction accuracy, with no possibility of going in-depth into the constellation of mutual relations between X variables allowing for such accuracy, is only a very preliminary step in the 'solution'. In order to obtain a real 'piece of novel knowledge', we must go beyond accuracy metrics [15]. We need to not only predict but also explain a given phenomenon: we need a theory. 'Theory' is, here, intended in a soft and broad sense as a representation of the studied problem incorporating domain knowledge, even at a largely metaphorical level [14]. I will go more in-depth into this definition of 'theory' in the following chapters.

Theoretical hints are of no use for further explaining the results originating from black-box deep learning ML methods based on multi-layer neural networks [16].

'Deep learning' usually indicates network models composed of different processing layers able to solve recognition tasks with multiple levels of abstraction. These methods discover intricate structures by navigating very large data sets by the backpropagation algorithm, indicating how the system should change its internal parameters (the 'synaptic weights' across the neurons of the network located in different layers) to optimize the recognition task [16]. In mathematical terms, these systems correspond to 'universal approximators' [17] that, in any case, are able to achieve perfect accuracy in their training set. On the contrary, test set prediction is not for granted and stems from factors that are independent of computational power and deeply 'theory-laden' [14]. These (often-overlooked)

factors falsify the 'disruptive' claim of the possibility of a 'perfectly objective' theory-free science fostered by the widespread application of the ML approach and damning the hypothesis-driven scientific method to obsolescence [18].

The basic point is that 'theory-free' perfectly objective data do not exist; every step of the process to generate any data set involves theory-informed choices, the most obvious being the following:

1. The choice of the descriptors (variables) of the statistical units composing the data set.
2. The choice of the inclusion criteria for a given statistical unit to make part of the training set.
3. The choice of an operative rule to define a test set as sufficiently homogeneous with the training set and the consequent definition of the boundary conditions of ML predictions.
4. The choice of the best 'structure-preserving' dimension-reducing approach for eliminating redundancies possibly biasing the ML procedure.
5. The choice of an error-free gold standard (Y variable) that remains stable across different data sets, acting as a 'class label' that univocally defines the statistical units.

The above-mentioned issues (and other more subtle but equally important ones) derive from the very basic notions of the scientific method, forming part of ordinary statistics and scientific methodology academic courses; thus, it seems unreasonable that many philosophers and scientists are unaware of them. My personal opinion is that the increasing fragmentation of scientific culture, together with the impressive progress of computational power, has provoked the emergence of 'data scientists' with a prevailing informatics background and only a surface knowledge of both statistics and experimental sciences. Data scientists tend to focus their interest on procedural issues (e.g., the efficiency and correctness of algorithms) while not paying much attention to the use of the algorithms to solve actual problems that are left to the so-called 'experts in the field'. This is a completely natural way of operating. The problem is that the evident success of technology has generated the pernicious idea that there is no difference between data and reality.

It is worth remarking that the use of low-transparency ML methods does not imply any 'theory-free' epistemology that only pertains to specific scholars (that do not, by chance, in the majority of cases, have a philosophical, more than scientific, background). The emphasis on this point comes from the errors arising from skipping some methodological points due to a too-simplistic focus on computational power and the almost perfect accuracy of the obtained results.

3. The Statistical Physics of Data from a System Science Perspective

In his visionary paper [19], Donald Mikulecky introduces a neat discrimination between 'constitutive' and 'network' principles, stating the following (emphasis added):

The network thermodynamic model of a system has two complementary, but distinct, contributions. Their explicit formal independence and strict complementarity are one of the most striking aspects of the formalism. These two intertwined facets are the constitutive laws for the network elements and the network topology. The use of constitutive laws for the network elements is the way the physical character of each network element is represented abstractly. It is a common feature of the material world. The topology or connected pattern of these elements in a network is an independent reality about the system.

The formalism of network thermodynamics stems from non-equilibrium thermodynamics and goes hand in hand with applications in chemistry and biology [19]. The adoption of this approach implies a shift in the basis of the unity of nature from the statement 'any entity is made of the same basic bricks' to the statement 'any entity can be thought as a set of interacting parts' [20]. This shift allows setting, in a correct way, the interaction between formal and natural systems [19].

A natural system (NS) is encoded into a formal system (FS) for the purpose of mimicking a causal event in the natural world by an implication in the formal system. Then,

decoding is performed to see if the system commutes. A commuting modeling relation is a model of the real world.

In other words, a formal model generates proper scientific knowledge if it is able to give accurate predictions of the modeled system behavior while, at the same time, allowing one to translate (decode) the wiring of the correlation network of the formal representation into actual (real world) interactions within the system at hand. This 'encoding'/'decoding' commutation process is the goal of system science [21], which traditionally privileges the 'network' over constitutive laws. Figure 1 (modified by [19]) gives a pictorial example of this style of reasoning.

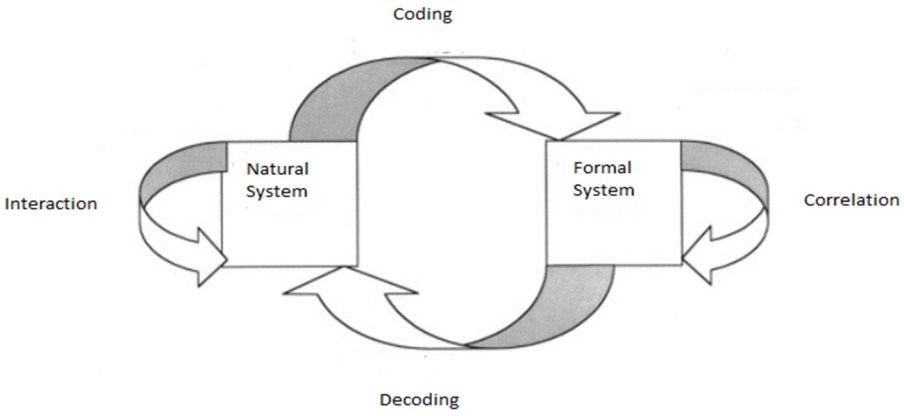


Figure 1. The analysis of the formal system (i.e., the data set with the different statistical units described as many component feature vectors) generates a set of empirical correlations between features. If the 'coding phase' is realistic (i.e., the adopted features catch the relevant properties of the natural system), then the correlation structure emerging from the formal system can be 'decoded' in terms consistent with the natural systems whose interactions between parts can be traced back to the correlations observed in the formal system.

The above strategy stems from Robert Rosen's concept of 'relational biology', which constitutes the theoretical background linking ML and modeling strategies [22] mediated by systems science. Rosen's basic claim can be summarized as 'when studying a complex system, one can forget the matter (constitutive laws of network elements) and focus on the organization (topological) laws'. In the case of biology, Rosen derived this claim by the consideration of organisms as metabolism–repair (M,R) systems. The material counterparts of metabolism and repair are catalysts (enzymes) and RNA molecules, respectively. Such MR systems generate closed causative loops: RNA molecules code for enzymes while, at the same time, needing enzymes to exert their actions. This circular causality rules out any strict mechanistic process in the form of quasi-deterministic pathways. Pathways (when considered in isolation and not embedded into closed networks) derive from Newtonian dynamics, in which there is a hierarchy of cause–effect relations that implies a sort of 'regressio ad infinitum' toward an initial cause placed in the most basic organization layer. On the contrary, pathways are only partial views of a network system that, in turn, at odds with Newtonian dynamics, implies a circular causality and asks for a different epistemology [19,22].

Besides biological considerations, what is important for the generation of suitable models of real systems from a mainly data-driven hypothesis-generating perspective is the possibility of decoding a formal correlation structure in terms of actual interactions between system elements. In the case of complex systems in which (like in thermodynamics) complete knowledge of the whole set of microscopic agents is impossible, we must abandon the differential equations style [23]. In a proper relational approach, the interaction network emerges from the empirical correlations present in the data set [24]. The separation between constitutive and relational laws makes the same relational principles able to explain the behavior of widely different systems, like a protein and a social organization. The

cross-disciplinary portability of such relational models defines the relational approach as 'theory-free', but this freedom from theory must be intended only in the very limited sense of independence from constitutive, field-specific, microscopic-level theories, as actually happens in thermodynamics.

Thermodynamics is usually a significant part of every physics textbook, but at odds with other physical theories, thermodynamics focuses on system properties that are independent of mechanisms [19,22]. It focuses on the actual state of a system and the state changes attained by different (largely unknown) mechanisms. Rather than focusing on the details of the dynamics of the system's parts, the relations between the parts are the center of attention. Relational thinking is an extension of thermodynamic reasoning; it says very little about mechanisms, and the emphasis is on a system's function. This implies a given system is described in terms of its functional components independently from its material parts.

This attitude allows discovering the same organizational principles in systems as different as a social network and a protein molecule.

The relational style of reasoning imposes a careful choice of ML approaches privileging so-called PINNs (physics-informed neural networks) [25] that incorporate explicit physical principles in both their structure and behavior. Hopfield networks are the most classic example of PINNs, allowing for a straightforward commutation between emerging correlations between network elements and the real world [26].

A Hopfield network is made up of a set of elements (neurons) whose mutual interaction is modulated by synaptic weights, mathematically equivalent to (not necessarily linear) correlation coefficients. The actual state of the network consists of the values of the components of an N-dimensional vector of features. The evolution in time of a state vector follows an energy function whose local minima are K 'memory' vectors, acting as attractors of the dynamics and corresponding to the patterns that the network stores in its weights. A Hopfield network is, thus, associative memory that can act as ML when presented with an initial prompt that resembles one of the memory vectors. The energy descent gradient finds the most similar pattern among the set of stored patterns, thus performing a recognition task [27] corresponding to the reaching of an equilibrium state in the network.

This strategy allows the generation of a physically motivated explanation of very complex phenomena, like the multiscale organization of biological tissues [27,28].

It is worth noting how, in this case, we enter into the realm of the 'simulation' approach, in which the systems science approach is able to generate theories focused on the network topology principles independent from the (often unknown) constitutive laws of the single elementary players.

4. The Coding/Decoding Circle: A Case Study

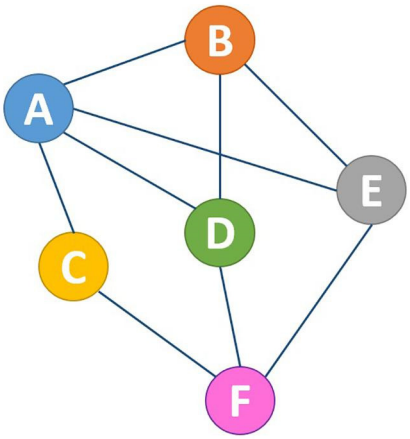
Relational thinking has its most fundamental mathematical counterpart in the concept of a network. A ´network´ is not necessarily a ´real´ thing; rather, it must be considered a ´cognitive schema´ [29], which is an abstract collection of concepts used to make sense of the unknown world of life. In other words, a network is a formal system arising from the correlation structure of the studied system that can eventually be decoded in terms of the original natural system interaction pattern. A network (graph) structure is fully described by its adjacency matrix, isomorphic to the usual node-and-edge representation (Figure 2).

Biological systems are complex entities that both adapt to their environment and interact with other systems while, at the same time, being naturally amenable to network formalization. Therefore, the peculiarities of information transfer across networks are crucial to understanding the basic principles of biological organization.

Protein molecules are the most microscopic objects displaying adaptation and interaction properties, being a perfect playground for the study of complex systems [31].

Proteins are biopolymers made of linear series of N (with N ranging from 30 to more than 5000) monomers (amino acid residues) held together by covalent chemical bonds between subsequent monomers. Proteins are composed of 20 different amino acid

species, and their linear ordering (primary structure) corresponds to a string in which the 20 different elements juxtapose with no evident periodicity. Protein molecules are the molecular agents responsible for the unique properties of life, such as metabolism, signaling, and the immune response, thanks to their ability to adapt their three-dimensional structures to carry out specific biologically relevant functions in which information transfer is of the utmost importance.



	A	B	C	D	E	F
A	-	1	1	1	1	0
B	1	-	0	1	1	0
C	1	0	-	0	0	1
D	1	1	0	-	0	1
E	1	1	0	0	-	1
F	0	0	1	1	1	-

Figure 2. Mathematically, every network (**left**) can take the form of an adjacency matrix (**right**). In this case, a network with undirected, unweighted edges corresponds to a symmetric adjacency matrix with 0/1 values for the absence/presence of connections. These binary values can be derived by any pairwise correlation index between system features (nodes) by the agency of a threshold on the actual correlation values (e.g., ($r > |0.7|$ with r = Pearson's correlation coefficient between two i,j variables) [30].

The most straightforward paradigm of information transfer through a network in proteins is the allosteric effect. Allostery is a neologism coming from the Greek language, which is related to the ability of proteins to transmit a signal from one site on a molecule to another in response to environmental stimuli. This ability stems from the transmission of information across the protein molecule from a sensor (allosteric) site to the effector (binding or active) site [32].

When in solution, proteins fold, acquiring a three-dimensional (native) structure corresponding to an energy minimum. Figure 3 reports a sketchy example of a protein molecule in solution.

Weak noncovalent forces between amino acid residues are responsible for information transduction across the network, with the consequent re-arrangement of the protein structure in response to external signals driving the allosteric process. It is worth noting the order of magnitude of these intermolecular forces approximately corresponds to the thermal noise the molecules experience in physiological conditions.

The molecule perceives ligand binding (or any other micro-environmental perturbation) happening at a distance from the active site (where the specific reaction catalyzed by protein takes place) and adapts its configuration accordingly. For example, a hemoglobin molecule senses the partial pressure of oxygen ($p[O_2]$) at the allosteric site, whereby when the $p[O_2]$ is high, the affinity of hemoglobin for oxygen increases, and the protein binds to oxygen molecules at the active site. On the contrary, when the $p[O_2]$ is low, the affinity decreases, and the bound oxygen is released into the cells. This process is crucial for life. In the lungs, there is a very high oxygen pressure, and the red blood cells containing hemoglobin must catch the oxygen molecules, which, in turn, must be released into peripheral tissues (with a low $p[O_2]$) to make oxidative metabolism possible. How can the protein molecule discriminate such a semantically (but not energetically) relevant signal from the continuous motions coming from thermal noise and transmit the information at a distance to reach the active site?

To answer this question, it is useful to consider a protein molecule as a network, with the amino acid residues as nodes and the noncovalent interactions between them as edges. The adjacency matrix of a protein contact network (PCN) has amino acid residues as nodes and the scoring of efficient non-trivial (where neighboring amino acid residues along the sequence have obliged and, thus, trivial contacts) contacts between residues as edges. When applied to hemoglobin, the network formalism gives rise to the pattern reported in Figure 4.

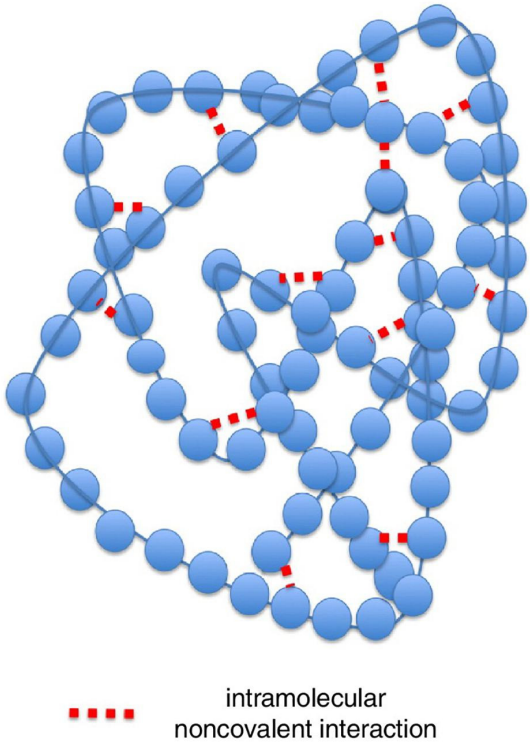


Figure 3. Spheres = amino acid residues; continuous blue line = covalent bond series responsible for the primary structure; dashed lines = noncovalent (weak) interactions between residues distant in the sequence put in contact by folding process (modified from [30]).

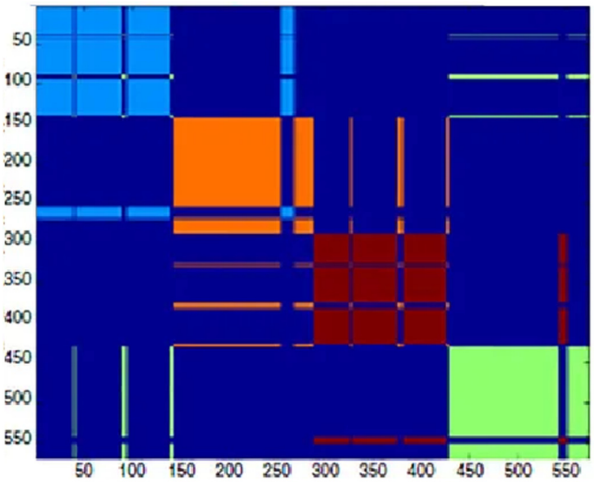


Figure 4. The numbering of the axes corresponds to the sequential order of residues along the primary structure. The adjacency matrix is shown as a clustering color map that reports the cluster partition along the sequence. The spectral-clustering technique decomposes the space through the adjacency matrix eigenvalues so that the partition relies on the topological role of the residues in the interaction network rather than on their spatial positioning (modified from [30]).

The adjacency matrix was colored by a spectral-clustering procedure [33], with specific color points corresponding to residues having a much higher number of contacts between them than with other nodes of the network and blue areas being devoid of intermolecular contacts. As expected, the clusters approximately correspond to residues located nearby along the sequence, pointing to the highly modular structure of the hemoglobin PCN. The long 'whiskers' evident in the figure as 'displaced contacts' (e.g., the 250–270-residue patch having the majority of contacts with the 'blue' cluster instead of the orange one 'nearer' in the sequence) correspond to the so-called 'fast lanes' of communication responsible for allosteric signaling. The 'whiskers' can be quantified in terms of the 'participation coefficient' (P) corresponding to the proportion of edges starting from node i and ending up in node j pertaining to a different cluster. A perturbation affecting specifically a ´high-P´ node travels a long distance across the network, passing by subsequent ´high-P´ nodes and arriving at the destination (the active site), thereby supporting allosteric effects. On the contrary, generic (noisy) thermal motion rapidly dissipates, distributing across non-directional cycles through intra-module motions. High-P nodes create a ´fast lane´ for relevant information neatly separated by noise. This finding, initially coming from hemoglobin analysis by a purely data-driven procedure (the only input data being the pairwise distances between residues coming from X-ray spectrographs), was experimentally corroborated by the simple inspection of the role of high-P nodes not present in other protein systems [34,35]. Moreover, in networks having completely different constitutive laws (e.g., genetic regulation networks where nodes correspond to the expression levels of different genetic elements), high-P elements play the same role of fast and reliable fast lanes for information transfer [36].

Let us now imagine an ML procedure to predict amino acid residues endowed with allosteric properties, i.e., in charge of transmitting a relevant environmental signal (in the case of hemoglobin, the oxygen partial pressure $p[O_2]$) to the active site and driving the molecular configuration change. The structural changes driving the allosteric behavior of hemoglobin have been known for many years [37]; thus, the training data set contains the three-dimensional coordinates of the 574 hemoglobin amino acid residues labeled as 'allosteric' and 'non-allosteric'. An ML algorithm exploiting the mutual spatial relations between the protein residues allows us to correctly predict the class label, while, at the same time, the network formalization permits us to 'decode' the obtained solution (the recognition of residues in charge of signal transmission) in topological terms. This relational (network-based) approach generates the hypothesis that 'the allosteric residues correspond to those having a high participation coefficient in the protein contact network', which can be immediately tested with other proteins (test sets) in which the allostery dynamics are unknown (see [35]). The obtained model of allosteric signaling is expressed in terms immediately understandable to a biochemist, maximizing the explainability of such an ML procedure [15].

5. Conclusions

Relational systems theory, exploiting the power of network thermodynamics [19], allows for the reconciliation of data- and theory-driven styles of reasoning. This reconciliation passes through the progressive blurring of the boundary between methodological and theoretical work, allowing for the discovery of organizational principles largely independent from specific scientific fields [38], as we observed in the previous chapter.

It is worth noting that the notion of a purely 'data-driven' research style relative to the network-based analysis of information spreading across PCNs can be misleading. As stressed in Chapter 2, 'theory-free' perfectly objective approaches do not exist. In the PCN case, scientists rely on theoretical principles coming from biochemistry, like the a priori definition of a distance threshold between residues for the establishment of an effective interaction between two amino acid residues or the choice of α-carbons as reference points for distance computations. The same implicit use of theoretical principles emerges from

methodological aspects of the described example, like the adoption of topological spectral clustering instead of more common Euclidean metrics.

In classical systems science, based on the relative controllability of different systems, the notion of a 'grey box' is adopted [39]. This notion points to the fact that any modeling approach is a hybrid integrating both empirical data and theoretical constructs to enhance model accuracy and interpretability [15,39]. In synthesis, we can affirm that the 'tension' between data and theory is by no means an opposition but a fruitful cooperation.

The relative balance between theoretical and empirical aspects strictly depends upon the studied system. Here, I stressed the possibility offered by a relational approach to enlarge the reach of the systems approach to complex entities, such as biological ones, almost totally out of reach of mechanistic laws [40]. Moreover, the adoption of a style of reasoning tailored to thermodynamics greatly simplifies the transfer of both solutions and hypotheses across different fields of inquiry.

It is worth stressing that the adoption of a network-based relational approach is not a panacea and, in some cases, can be counterproductive, like in situations in which the definition of the atomic elements (the nodes of the network) is problematic or when in the presence of continuous variables.

From a more general perspective, it is worth noting that relational systems thinking asks for a re-shaping of scientific education; it is useless to put together an interdisciplinary group made of different specialists if they do not share a common cultural basis. On the contrary, we urgently need to raise a new generation of scientists able to encode (and then decode in the terms proper to the different scientific fields) the studied phenomena in systems science terms.

It is not an easy task to offer specific recommendations for changing scientific curricula in order to raise such a 'new generation', but, in my opinion, we should take inspiration from the artisan nature of modeling activity. Like in all artisan activities, in the case of data analysis (in the broad sense of systems science, statistics, and operation research), we deal with a relationship between a client (the expert in the field) and an artisan (the data analysis person). A good relationship is reached when the client can go inside the logic of the proposed solution, and the artisan understands what the client really needs. This asks for the hybridization of the specific knowledge of both the artisan and the client, which can be reached only by a drastic simplification of the data analysis methods [11,24], reducing the need for formalism to the minimum to make possible an immediate translation of the suggested analytic procedure in the language of the client. Meanwhile, the client should be trained to acquire an intelligent use of perspective via an educational style that makes clear the separation between key concepts and specialist details. The exaggerated emphasis on the 'last breakthrough' blurred the above perspective, increasing the fragmentation of scientific culture. In terms of scientific curricula, I do not think that we should eliminate or add some specific course but instead promote a global change in style to place much more emphasis on the 'what is it?' than on 'how can I do it?' questions.

In this respect, I am thankful to an anonymous reviewer who drove my attention to an illuminating website (https://norvig.com/chomsky.html accessed on 10 October 2024) in which the prejudices arising from the fragmentation of scientific fields are very clearly exposed and criticized. The most perturbing prejudice (arising from the prevalence of 'how can I do it?' over 'what is it?' questions) is the contempt for the statistical approach that (even by prominent scientists) is put in evidence by the derogatory statement, 'it is only statistics'.

The contempt for statistics does not only come from the side of 'experts in the field' but also from 'pure computer scientists', who often equate the actual physical entity (e.g., a specific i-th patient) to the corresponding feature vector within a data set. This acritical superposition between real and formal systems is related to overlooking the context in which the selection of statistical units (e.g., patients) happens. In their work in [41], Beaulieu-Jones and colleagues, by the analysis of a huge data set containing millions of patient records, offer an illuminating view of the problem. The authors of [41] observed that

two i,j statistical units (patients) having exactly the same feature vector (and, consequently, not being distinguishable by a data-driven ML approach) have a widely different average life expectancy in the case of the feature vector derived from routine examinations or following a specific suggestion by a clinician. This is both vivid proof of the inconsistency of any 'theory-free' scientific ideal and of the urgency of fostering a fruitful exchange between different scientific fields. I hope this work can represent a (very small indeed) contribution to this goal.

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Theoretical Reflections on Reductionism and Systemic Research Issues: Dark Systems and Systemic Domains

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Abstract: In this article, we explore some theoretical issues related to reductionism and systems. Fundamentally, reductionism neglects that a system can acquire properties. Among various possible reductionist approaches, we consider the reduction of sufficient conditions to necessary conditions in systems, the reduction of emergence to functioning, and the general linearizability of non-linear systems. Furthermore, we consider the reductionistic deductibility of the macroscopic from the microscopic (as a matter of scalarity without intermediary emergence). We examine "reductionistic interacting" as it relates to multiple sequenced interactions being zippable into a single interaction. We consider the theoretical dynamic mixed usage of reductionism and non-reductionism. We then elaborate on theoretical systemic issues around opaque dark systems (as non-evident systems requiring both change in scale and change sequences). We investigate how a phenomenon can be improperly modeled as a system. This is often undertaken for the convenience of an observer (who takes advantage of the readily available approaches and models). We elaborate on the interdependence and possible equivalence of these phenomena's theoretical incompleteness and the logical openness of their modeling. We also consider the theoretical issue of systemic domains as space. Here, an entering entity only has access to certain actions and degrees of freedom due to the predominance of a previous systemic phenomenon. We conclude by considering the centrality of theoretical research in systems science.

Keywords: coherence; emergence; incompleteness; reductionism; quasiness; structural dynamics; systemic domain

1. Introduction

The purpose of this article is to elaborate on some theoretical objections against the misdirected use of reductionist approaches and narratives. Their consequences often have the detrimental effect of oversimplifying a problem in general, and even more so when we are confronted with highly complex and interconnected structures such as collective, ecological systems or the economy, for example. This article also elaborates on some unusual systemic theoretical issues such as dark systems, reverse reductionism, and systemic domains.

The theoretical nature of this elaboration relates specifically to (a) abstract systemic representations allowing for the identification of models, rules, and simulations, and (b) the properties suitable for application, generalization, and research approaches.

The theoretical nature is particularly suitable for dealing with the systemic complexity, identifying, for example, its emergent, non-linear, multiple nature, having high sensitivity to initial conditions that a macroscopic, simplifying, reductionist approach assumes as neglectable, approximal, or ignorable. This assumption often occurs because users, observers, and operators do not have a theoretical understanding of the complexity involved.

In Section 2, we consider the generic concept of reductionism.

In Section 3, we consider this concept's theoretical aspects. We deal specifically with (1) the reduction of sufficient conditions to necessary conditions, (2) reducing emergence to functioning, (3) the general linearization of non-linear systems, (4) hierarchical considerations related to microscopic and macroscopic levels (specifically whether the latter

are deductible from the former), neglecting any possible emergence between levels; and (5) reductions that putatively occur when different interactive processes are assumed to be zippable into a single process; (6) reductionism in social systems; and (7) reverse reductionism, that is, cases where a phenomenon is forcibly approximated or modeled as a system when it is not.

In accordance with the topics of this Special Issue, in the following three sections, we consider theoretical issues about systems science other than reductionism.

In Section 4, we consider the theoretical research issue related to opaque dark systems. Regarding opaque dark systems, we consider cases where the systemic nature of phenomenological dynamics and properties are hidden (due to, e.g., the assumed level of description and scalarity, and the models an observer takes into consideration).

In Section 5, we elaborate on theoretical incompleteness and logical openness. We also discuss their interdependence and related models.

In Section 6, we examine the concept of a *system domain*. This relates metaphorically to a *systemic field* where interacting elements are induced to behave like components of a predominant system.

In the conclusion, we mention how systems research should not exhaust itself creating models and simulations, but consider theorizations mixing theoretically symbolic, non-symbolic, and data-driven approaches, allowing for soft theorization and incomplete theorization. Researchers should not just pursue the (funded) decided objectives. They should, instead, pay due attention to pertinent theoretical issues.

2. Reductionism

Ontological reductionism relates to a whole consisting of a minimal number of parts. Methodological reductionism relates to the general possibility of an explanation of the whole in terms of ever-smaller entities [1].

Reductionism must be distinguished from a scientific method which considers quantitative aspects, that is, the collection of measurable quantities. For example, when dealing with an apple, we consider measurable variables such as its acidity (pH), color, density, size, hardness, shape, odor (odorimetric unit), surface area, volume, and weight as sufficient to take appropriate approaches, e.g., conserve and cook it. Considering measurable aspects is not a reductionist but a scientific approach. In the case of an apple, reductionism lies in considering it as a set sum of the elements that compose it, such as molecules, without considering, for example, the structures and their changes, coherence, internal processes, and local changes, e.g., apple ripening, molecular aggregations, context sensitivity, adaptability, maturation, or rotting over time: That is, neglecting that the apple is a system having the property to acquire properties.

According to Russell Ackoff [2], reductionism is a doctrine defending the idea that all entities and events (plus their properties) are made up of ultimate and indivisible elements. Systems are then made up of the sum of their parts.

In reductionist approaches, non-linear interactions and emergence processes are neglected. Complex properties are taken to be non-complex; they are treated as being completely computable and foreseeable. This is the matter of non-systemic uses of systems (reducing to objects possessing proprieties) [3].

Reductionists treat the *acquired* systemic properties as non-systemic properties. Acquired properties include traffic patterns and behaviors, whirlpooling, bird flocks, the weather, swarm intelligence, the behavior of a double pendulum, and various chaotic phenomena (evolving systems that are extremely sensitive to the initial conditions). In other words, reductionists treat acquired properties as *possessed* properties (e.g., age and weight).

In the philosophy of science, theoretical reductionists maintain that theories, entities, or laws from previous scientific theories can be logically derived or deduced from newer, broader scientific theories. This is purported to allow us to understand the relevant theories, entities, or laws as more basic or elementary. So, Newtonian mechanics, for example, should be derivable from special and general relativity. There is also an assumption that

scientific theories can be reduced to more basic scientific theories (e.g., biological theories being reduced to physical theories). However, this kind of reductionism is premised on neglecting the intrinsic multiplicity of complex systems (in which emergent, self-organizing, and chaotic phenomena occur, as introduced below). Multiplicity is related to both (a) the different possible non-equivalent levels of representation and (b) multiple interactions and multiple roles for component parts (as seen in ecosystems) [4–6].

We will elaborate on how multiple systems are intrinsically incomplete and therefore logically open. They require multiple non-equivalent models. Well-defined, monolithic systems include electronic devices. In contrast, multiplicity makes multiple systems adaptive, robust, and tolerant to structural perturbations and changes. An example is a structurally changing whirlpool, which can resume its dominant specifying properties despite perturbations.

3. Theoretical Aspects of Systemic Reductionism

We now elaborate on some aspects of systemic theoretical reductionism as it relates to systemic properties and their acquisition processes. We will deal specifically with theoretical aspects of systemic reductionism, its recurrence, and dual probable inevitability.

Note that we are not concerned with a simplistic notion of reducibility (as identifiable in Simplicio's famous defense of the Ptolemaic worldview) [7]. Moreover, a simplistic distinction between reductionism and non-reductionism itself seems reductionistic. The boundaries are not clearly identifiable. This is exemplified in concepts like the following: (1) a quasi-system (where the predominance of a systemic nature is only present in variable percentages) [8] (pp. 155–157), (2) theoretical incompleteness (understood as the inherent incompleteness necessary for emergence) when phenomena are incomplete enough to permit the establishment of a space of equivalences constantly incomplete, in that no specific single order or structure predominates [8], (pp. 116–122), [9] (see Section 5), and (3) multiple systems (e.g., when a system's variables are also other systems' variables) [10]. The introduction of these concepts calls into question our classical understanding of systems (as analytically identifiable and distinguishable from non-systems).

We mention how a quasi-system may be defined by its inhomogeneous possession of systemic properties. For instance, in ecosystems, different levels of openness are possible depending on the spatial location, e.g., when some areas are icy or shielded from light. Furthermore, a quasi-system may be open on the account of different variable aspects, such as being open to energy but not to information, or having such openness at different levels over time. A further example of a quasi-system is a biological system with multiple dynamically interacting co-occurring pathologies, varying its systemic multiplicity: see, for instance, [11].

Furthermore, a collective system may be able to assume intelligent behavior or acquire collective intelligence, and only in the face of specific events.

There may be reason to doubt the reducibility of (1) quasi-systems and multiple systems to systems, (2) the incomputable to the computable, and (3) theoretical incompleteness to completeness (related to completable incompleteness or neglectable incompleteness).

We are interested in how systemic quasiness supposedly relates to entities having (1) levels of tolerance regarding a temporary loss of systemic interactions, (2) levels of instability, (3) irregular collapse alternations, and (4) coherence recoveries. These typically apply to collective systems, which partially dissolve and recompose over time in response to external perturbations. Other examples of such systems include self-organizing nonlinear systems like, in fluid thermodynamics, whirlpools and so-called Rayleigh–Bénard convection, when a fluid heated from below develops a regular pattern of convection cells.

The classical approach is based on looking for a unique and best-performing model. However, this style of reductionism is called into question by the intrinsic multiplicity and quasiness of complex systems.

Part of our focus will be the conceptual framework of Dynamic Usage of Models (DYSAM) (introduced in [12] (pp. 64–70) and elaborated in [8] (pp. 201–204)). Here, the emphasis is on multiplicities of phenomena (e.g., complex phenomena) that are inex-

haustible using a single approach or level of description. The general idea is as follows: "In these cases, the goal is not to find the 'best' and 'unique' approach but to use different approaches together, in such a way as to reproduce the coherent evolutionary multiplicity of real processes. This is a step towards understanding the multiple and dynamical unity of science glimpsed by von Bertalanffy" [8] (p. 9).

Some of DYSAM's theoretical roots can be identified in the Bayesian method. Following Bayes' theorem, one employs a statistical treatment based on the "continuous exploration" of events occurring in the environment under study. So-called ensemble learning algorithms are also important. They use traditional machine learning algorithms to generate multiple basic models. These are then combined into an ensemble model, which usually performs better than a single model. Another root is evolutionary game theory (based on von Neumann's "minimax theorem" [12] (pp. 64–70)).

Along with incompleteness, multiplicity, and quasiness, we are also concerned with contextual occurrences of linearity and non-linearity, involving levels of non-linearity related to networks and their properties; neural networks and their architectures; layers and weights; and metastructures (structures whose elements are also structures) [13]. When dealing with interactions between different structured coherent domains, such as those within liquids and magnetic materials, metastructures may come into play [14]. The interest in the theory of metastructures has arisen after the introduction of so-called mesoscopic physics [15]. Mesoscopic variables relate to an intermediate level between the micro- and macro-scale, in which the micro-scale is not completely neglected when adopting macro-scale levels. The mesoscopic level can be considered the place of continuous negotiations between the micro- and macro-scale. At this intermediate level, a large variety of mesoscopic representations is possible, such as considering undefined numbers of possible clusters and their intra-structural properties.

A situation similar to contrasting completeness and incompleteness, single models and multiple models, occurs when we contrast objectivism and constructivism [8] (pp. 188–194). When objectivism and constructivism are mixed, contextual usage represents daily practice.

We will conclude that a dynamic usage of reductionism and non-reductionism is desirable. The problem lies in making one approach absolute (to the detriment of the other). We should not overlook a mixed, variable, temporary, and possibly superimposed approach.

We now consider some theoretical issues related to systemic reductionism.

3.1. Reducing Sufficient Conditions into Necessary Conditions

Sufficient conditions are not necessarily necessary and necessary conditions are not necessarily sufficient. Sufficiency is more powerful than necessity because something sufficient might not be necessary. However, sufficiency can be established if different conditions are added to the necessary conditions. A package of necessary conditions is invariant if not for equivalences. A package of sufficient conditions can then be composed of different conditions and equivalent conditions. For example, the property of being a rectangle is necessary to being square; however, the property of being a rectangle is not for being square. The property of being a square is sufficient for being a rectangle; however, the property of being a square is not necessary for being a rectangle.

Sufficient conditions can both fulfill the necessary conditions or be non-necessary conditions. Of course, this does not apply when necessary and sufficient conditions coincide. An example of a necessary condition is that Q cannot be true without P being true. Conversely, in the proposition "If P, then Q", P is sufficient for the truth of Q. However, P being false does not always imply that Q is false. We can also have propositions like "If $S(\neq P)$, then Q" and "If P, then $R(\neq Q)$". It is thus possible to have both more and different sufficient conditions.

Consider in N the whole integer numbers $p > 2$. Being odd is necessary for p to be prime (since 2 is the only even and prime number). However, being odd, it is not sufficient in being prime; p must also be solely divisible by itself. We might think of approximating

the relationship between the set of prime numbers and the set of odd numbers as an instance of reductionism.

Consider necessarily interacting, networking, and boundary conditions as sufficient for establishing the collective behavior of a system. Here, the neglect (often unknown) of modalities (e.g., establishing coherence and long-range correlations) is a case of reductionism. Considering, in general, that all necessary conditions approximate or exhaust all sufficient conditions is a case of reductionism.

Considering processes of economic growth in social systems to be instances of development is another case of reductionism (viz. reducing development to growth). We then think about how the growth process can be conceptually understood as a sequence of increments. Such increments are often taken to be repeatable without limit. But this is often assumed without considering (a) their sustainability and (b) side effects and interactions with other processes (e.g., other growth processes). Development can be understood as the process of property acquisition, e.g., coherence, in suitable growth processes and their configurations. It should be noted that good development or bad development (understood as sustainable or unsustainable property configurations of growth systems) is inevitable. Growth processes inevitably interact, even without organization or decision-making, and acquire new properties. This can give rise to unwanted properties, including environmental and social negative effects.

3.2. Reducing Emergence to Functioning

A device is said to be functioning when it performs the action or activity for which it was designed. This can happen when components are suitably interconnected by way of fixed networks (e.g., in mechanical, electronic, hydraulic, or thermodynamic devices). Functioning takes place when devices are suitably powered, and the components are then allowed to interact, establishing a structured system. A set of structured components takes on acquired properties to perform a certain function. If the power supply is cut, then their key properties disappear. The structured system of components degenerates into its components. Functioning is also assumed to be adjustable and repeatable.

Components of complex systems interact in multiple ways and follow dynamic local rules [16]. This is particularly noticeable in (1) chaotic phenomena (e.g., the double pendulum and atmospheric conditions [17]), (2) self-organization (e.g., whirlpools, Bènard rolls [18], and the patterns formed in the Belousov–Zhabotinsky reaction [19]), and (3) emergence (as in collective systems like bird flocks, insect swarms, ecosystems, the morphological properties of cities, and networks [20–26]).

Self-organization is the process of unstructured acquisition of the "same" property over time (as in the whirlpools and Bènard rolls mentioned above). Emergence, in contrast, is the continuous and unpredictable acquisition of multiple coherences. It involves the acquisition of multiple properties by way of undesigned interactions and structural dynamics. Such dynamics involve variation in structure between variable components. This is observable in ecosystems that exhibit multiple and continuously changing, albeit coherent, behavior. We can say that coherence replaces structure. Another example is emergent computation [27]. This occurs when it is impossible to find an algorithm capable of computing the end state of an evolution without computing all the discrete intermediary states. Neural networks and cellular automata are prototypical examples (even if cellular automata are defined as having fully deterministic evolution rules); see Section 3.5.

Complex systems can be generated via chaos, self-organization, emergence, or quantum phenomena (and their eventual combinations). An example is multiple dynamical attractors and the properties of their dynamics. This is equivalent to considering superimposed abstract spaces of multiple attractors [8] (p. 265), [28].

Note that emergent processes require incompleteness and the multiple equivalences of quasi-systems [8]. Quasiness relates to equivalences, inhomogeneity, multiplicity, nonregularity, partiality, and the dynamics of loss and recovery. A feature of quasi-systems is that they are not always the same system. In fact, they are not always systems [8] (pp. 155–161).

Quasiness represents the incompleteness of the interaction mechanisms. This incompleteness is necessary (if not sufficient) for the realization of emergent processes. Completeness extinguishes emergence, reducing it to computable dynamics [8,10]. We mention some roots of the concept of quasi, such as quasicrystals, where, contrary to crystals, the atoms are arranged in a non-deterministic, not periodic or repetitive, structure [29]. In mathematics, quasiperiodicity relates to recurrences whose periodicity has irregular or unpredictable components.

Despite the above, reductionism remains if we mistake incompleteness for completeness. This is a matter of logical closedness contrasting with logical openness (see Section 5; see also [11] (p. 75).

Stipulating finite and limited degrees of freedom allows us to mistake incomputability for computability [27]. Ignoring incompleteness, multiplicity, and quasiness (or assuming their computability) can result in attempts at the reduction of complex systems to (or their, less dramatic, approximation as) non-complex systems. This can lead to approaches that are both wrong and counterproductive, approaches that attempt to deal with nonexistent systems [3]. Complex systems cannot be regulated or decided. They can only be suitably and interactively oriented or influenced. This occurs when we act, for instance, on environmental conditions, available energy, noise, and changing initial conditions [8] (pp. 208–210).

3.3. General Linearization of Non-Linear Systems

It is well known that a linear function satisfies the following two properties:

i. Additivity: $f(x + y) = f(x) + f(y)$.
ii. Homogeneity: $f(\alpha x) = \alpha f(x)$ for any parameter α.

However, the common understanding of "linear" often equates it to proportional. An increment of x is supposed to correspond to an increase that is suitably proportional (even negative) to y. This does not apply to non-linear functions (e.g., $f(x) = x^n, f(x) = sinx$). Non-linear functions model the non-linearity of non-linear systems for which the current state and output do not linearly correspond to the previous state and input. Examples include chaotic systems (which exhibit high sensitivity to the initial conditions) and collective systems (which have vast dynamics and a variety of local non-equivalent rules).

In his seminal *General System Theory*, Ludwig Von Bertalanffy writes as follows: "Application of the analytical procedure depends on two conditions. The first is that interactions between 'parts' be nonexistent or weak enough to be neglected for certain research purposes. Only under this condition, can the parts be 'worked out', actually, logically, and mathematically, and then be 'put together'. The second condition is that the relations describing the behavior of parts be linear; only then is the condition of summativity given, i.e., an equation describing the behavior of the total is of the same form as the equations describing the behavior of the parts; partial processes can be superimposed to obtain the total process, etc. These conditions are not fulfilled in the entities called systems, i.e., consisting of parts 'in interaction'" [30] (p. 19).

Linearization is used to approximate a non-linear system as a linear system exhibiting similar behavior (especially in the vicinity of a designated point). Examples of the methods used to linearize a non-linear system are the Taylor series expansion, state-space linearization, feedback linearization, and Jacobian linearization (which involves approximating a system's behavior to its Jacobian matrix). Linearization is used to make non-linear systems tractable (as in the linearization of the Lorenz system [31]). Examples of non-linear systems acquiring non-linear properties as behaviors include chaotic systems, adaptive systems, learning systems, evolving systems, and collective systems.

Despite the above, it can be dangerously reductionistic to assume the indiscriminate generalizability of linearization without considering validity contexts and suitable levels of representation. This can hide complex behavior-characterizing aspects of the system under study. Such aspects include bifurcations, fluctuations, a high dependence on initial conditions, long-range correlations, polarization, power laws, remote synchronizations, scale

invariance, self-similarity, symmetry breaking, temporal phenomena, local synchronizations, and network properties (e.g., the occurrence of small worlds when distant neighbors can be reached from every other node via a small number of intermediate links. Some examples are the electric power networks and the neural networks of brain neurons. Linearizing complexity induces the use of linear approaches [3]. However, structural approaches to complex systems require that we consider aspects whose effects are only approximated in linearization.

3.4. The Macroscopic from the Microscopic

We should begin this section with some introductory definitions.

Firstly, at the microscopic level, it is possible to deal with single elements (e.g., cells, molecules, and particles) that are separable (even if we do not take their distinguishability for granted).

Secondly, the macroscopic level relates to various collections of microscopic entities characterized by their aggregations and (acquired or possessed) properties.

These two levels (microscopic and macroscopic) can be thought of as two extreme hierarchical levels [8] (pp. 38–41). That said, the scalarity is variable if not for elementary particle physics. The study of elementary particles is devoted to researching the very lowest level of the micro–macro hierarchy. In elementary particle physics and condensed matter physics, fundamental particles (i.e., subatomic particles) are not thought to be composed of other particles. This distinguishes the lowest level from supposedly higher levels.

With a reductionistic approach, the hierarchical levels between micro and macro are analytically connected in fixed (often bidirectional) ways. The reductionistic approach is largely based on the idea that such an analytical reconstruction renders the macroscopic explainable by the microscopic. The microscopic is intended to be the so-called seat of truth; it is the source of necessary and sufficient ultimate causes. However, this might only be conclusive for a specific reductionistic explicatory model employed by an observer. Reductionism assumes analytical composability and decomposability. It assumes that there are hidden causes and generative processes responsible for the formation of the macro. Correlation is often reductionistically identified alongside causation. The problem is that correlation does not imply causation (see, e.g., [32,33]). In genetic research, for example, one might consider how a high percentage of human genes can be related to cancer. This relation makes us realize that a high percentage of human genes being cancer-related is actually irrelevant, as is the related biological research [34].

In contrast, a non-reductionistic understanding takes hierarchical levels between the micro and the macro to (a) be non-reversibly emergent and (b) contain layered phenomena of emergence (as in biological systems and ecosystems) [8] (pp. 269–273). When it comes to cancer research, what we observe at a specific level (e.g., a population of cells) can be different from what we observe at another level (e.g., a single cell).

That said, the reductionist approach is suitable for entities and systems with zero or low structural dynamics. In such cases, there is often a simple and stable interscalability between the micro and the macro. An example is approximating the Earth's surface as flat when journeying over short distances.

The concept of emergence is suitable in cases where complex systems have multiple levels of emergence, that is, when emergent entities become entities of an emergent phenomenon [8] (pp. 255–260).

3.5. Reductionistic Interactions

Two elements are said to interact when the behavior of one element influences the behavior of another. An example is a system model consisting of ordinary differential equations where f_1 represents the exchange of kinetic energy between x_1 and x_2:

$$\begin{cases} dx_1/dt = f_1(x_2) \\ dx_2/dt = f_1(x_1) \end{cases} \quad (1)$$

The situation becomes more complex when, for example, there is simultaneous validity of (1) and (2):

$$\begin{cases} dx_1/dt = f_2(x_3) \\ dx_3/dt = f_2(x_1) \end{cases} \tag{2}$$

If interactions f_1 and f_2 occur simultaneously, then we have:

$$\begin{cases} dx_1/dt = f_1(x_2) \\ dx_2/dt = f_1(x_1) \\ dx_1/dt = f_2(x_3) \\ dx_3/dt = f_2(x_1) \end{cases} \tag{3}$$

One might think of a "summarized" system of interactions:

$$\begin{cases} dx_1/dt = G(x_2, x_3) \\ dx_2/dt = f_1(x_1) \\ dx_3/dt = f_2(x_1) \end{cases} \tag{4}$$

where G is a composition $G = f_1 \otimes f_2$. This eventual composition is based on a reductionistic assumption related to the simultaneity of the occurrence:

$$\begin{cases} dx_1/dt = f_1(x_2) \\ dx_1/dt = f_2(x_3) \end{cases} \tag{5}$$

intended to coincide with

$$dx_1/dt = G(x_2, x_3) \tag{6}$$

where $G = f_1 \otimes f_2$. However, the time granularity is lost. In system (4), the configuration of values dx_n/dt at time t_n is input to the system at time t_{n+1}. The reductionist view assumes the validity of G. This dynamic is assumed to be then zippable (or, more elementarily, summable) into G.

There are several examples where such zippability is theoretically impossible [26]. As mentioned in Section 3.2, it is impossible to zip the evolution of a cellular automaton or neural network into a single algorithmic step without computing all the discrete intermediary states. One cannot compute the end state in "one fell swoop".

In a cellular automaton, which involves the simulation of a universal Turing machine that can self-replicate, the state of a cell can only depend (via a local transition rule) on the state of the cell itself, on the state of two adjacent cells, and on others depending on the dimensionality of the cellular automaton.

Considering two-dimensional cellular automata with square cell lattices, we now mention two types of neighborhood relationships, i.e., the so-called:

- Moore neighborhood, which includes, besides the cell under consideration, the eight neighboring cells that share at least one vertex with it;
- Von Neumann neighborhood, where the cell under consideration shares at least one edge with its four neighbors.

The number N of different possible local transition rules increases with the number k of different allowed states per cell and with the number r of cells included within the neighborhood of the cell under consideration, so that:

$$N = k^q, \text{ where } q = k^r. \tag{7}$$

Here, even with small values of k and r, N can be very large. For instance, when considering a two-dimensional cellular automaton with a Moore neighborhood, where $r = 9$ and $k = 10$, we have $N = 10^{10^9}$ [35].

Reductionistic zippability also assumes that we can ignore the subsequence of effects (e.g., interacting with the single summative energy involved, which is considered

undistributed in subsequent events). There is an assumption that the resulting sum (or composition) of all the interactions will be equivalent to their sequence. But this ignores single-element interactions. Zippability only takes standardized behavioral reactions into account. It ignores the possibility of interacting elements in autonomous systems being able to process, learn, and adapt (e.g., bird flocks, insect swarms, and social systems). In mechanical systems, we are dealing with breakages rather than wear and tear.

In social systems, this kind of reductionism can lead one to disregard unwanted effects and side effects, which are often misunderstood as the price to pay for rendering the relevant phenomenon treatable.

3.6. Social Systemic Reductionism

Dealing with social systems, reductionism may be defined as the simple transposition of models and concepts used for physical and biological systems, reducing cognitive interaction to physical ones, essentially reducing cognitivism to forms, albeit of a certain complexity, of behaviorism.

Furthermore, as regards social systems, it is necessary to mention specific themes of reductionism [36].

In education, for instance, a critique of reductionism is very important to protect against misleading simplifications. The concept of reductionism has rarely been considered in education, where its use has been applied to very specific issues or as a vague term [37–39].

A similar situation is found when considering aspects of other kinds of social systems, such as in the field of management and healthcare, when reductionism consists of considering emergent and non-linearly caused properties to be organizational and functional.

Furthermore, as regards social systems, it is necessary to mention the introduction of specific systemic issues not coinciding with those mentioned above. A general, original theoretical systemic [40] approach was introduced by Niklas Luhmann's social theory and approaches to social systems [41].

His original systems theory focuses mainly on three topics: systems theory intended as societal theory, as communication, and as evolution theory. A system is identified by the boundary between itself and its environment. The boundary separates it from an indefinitely complex exterior. The "interior" of the system is thus a zone of so-called "reduced complexity", where interior communication occurs by selecting only a limited amount of all the information available outside.

The distinctive identity of each system is continuously reproduced in its communication and depends on what is considered meaningful or not. When a system fails to maintain this identity, it disappears as a system and dissolves back into the environment it emerged from. Luhmann terms this process of reproduction from elements previously selected from an over-complex environment as "autopoiesis", using the same term introduced by Maturana and Varela to identify the ability of systems to self-reproduce. Luhman considers social systems to be "operationally" closed since they use environmental resources, but they do not become part of the systems' operation.

Regarding reductionism, Luhmann wrote:

> "For a long time, in sociology the representatives of an individualistic reductionism claimed to have achieved special access to the elementary, empirically graspable foundations of social life" [41] (p. 256).

and

> "Every version of individualistic reductionism has encountered the objection that, as reductionism, it cannot be fair to the 'emergent' properties of social systems. We would object further that the issue is not even reductionism, but relating (in an extremely abbreviated way) to psychic rather than social systems." [41] (p. 257).

This reductionism relates mostly to emergentism in sociology. While in systemic emergence, the core problems considered above are, for instance, causation and reductionism, for Luhmann's theory, they are problems of meaning and self-reference [42].

At this point, we mention an interesting correspondence between the concepts of theoretical incompleteness and multiplicity introduced above, and what was considered by Luhman:

> "He wanted to avoid above all else the idea that one could capture 'the truth' or essence of modern society in one theoretical account. No theory, not even closed systems theory or autopoiesis, can have the last word or give an exclusive or true account of what society, in its totality, is and how it operates. One could even suggest that the first principle of Luhmann's sociology is that the possibility not only of seeing things differently but of society actually being different is always present. . . .What he wished to offer, therefore, was a social theory of social theories—a social theory which considered multiple ways of perceiving and understanding society." [43] (p. 1).

Regarding reductionism:

> "He fully realized that one could never completely escape reductionism, since any attempt to address and understand events socially necessarily involves selection, rejection and interpretation." [43] (p. 1).

3.7. Reverse Reductionism

Reverse reductionism is the opposite of unwarranted reductionism. It occurs when a phenomenon is forcibly modeled as a system. The phenomenon is adjusted and measurements are adapted so that a system appears to be present. Reverse reductionism can occur when available systemic models appear to be good approximations of unmodeled processes exhibiting the same unexplained regularities. Reverse reductionism loads a systemic nature onto some phenomenon under consideration.

For instance, an observer might recognize supposedly predominant systemic behaviors in (1) populations that exhibit Brownian motion, the irregular but continuous random thermal agitation of molecules in heated liquids or gasses caused by thermal energy, and (2) the turbulence found in smoke diffusion, terrestrial atmospheric circulation, and the mixed oceanic and atmospheric layers of ocean currents. The same occurs when recognizing systems in populations of arbitrarily inhomogeneous elements whose interaction is also only supposed and not detected.

Certain cases should, nonetheless, not be confused with reverse reductionism. These include the use of systemic models developed in a specific disciplinary context. This occurs in interdisciplinarity when approaches, problems, and solutions from one discipline are considered in terms of another by changing the meaning of variables or transforming one problem into another. The goal is to render such problems more easily treatable. This can take the shape of transforming geometric problems into algebraic ones, military problems into economic ones, energy consumption problems into social ones, medical problems into chemically treatable unbalances, and vice versa. In these cases, we can recognize the same systemic structure in different disciplinary contexts. This is a matter of using the same approaches and models. Such approaches and models are, however, applied in different contexts by changing the meanings of variables. Examples include Lotka–Volterra equations of prey–predator systems or chaotic climatic behavior being transposed onto economics. The adequacy of the systemic model's transposition decides its validity or its forcing. When the transposition is forced, we have reverse reductionism rather than interdisciplinarity (or forced interdisciplinarity).

4. Opaque Dark Systems

In this section, we consider phenomena whose systemic character is implicit and only detectable using appropriate variables, appropriate variations in scale, and an appropriate level of representation.

We now consider cases where the systemic nature of phenomenological dynamics and properties is hidden. This hiddenness might be due to the level of description assumed (i.e., scalarity) and the models an observer takes into account.

We use the term "opaque systems" metaphorically. Following Giuseppe Vitiello, "...opacity and transparency can be considered as a response of the body to the interaction with light, deriving, on the one hand, from the behavior of the body elementary components and structural properties, on the other from the intensity and frequency of light. One can have different responses to different light intensities and frequencies, also depending on whether the body has, for example, a crystalline or amorphous structure. Opacity and transparency are, therefore not intrinsic properties of bodies. They describe the way the body 'manifests' when using light as an instrument of observation" [44] (p. 42).

We use the term "dark systems" in a similarly metaphorical way. The term refers to the phenomenon of dark matter (dark because its presence is determined by its gravitational properties rather than its luminosity).

"Hidden", "opaque", and "dark systems" can be designated in two different ways: (a) constructively (i.e., supposed to explain and model phenomena) and (b) as discovered via sophisticated and dynamic scalarity changes.

Examples of opaque dark systems include (1) supposed systemic rules of phenomena at large temporal and spatial scales (as in astrophysics and anthropology), (2) the effects of the shadow economy, (3) pandemic effects (e.g., COVID-19), and (4) hidden natural systems at scale (e.g., Bènard rolls in fluid dynamics when considered in atmospheric phenomena) [45].

Are there approaches that might be suitable for discovering hidden opaque dark systems? Can we (idealistically) suppose the possibility of these kinds of system detectors?

Finally, and in reference to opaque dark systems, we mention how the Heisenberg Uncertainty Principle expresses the fact that it is not possible to determine simultaneously both the frequency and the time location of the waves' components with arbitrary precision. The Heisenberg Uncertainty Principle { XE "Uncertainty Principle" } has been generalized and related to the theory of "statistical estimates", introducing so-called Fisher information [46,47].

Very briefly, we can say that Fisher information is a measurement of the amount of information that an observable X carries about an unknown parameter of distribution that models X.

Let the level of Fisher information at the source have the value I. Let the observed level of Fisher information in the data have the value J. The Extreme Physical Information (EPI) principle states that $J - I$ = extremum. When this extremum is the minimum, the observed level is considered to match up with its source.The EPI principle is based on the idea that the observation of a "source" phenomenon is never completely accurate and the related information is necessarily lost from source to observation. Furthermore, intrinsic random errors are intended to define the distribution function of the source phenomenon.

Some authors [48–50] have considered Fisher information a grounding principle from which it is possible to derive physical laws.

The study of highly complex systems, for instance, cognitive and socio-economic ones, needs suitable generalizations of the Uncertainty Principle { XE "Uncertainty Principle" }. This is the case for highly complex systems characterized by the fact that every model adopted is, in principle, partial, having inevitable aspects of uncertainty, and can represent only certain particular features of the system under study, neglecting inevitably other features of no less importance, representing the opacity of systems.

The notion of open dark systems may provide a shortcut to the description of complex systems, and might be simply defined as complex systems/phenomena that are not easily understood or observed due to their inherent complexity, their lack of transparency, or the limited accessibility of information. These systems are often characterized by numerous interdependent and non-linear processes, making them difficult to analyze and predict using traditional reductionist approaches. Fisher information, generalizing the Uncertainty

Principle, may be suitable to seek out the uncertainties in complex systems like using Roy Frieden's Extreme Information Theory [49].

5. Theoretical Incompleteness and Logical Openness

In this section, we outline the concepts of theoretical incompleteness and logical openness. We will focus on their interrelations as theoretical research issues related to high levels of equivalence.

5.1. A Note on Theoretical Incompleteness

Theoretical incompleteness lies in facts like the following: (1) a single model is not sufficient to represent complexity, (2) system variables (degrees of freedom) vary in number and are continuously acquired, (3) non-equivalent properties are continuously acquired, and (4) systems can assume many equivalent states (as determined by fluctuations). Theoretical incompleteness is incompletable in principle. Examples of theoretical incompleteness include (1) the Uncertainty Principle in quantum mechanics (where accuracy in measuring one variable comes at the expense of another), (2) the Complementarity Principle in theoretical physics (between wave and particle natures), and (3) Gödel's incompleteness theorems [51].

As noted in the literature on complex systems, incompleteness is intended to be a theoretically necessary condition for emergence in a dynamic of equivalences. However, incompleteness is not sufficient for the assumption of coherence in the emergence of complex systems (e.g., for bird flocks and insect swarms) [8,20] (pp. 158–159), [52,53].

The emergence of complex systems requires theoretical incompleteness. Completeness can be thought of as the "enemy" of emergence. This is because it produces ruled contexts without a place for equivalences and multiple roles [8] (pp. 161–170), [20].

Regarding modeling theoretical incompleteness, we should mention elementary approaches and cases.

An elementary case consists of a system of equations containing fewer equations than variables (the number of the former is less than the number of the latter). This leaves one or more variables undefined in terms of the other variables. It is then an incomplete system.

One can also consider a case where the subsequent computational steps do not use the same system of equations. Instead, there are different (complete or incomplete) versions of the system. Equations come into play in different subsequent combinations. This is another example of the conceptual modeling of structural dynamics mentioned in Section 3.2.

We can think of theoretical incompleteness as taking place when systems of equations assumed to completely represent phenomena turn out to apply non-completely. In other words, they apply in non-completed combinatorial sequences that model aspects of quasiness and the structural dynamics of the phenomena under study. Examples include the incomplete variable sequences of deterministic chaos equations, of the Van der Pol and Lotka–Volterra models. Examples of theoretical incomplete systems include ecosystems and collective systems.

5.2. A Note on Logical Openness

The concept of logical openness has been introduced as an extension of thermodynamical openness and in contrast to logical closedness [54].

Logically closed modeling relates to thermodynamically closed systems. The evolution of such systems can be represented as follows:

i. Formal and complete descriptions of relationships between a system's state variables are available.
ii. Complete and analytically describable representations of interactions between a system and its environment are available.

Logical closedness is given by the fact that knowledge of these two points allows us to deduce all possible states a system can assume.

Returning to the discussion of emergence and functioning from Section 3.2, we might consider the logical closedness of a Laplacian clocklike world (understood as functioning rather than emergent). There is conceptual correspondence with the notion of computability when an algorithm (a complete computational procedure) is available. More generally, the reference is to the availability of a procedure intended to completely represent a certain process.

In contrast, logically open modeling or logical openness occurs when there is a violation of the above two points. We can think of logical openness as being given by the occurrence of an infinite or non-depleting number of degrees of freedom for a system (including its environment) [8] (pp. 47–51), [26]. This renders a representation of the system theoretically incomplete. This is the case for complex systems whose degrees of freedom (the system variables) vary in number and are continuously acquired. The corresponding modeling uses n levels of representation characterized by (1) non-equivalence, (2) approaches for moving between levels (thereby allowing the simultaneous use of more than one level), and (3) the need to find comprehensive indexes, including measures of coherence, long-range correlations, network properties (e.g., the occurrence of small worlds), and properties of attractors in chaotic phenomena.

The incompleteness of logical openness is marked by (1) the use of a variable number of non-equivalent models, (2) the abductive and constructivist indefiniteness of n levels of representation due to observer-generated representations and models, and (3) the relevant indexes employed [10] (pp. 157–165), like global ordering and polarization.

5.3. Logical Openness of Theoretical Incompleteness

Logical openness is a property of modeling [8] (pp. 45–51), [28], while theoretical incompleteness is a phenomenological property.

We now explore how logical openness relates to theoretical incompleteness. On the one hand, logical openness is a property of modeling incomplete theoretical phenomena. On the other hand, incomplete theoretical phenomena require logical openness in modeling. This duality is expressed in Table 1.

Table 1. Logical openness of theoretical incompleteness.

Logical Openness	Theoretical Incompleteness
Modeling uses n levels of representations characterized by the following: - Non-equivalence, - Approaches for moving between levels (thereby allowing the simultaneous use of more than one level), - The need to find comprehensive indexes, including measures of coherence, long-range correlations, network properties (e.g., the occurrence of small worlds), and properties of attractors in chaotic phenomena.	Characterized by: Dynamics of multiple equivalences, A single model is not sufficient to represent the complexity of a system, The system variables (degrees of freedom) vary in number and are continuously acquired, Non-equivalent properties are continuously acquired, Systems can assume many equivalent states (as determined by fluctuations).

The validity domain of logical openness can be broader than that of theoretical incompleteness. This can occur when theoretical incompleteness is a quasi-property of systems that have mixed temporary behaviors alternating between completeness and incompleteness (e.g., flying bird flocks, bird flocks resting on the ground during the night, and bird flocks that gradually form from elements on the ground. A corporation acts a system only during the working hours, while some departments may act as assembly lines, i.e., as structured sets. An electronic system may constitute subsystems activated on request that are otherwise inactive).

Furthermore, a system can decide its level of openness (e.g., context sensitivity, interfacing, learning and usage of memory, and processing uses). This is facilitated by selecting and assuming limitations. This occurs in the processes of abduction, a hypothesis-inventing process that can be considered a kind of selection between suitable alternatives [55–58].

A generic instance of logical openness occurs when one deals with incompletely modellable phenomena. Such phenomena are (a) non-zippable into single equations (as in complex systems where the degrees of freedom vary in number) and (b) continuously replaced and acquired (as in collective systems). One requires a DYSAM-like approach based on the dynamical assumption and replacement of models. Specific cases relate to the non-proceduralization of certain phenomena [9]. The prototypical example of a procedure is an algorithm that allows for complete decidability. The general idea is that one needs step-by-step methods prescribing how and when to do something.

A sequence, the processing of the system states representing its behavior, may be considered algorithmic, i.e., Turing-computable. For instance, the system assumes a finite and limited number of configurations, degrees of freedom, and numbers of states, as found for logically closed systems. That is, the system's behavior is representable as a procedure.

Non-algorithmic, non-proceduralized sequences of the states of a system may assume unlimited configurations, degrees of freedom, and numbers of states, as determined for logically open systems of which the behavior is not representable as a procedure. Namely, it is not globally Turing-computable even if, possibly, it is locally Turing-computable, as for the sub-symbolic [26] processing of artificial neural networks (ANNs) and their deep machine learning using recurrent neural networks [59].

Furthermore, sequences of the states of a system cannot be proceduralized when, for instance, each step depends on:

- fluctuations, the breaking of equivalences and symmetries, weak forces, external influences, and randomness in physical systems;
- adaptation and learning in autonomous systems: in short, sequences of processes of emergence and self-organization are not summable and cannot be procedularized or zipped into the resulting one.

In such cases, typical of emergent complex systems, the process is not identically repeatable. The representation of phenomenological interactional mechanisms and process sequences are not analytical but adaptive and ongoing, as represented by natural computation [60,61].

Generally speaking, a procedure is intended to consist of generic instruction manuals. Examples include maintenance and job security procedures that are assumed to be complete (i.e., necessary and sufficient). Investment in security is a necessary condition for job security, but it cannot exhaust the problem of reaching 100% security. A sufficient condition (converging to completeness) constitutes managing job security as an emergent property, one that is continuously acquired by a working community (as in the Tenaris experience) [62]. Job security cannot be proceduralized. Examples of this in social organizations (e.g., corporations) include mixing well-structured aspects (e.g., wearing overalls and helmets, respect shifts and times) with undefined aspects (e.g., the psychological state of workers, the ability to communicate and cooperate). This leaves room for adaptation and learning. The system can also decide the level of openness (or completeness) by selecting and assuming limitations (as in abductive processes).

6. The Establishment of Predominant Systemic Domains

This concept was anticipated in related research about, for instance, the phenomena of systemic propagation [8] (pp. 170–175) and pre-properties (establishing compatibility) [8] (pp. 146–151). The concept of a field might be metaphorically helpful for identifying the concept of a domain. However, the contrasts and differentiations between them are suitable for specifying the general concept of a systemic domain.

In physics, each point of a field is intended to have the precise value of a definitory variable (e.g., electromagnetic or gravitational).

Systemic domains are spatial regions of possible options available to entering entities. An example of an available option is the admissible and compatible states of an entity that respect the relevant constraints and degrees of freedom (dimensions of the space).

A systemic domain is assumed to be given by configurations of variables, degrees of freedom, ranges of values, and admitted changes to an entering entity. This contrasts with fields (where only one value of the defining variable is available at each point). Systemic domains allow for multiple achievable, admissible, compatible, incomplete (partial or fuzzy), subsequent, equivalent, and non-equivalent choices [20] (pp. 6–10). The systemic domain is then taken to be represented over time by multiple authorized value intervals (which are available for the subsequent change). The system domain is intrinsically time-dependent. In other words, domains are dynamic and dependent on previous domains. Systemic domains are generated by the dynamics of a system, possibly even multiple, being active in the space (e.g., collective systems and ecosystems). For an incoming entity to be sensitive to the domain, it must be compatible with entities in the generating system. Consider the circular swarming of mosquitos around a light. The swarming imposes itself on any incoming mosquito but does not influence different insects and peripheral entities (e.g., plant particles blown by the wind). This also applies to a whirlpool, which makes incoming liquid flow the same way as the liquid already contained in the whirl. Such scenarios can be represented by the basin of an attractor [63].

System domains predominate in the face of non-destructive inputs. This occurs by way of factors like suitable compatibility, quantities, and timing. The properties of domain sequences can be considered to represent the evolution of the generative system. There is also the possibility of inserting an input with its own systemic domain to replace a current one. The former then becomes predominant (as a collective behavior in Brownian motion). Examples of possible applications include market behavior and crowd behavior. This approach can also increase the tolerance or robustness of a system by inducing the recovery of temporarily lost properties (e.g., coherence).

7. Conclusions

In this article, we introduced theoretical issues, some related to reductionism and others that could more properly be understood as systems research topics.

The issues related to reductionism were: (1) the reduction of sufficient conditions to necessary conditions, (2) the reduction of emergence to functioning, (3) the general linearizability of non-linear systems, (4) attempts to deduce the macroscopic from the microscopic, (5) the zippability of sequenced interactions into a single resulting interaction, (6) dynamic and theoretical mixed uses of reductionism and non-reductionism, and (7) reverse reductionism.

The issues related to theoretical research topics were: (8) opaque dark systems, (9) theoretical incompleteness as logical openness, and (10) systemic domains.

With reference to the theoretical nature of the topics covered, we take this opportunity to urge systems researchers not to exhaust their efforts in creating models and simulations. Admittedly, such devices can facilitate unique and important ways of studying complex systems (e.g., the study of stochastic chaos).

However, the increasing availability and amount of data, for instance, via simulations, is useless since data are meaningless if there are no related hypotheses and theories.

We mention how the generalization of the possibility of theory-less knowledge, with theory being replaced by suitable concordance, correlation, and correspondence, for instance, within Big Data, is untenable. Actually, it is possible to detect many cases of specific knowledge being produced without the availability of, or search for, theories, by using concordance, correlation, and correspondence in a data deluge, so-called Big Data [64], using data-driven approaches within very large databases [65]. However, in this regard, the assumption that correlation supersedes causation and theorization has been determined an improper generalization [33].

On the other side, theories should not be understood as the only ideal representations, effective in completely representing and explaining processes and phenomena. In this latter case, real data are considered coincident with solutions of suitably explicit symbolic formal models, i.e., suitable equations even intended as laws, such as in mechanics

and thermodynamics. We may consider examples where we deal with a lack of explicit, symbolic understanding. This is the case, for example, for complex phenomena and processes with multiplicities irreducible to each other, as considered above with DYSAM (see Section 3). This is a matter of non-zippability in formal representations such as processes of emergence, representations, and simulations carried out using sub-symbolic devices, for instance, neural networks whose properties cannot be analytically, symbolically explained but are attributable to the connection weights and levels in the context of equivalence (see Section 5.3).

This, however, does not affect the possibility of establishing effective approaches showing, for instance, the effectiveness of connectionism, evidence-based medicine, and homologous variables, emergence lacking comprehensive theory, the use and modification of networks, and the effects of uncertainty principles. More realistically we should consider future contexts mixing theoretically symbolic, non-symbolic, and data-driven approaches allowing soft theorization and incomplete theorization [65–67].

However, there should also be a focus on pending theoretical topics as the ones considered in this Special Issue *Theoretical Issues on Systems Science*. Research can then have a theoretical nature, which contrasts with the notion of implementing finalized research on demand [68,69]. This seems particularly relevant to contemporary research projects that are pursuant of specific (funded) objectives. We conclude by considering the centrality of theoretical research in systems science, currently disciplinarily oriented rather than inter-disciplinarily oriented, as theoretical research inevitably is.

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Discrete Event Systems Theory for Fast Stochastic Simulation via Tree Expansion

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Abstract: Paratemporal methods based on tree expansion have proven to be effective in efficiently generating the trajectories of stochastic systems. However, combinatorial explosion of branching arising from multiple choice points presents a major hurdle that must be overcome to implement such techniques. In this paper, we tackle this scalability problem by developing a systems theory-based framework covering both conventional and proposed tree expansion algorithms for speeding up discrete event system stochastic simulations while preserving the desired accuracy. An example is discussed to illustrate the tree expansion framework in which a discrete event system specification (DEVS) Markov stochastic model takes the form of a tree isomorphic to a free monoid over the branching alphabet. We derive the computation times for baseline, non-merging, and merging tree expansion algorithms to compute the distribution of output values at any given depth. The results show the remarkable reduction from exponential to polynomial dependence on depth effectuated by node merging. We relate these results to the similarly reduced computation time of binomial coefficients underlying Pascal's triangle. Finally, we discuss the application of tree expansion to estimating temporal distributions in stochastic simulations involving serial and parallel compositions with potential real-world use cases.

Keywords: modeling and simulation; paratemporal methods; tree expansion; systems theory; stochastic simulation; computation complexity; temporal distributions; serial and parallel compositions; computation complexity; temporal distributions; serial and parallel compositions

1. Introduction

Stochastic simulations require large amounts of time to generate enough trajectories to attain statistical significance and estimate desired performance indices with satisfactory accuracy [1–3]. Complex problems such as climate change mitigation, network design, and command and control decision support require search spaces with deep uncertainty arising from inadequate or incomplete information about the system and the outcomes of interest [4–10]. Furthermore, simulation models for system engineering analyses present challenges to today's computational technologies. First, questions addressed at the Systems of Systems (SoS) level require large detailed models to provide sufficient representation of relevant system-to-system interactions of stochastic nature. Second, they also require multiple executions with multiple random seed state initiations to cover the wide range of configurations necessary to obtain statistically significant measurement of performance outcome distributions.

Surrogate models, i.e., simplified models which drastically reduce computation while providing useful guidance, have successfully helped find global optima of computationally expensive optimization problems for real-world applications [11–16]. The methods using such models are often referred to as multifidelity/multilevel/variable-fidelity optimization. We note that the term fidelity is often employed to refer to ambiguous combinations of resolution and accuracy [17,18]. A generic framework was defined [19] in which models

of different accuracy and computation costs are selected algorithmically to reduce the overall computational cost while preserving the accuracy of the simulation analysis. While such frameworks exist, they do not by themselves provide the surrogate models or more generally methods for speeding up the simulation of stochastic systems to support more timely systems analysis and optimization [20–25].

The parallel execution of simulations offers another avenue for the speedup of complex simulations. Unfortunately, exploitation of the parallelization of simulation models for generic system engineering analyses presents challenges to today's computational technologies [26,27]. Although technological advances at the hardware level will enable more and faster processors to handle such simulations, with cloud services adding access to additional resources, such computational support is destined to reach its limit. Therefore, the imperative remains to formulate parallelization in more model-centric ways. Paratemporal and cloning simulation techniques have been introduced that increase opportunities for parallelism [28,29].They also exploit abstractions that recognize the effect of random draws on system evolution as constituting choice points with opportunities for reuse [30]. However, *scalability*, the ability to overcome the combinatorial explosion of branching arising from multiple choice points, presents a major hurdle that must be overcome to implement such techniques.

Nutaro et al. [31] examined the use of tree expansion methods in lieu of the conventional sampling of outcomes when working with the uncertainty inherent in stochastic simulations. Conventional techniques simulate a large number of randomly sampled trajectories from start to finish in one-at-a-time fashion. As illustrated on the left side of Figure 1, such trajectories can be viewed as paths from an initial state of the stochastic system (the root of the tree) to one of the terminal states, leaves of the tree, in a manner consistent with random sampling. The advantage of tree construction is that states of the model that have been reached at any point—nodes of the tree—can be cloned for reuse, thus avoiding duplication. Branches in the tree from a state correspond to draws of the random variable whose values determine the subsequent course of the model from that state.

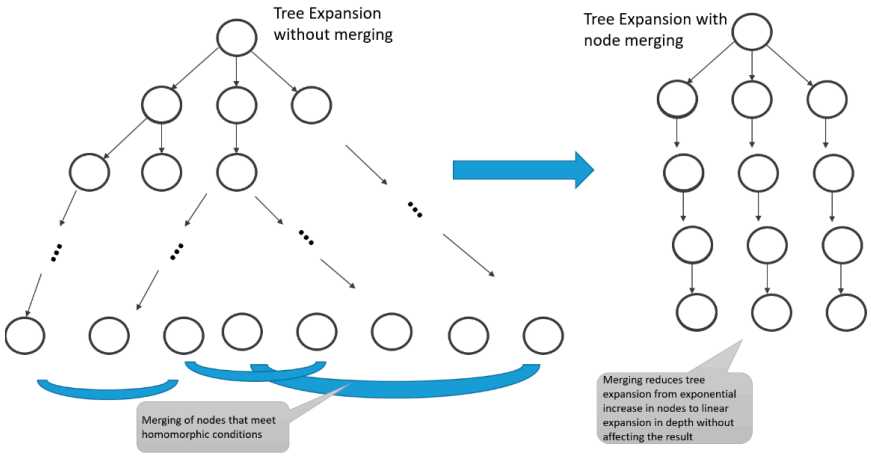

Figure 1. Tree expansion generation of state trajectories (left) and the effect of node merging on tree growth.

In particular, tree expansion with breadth-first traversal can significantly speed up the computation required to generate the same sampling outcomes as the one-at-a-time technique [31]. However, the speedup is limited by the exponential growth of the tree with increasing depth. Zeigler et al. [32] introduced merging of states based on homomorphism concepts to mitigate against such growth. As illustrated on the right-hand side of Figure 1, they showed that such merging can reduce tree growth from exponential to polynomial in depth, thus significantly speeding up computation over that possible with cloning alone.

Parallelizations of such simulations have been developed in which simulations are run until a stochastic decision point is reached. At this point, the current simulation states and

probabilities of branching are saved. Simulations are then spawned for possible branchings until successive downstream branching points are reached, and the process is repeated until a satisfactory level of confidence in outcome distribution has been attained. Besides being efficient in exploration, this "paratemporal" approach is extremely parallelizable for great efficiency in execution on multiple processors.

However, although paratemporal simulations with a small number of branchings and state saves have been demonstrated to be effective, simple implementations of such solutions do not scale as the number of branches increases rapidly for large SoS of current interest.

In this paper, we tackle the scalability problem by first developing a formal framework covering conventional and proposed tree expansion algorithms for speeding up stochastic simulations while preserving the desired accuracy. Based on the theory of modeling and simulation, we review the definition of a discrete event *stochastic* model as an instance of a timed non-deterministic model. Then, we show how a reduced *deterministic* model with random inputs can be derived from such a stochastic model that represents the results of cloning state and transition information at branching points. The reduced model is shown to be a homomorphic image of the original based on a correspondence restricted to non-deterministic states and multi-step deterministic sequences mapped into corresponding single-step sequences. An example is discussed to illustrate the tree expansion framework in which the stochastic model takes the form of a binary tree isomorphic to the free monoid, {0,1}*. At each node, branching occurs with equal probability to nodes at the next level. A computation time of 1 unit is taken to transition from a node to its successor. The output at a state is the number of 1′s in its label. We derive the computation times for baseline, non-merging, and merging tree expansion algorithms to compute the distribution of output values at any given depth. The results show the remarkable reduction from exponential to polynomial dependence on depth effectuated by node merging. We relate these results to the reduced computation of binomial coefficients underlying Pascal's triangle and discuss the application of tree expansion to estimating temporal distributions in stochastic simulations involving serial and parallel compositions. Finally, we mention use cases estimating times to completion for complex processes and potential real-world applications.

2. Formal Framework for Tree Expansion for Stochastic Simulation

We employ the theory of modeling and simulation [33], based on systems theory [34], to develop a formal framework based on Discrete Event Systems Specification (DEVS) for framing the representations needed for paratemporal simulations. As in Figure 2, to capture the effect of cloning on the source stochastic simulation, we derive other representations including concepts of non-deterministic models and semigroup monoid algebras.

2.1. Definitions

We review some definitions to proceed.

Definition 1. *A **timed non-deterministic model** is defined by M = <S, δ, ta>, where $\delta \subseteq S \times S$ is the non-deterministic transition relation and ta: $\delta \rightarrow R^{\infty}_{0}$ is the time advance function.*

We say that M is as follows:

- *Not defined* at a state, if there is no transition pair with the state as its left member;
- *Non-deterministic* at a state, if the state is a left member of two transition pairs;
- *Deterministic* at a state when there is exactly one outbound transition (a left member of exactly one transition pair).

Remark: Formulating a transition system in relational form as in Definition 1 allows us to include both stochastic and deterministic discrete event systems within a common framework as follows:

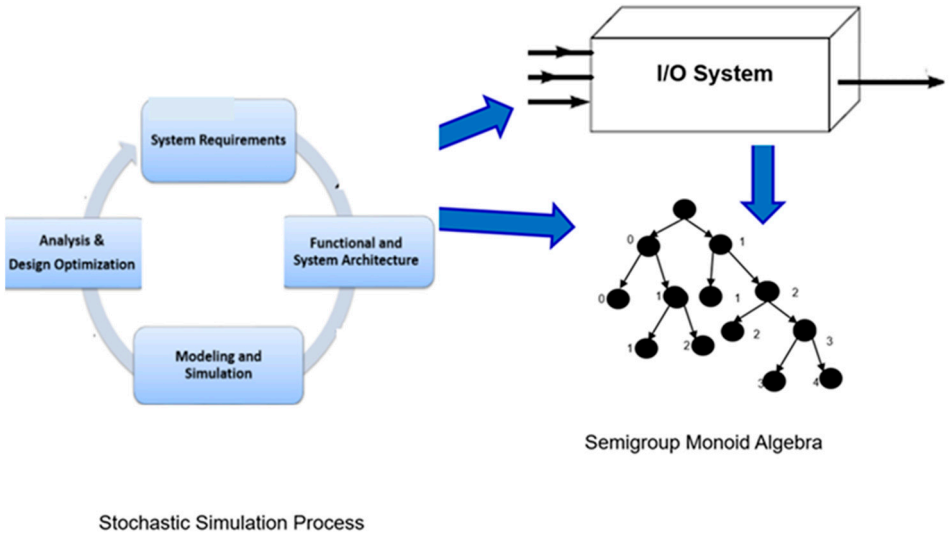

Figure 2. DEVS-based framework for framing the representations needed for paratemporal simulations.

A *stochastic* model is a timed non-deterministic model defined in all of its states.

A *deterministic* model is a timed non-deterministic model (Figure 3) deterministic in all its states.

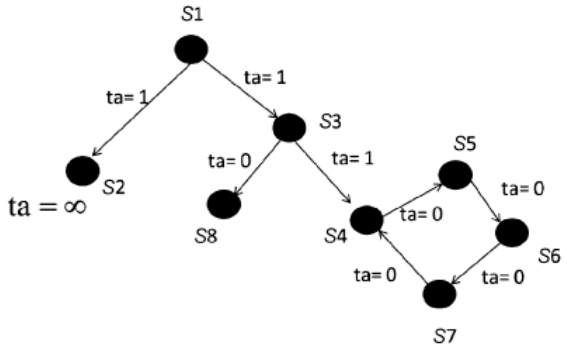

Figure 3. Timed non-deterministic model.

Clearly, deterministic models are a subset of stochastic models.

In application to paratemporal simulation, a non-deterministic state is known as a *random draw state*. We make this identification in a later section after introducing DEVS Markov models.

Definition 2. *A state trajectory connecting a pair of states, s and s′, is a sequence* $s_1, s_2, \ldots, s_n$ *which starts with s and ends with s′ and satisfies the transition relation, i.e., where* $s_1 = s$, $s_n = s'$ *and* $\delta(s_i, s_{i+1})$ *for* $i = 1, \ldots, n-1$.

Definition 3. *A deterministic state trajectory is a state trajectory containing only deterministic states. The time to traverse a deterministic state trajectory is the sum of the transition times associated with the successive pairs of states in its sequence.*

We can remove deterministic states from a stochastic model and replace multi-step deterministic trajectories with single-step trajectories to represent the effect of cloning simulations. Given a stochastic model, $M = <S, \delta, ta>$, we define a reduced version that contracts deterministic sequences into single-step transitions:

Definition 4. *The clone-reduced version of stochastic model* $M = <S, \delta, ta>$ *is*

$$M' = <S', \delta', ta'>$$

where

$S' \subseteq S$ *is the subset of non-deterministic states of M*
$\delta' \subseteq S' \times S' = \{(s,s') \mid$ *if there is a deterministic state trajectory connecting s and s'}*
and ta': $\delta' \rightarrow R_0^{\infty}$

where

$$ta(s,s') = ta(s,s')\ if\ both\ s\ and\ s'\ are\ non-deterministic states = the\ traversal\ time\ of\ the\ deterministic\ state\ trajectory\ connecting\ s\ and\ s'$$

We can prove the following.

2.2. Assertion 1

The reduced model is a homomorphic image of the original based on a correspondence restricted to non-deterministic states and multi-step deterministic sequences mapped into corresponding single-step sequences (Figure 4).

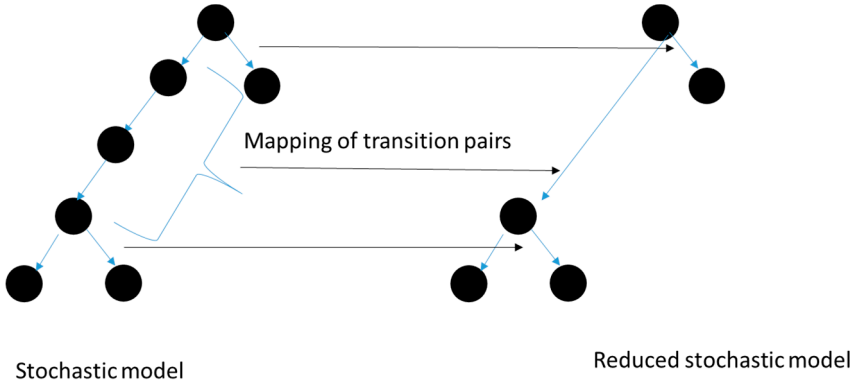

Figure 4. Mapping of timed non-deterministic model to reduced version.

We note that the transversal time from any non-deterministic state to any other is preserved in the reduced version. However, the advantage of constructing this representation is that the computation (in simulation) of a multi-step sequence can be replaced by a look up of a table (cloning) when the branching is encountered subsequently.

Definition 5. *A stochastic input-free DEVS has the following structure* [33]*:*

$$M_{ST} = \langle Y, S, G_{int}, Pint, \lambda, ta \rangle$$

where Y, S, λ*, and ta have the usual definitions* [35].

Here G_{int}: $S \rightarrow 2^S$ is a function that assigns a collection of sets $G_{int}\ (s) \subseteq 2^S$ to every state s.

The probability that the internal transition carries a state s to a set $G \in G_{int}\ (s)$ is given by a function $P_{int}\ (s,G)$.

For S finite, we let

$$P_{int}(s,\ G) = \sum_{s\_ \in G} Pr(s,\ s')$$

where $Pr(s, s')$ is the probability of transitioning from s to s'.

As defined in [33], the key to formalizing a semi-Markov model in DEVS is the definition of two structures. One corresponds to the usual matrix of probabilities for state transitions. The other assigns to each transition pair a probability density distribution over time. The choice of the next phase in the DEVS is made first by sampling the first matrix. Then, the transition from the current phase to the just-selected next phase is given a time of transition by sampling the distribution associated with that transition. More formally, this is formulated by the following:

Definition 6. *A pair of structures, probability transition structure, PTS = <S, Pr>, and time transition structure, TTS = <S, τ>, gives rise to an input-free DEVS Markov model* [33]. M_{DEVS} = <Y,$S_{DEVS,}$ δ_{int}, λ, *ta*>, *where* $S_{DEV\,S}$ = $S \times [0, 1]^S \times [0, 1]^S$, *with typical element* (s, γ_1,γ_2) *with* γ_i: $S \rightarrow [0, 1]$, $i = 1, 2$, *where,*

δ_{int}: $S_{DEV\,S} \rightarrow S_{DEV\,S}$ *is given by*
δ_{int} (s, γ1,γ2) = s′ = (*SelectPhase* G_{int} (s, γ1), γ1′, γ2′)
and ta: $S_{DEV\,S} \rightarrow R^{+}_{0,\infty}$ *is given by*
ta(s,γ1,γ2) = *SelectSigma* $_{TT\,S}$ (s, s′,γ2)
and γi′ = Γ(γi), $i = 1, 2$.

The input-free DEVS Markov model is introduced as a concrete implementation for non-deterministic models. On the one hand, such models are constructible in computational form in such environments as MS4 Me [36]. On the other hand, we can explicitly define how such models give rise to non-deterministic models as in the following:

2.3. Assertion 2

An input-free DEVS Markov model $M_{DEV\,S}$ = <Y,$S_{DEV\,S,}$ δ_{int}, λ, *ta*> specifies a non-deterministic model M = <S', δ', *ta'*>, where S'= S_{DEVS}, $\delta' \subseteq S' \times S'$ is given by (s_1,s_2) is in δ' if, and only if, there exists γ_1 in [0, 1],γ_2 in [0, 1], such that, δ_{int} (s_1, γ_1,γ_2) = s_2, and *ta'*: $\delta \rightarrow R^{\infty}{}_0$ is given by *ta'*(s_1,γ_1,γ_2) for the same pair (γ_1,γ_2) that placed (s_1,s_2) in δ′.

Essentially, this assertion shows how a transition from state s_1 to s_2 is possible if there is a random selection of s_2 from the set of possible next states of s_1 (as determined by the seed γ_1), and the time for such a transition is given by a sampling from the distribution for traversal times determined by the seed γ_2.

3. Illustrative Example

To create the models needed to illustrate the framework of Figure 1, consider a binary tree of depth 3 with root labelled by the empty string and each node labelled by a string of 0's and 1's corresponding to the path to it from the root. At each node, a choice is made to select the successor to which to transition with equal probability. A computation time of 1 unit is taken to transition from a node to its successor. The output at a state is the number of 1's in its label. We write the formal representation as a DEVS Markov model as follows:

$$M_{DEV\,S} = <Y, S_{DEV\,S,}\ \delta_{int}, \lambda, ta>$$

$$Y = \{0, 1, 2, 3\}$$

S = {0, 1, 00, 01, 10, 11, 000, 001,. . .111} (nodes in a binary tree of depth 3 labelled by strings corresponding to the path accessing them). $S_{DEV\,S}$ is the set of pairs of the form *(s,* γ*)* where s is a member of S (a node) and γ is a state of an ideal random number generator, such that Γ *(*γ*)* is the next state of the random generator (for simplicity, the time advance will be constant so an additional random variable is not needed).

G_{int} *(s)* = {s_0, s_1}, the subset of nodes that are immediate successors of node s in the binary tree and

$$s' = \delta_{int}\ (s, \gamma) = (SelectPhase\ Gint\ (s, \gamma), \Gamma(\gamma))$$

where *SelectPhase* G_{int} *(s,* γ*)* uses the random number state γ to select the successor node from G_{int} (s) with equal probability.

$$ta(s,\gamma) = 1$$

And λ*(s)* is the number of 1's in the label of s.

The desired outcome of the simulation is the average of the values of the nodes.

To illustrate the applicability of homomorphism and the minimal realization concept, we will show how it provides insight into the merging of states for tree expansion.

We will compare the following three algorithms:

1. The baseline algorithm generates all trajectories one at a time, accumulates the number of 1's for each, and averages the results.
2. The tree expansion algorithm generates all nodes in breadth-first traversal without repetition, obtaining the same information and performing the same average.
3. The node merging algorithm based on the minimal realization modifies tree expansion by maintaining only the representatives of equivalent classes as successive levels are generated while maintaining the size of the classes as they are developed. The values of the classes are summed weighted by the respective sizes to obtain the desired average.

The node merging Algorithm 1 is sketched in the following:

Algorithm 1. Node merging tree expansion algorithm.

A node n contains data {s, num) where s is a string in {0,1}* and num is the number of nodes equivalentTo n.
The root node = (λ,1) //λ is the empty string
is the empty string
Initiation: Current node = root node; newLeaves = {}, oldLeaves = {(λ,1)}
Termination: depth = D
Output: For each i = 1,2,. . .,D the number of strings having number of ones equal to i.
Depth = 0

Recursive step:
While (depth < D)
For each node, n = (s, num) in leaves{
For each branch, b in {0, 1}{
Create child, c = {sb, num) // extend parent's string and inherit parent's number of represented equivalents
If c is Equivalent To some node, m = {t, num') in newLeaves,
Then set m = {t, num'+num)
Else add c to newLeaves.
}
depth = depth+1
oldLeaves = newLeaves,
newLeaves = {}
}
n = (s, num) isEquivalentTo m = {t, num') if, and only if, s and t have the same number of ones
//Note that only the leaves at each level (including at the final depth) are kept as the expansion advances as required by the required output.

To analyze this example, we will start with the semigroup monoid system (as in the Appendix A) unfolded to the depth = 4, as shown in Figure 5. The leaves of the tree are labelled with the final states listed above, and traversing the tree from root to leaves reveals 16 branching routes. We will proceed to obtain various computation times generalized to the case of a tree of arbitrary depth n, as presented in Table 1. The computation time for the baseline algorithm is computed as the number of branching routes (2^n) times the depth (n) taking unit computation time per step. The smallest number of computations when reusing earlier nodes is to expand the tree starting at the root and proceeding to expand new leaves successively at each level in breadth-first traversal. This requires $2(2^n-1)$ computations, as shown in the table. Therefore, the reduction in computation time is $n2^n/2(2^n-1)$ which is of order O(n).

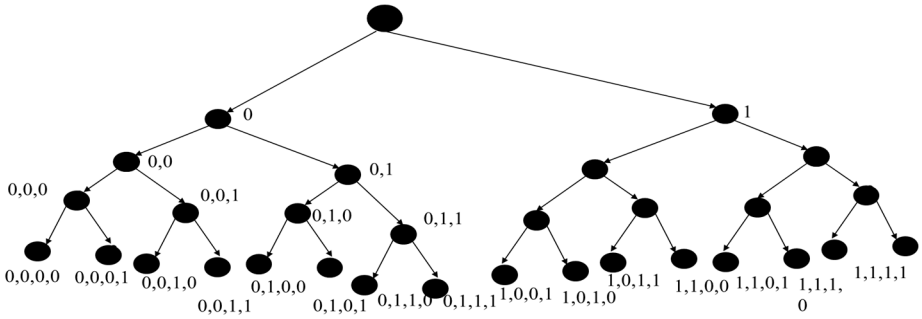

Figure 5. Semigroup monoid system of illustrative example.

Table 1. Analysis of illustrative example.

Computation Time for	General Case	Illustrative Example n = 4	Reduction Ratio
Baseline algorithm	$n2^n$	$4 \times 16 = 64$	
Reuse earlier nodes	$2(2^n - 1)$	$2 \times (2^4 - 1) = 30$	O(n)
Minimal realization	$n(n + 3)/2$	$2 + 3 + 4 = 9$	$O(2^n/n^2)$

The minimal realization of this model, shown in Figure 6 to depth = 3, recognizes that all nodes labeled (x1,x2,x3) with the same sum (x1 + x2 + x3) can be grouped into the same congruence class. The justification of congruence is easy to see in this case: the 0 input keeps such an element in the same class, while the 1 input transitions it to the class having a sum increased by 1. With the merging of nodes, the tree expands in a manner emulating Pascal's triangle for computing binomial coefficients [37]. At any depth n, there are a total of 2^n subsets of sizes ranging from 0 to n with cardinalities given by the binomial coefficients. For example, at depth 3, there are 1,3,3,1 subsets of sizes 0,1,2,3, respectively. With the size of a subset representing the number of 1's in the same equivalence class, we see that the average number of 1's will equal n/2, as expected. Importantly, the number of nodes, and hence the computation time, grows only as the square of n rather than exponentially, as shown in Table 1. The computation time is now $O(n^2)$ (square) in the depth of the tree, and the reduction is of *exponential order—which would be exceedingly impressive to achieve in real-world application*!

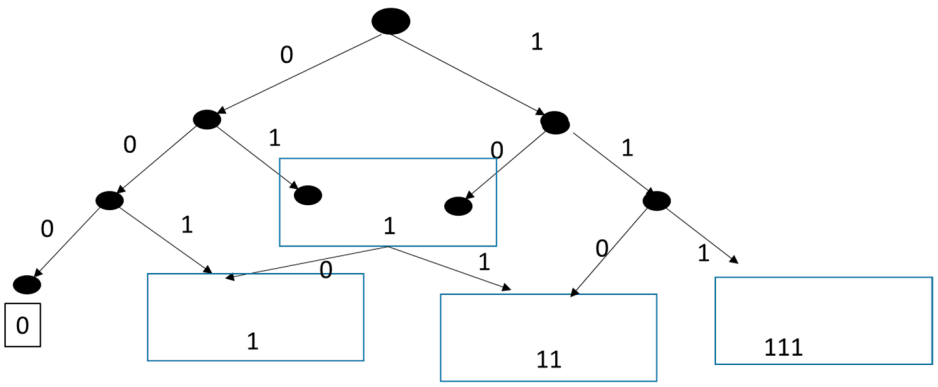

Figure 6. Minimal realization of example tree.

4. Empirical Confirmation of Theory Predictions

To test the theory and its implementation, the illustrative example was implemented in Java and executed to compare computation times with those predicted from Table 1. Figure 7 shows that the relative computation times of the merged, unmerged, and baseline algorithms fall in the order of that predicted in Table 1. However, Figure 8 shows that the

actual speedup realized by merging relative to the baseline is approximately 50 times less than predicted. Nevertheless, the speedup achieved at depth 22 of approximately 7000 is still highly significant. Note: the baseline algorithm exceeds the memory available at depth 23 due to the exponential node growth. Trees up to depth 1000 with 10 replications for each were tested to obtain the timing results, and all yielded the correct outcome distribution.

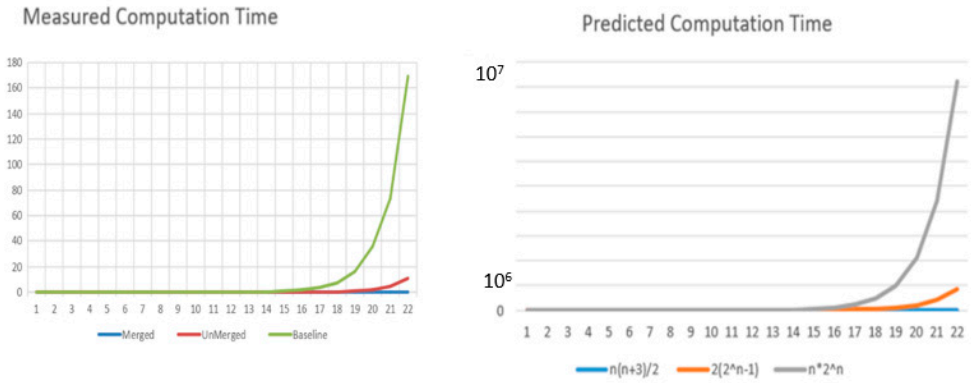

Figure 7. Charts of measured and predicted computation time resp. (in seconds).

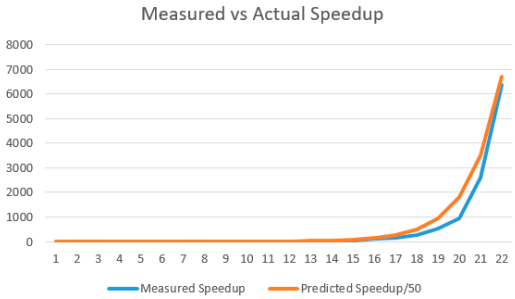

Figure 8. Measured speedup of baseline relative to merged tree expansion vs scaled predicted speedup.

5. Tree Expansion with Merging Applied to Serial and Parallel Compositions

Serial and Parallel compositions of simple DEVS Markov models illustrate how merging in tree expansion can work in a large class of stochastic systems to greatly control node generation and computation time. To succeed, a serial composition entails the success of each of its components; likewise, it fails if any one of its components fails [38]. In contrast, the success of a parallel composition requires that only one of its components succeeds, while its failure entails the failure of all the components.

The component models in the compositions are of the form of a DEVS Markov model (not including input and output), as shown in Figures 9 and 10.

The transition structure of the model is specified by two parameters, $P_{Succeed}$, the probability of success, and $\tau_{succeed}$, the probability distribution for the time required to achieve success. These populate the values of the probability and the time transition structures needed for the definition of the model, which is given as follows:

$$M_{DEV\,S} = < Y,\ S_{DEV\,S},\ \delta_{int},\ \lambda,\ ta >$$
$$Y = \{Succeed,\ Fail\}$$
$$S = \{Start,\ Succeed,\ Fail\}$$

$S_{DEV\,S}$ is the set of triples of the form (s, γ, μ) where s is a member of S (a node) and γ, μ are states of ideal random number generators for selecting between the transitions from *Start* to *Succeed* or *Fail* and for selecting the time distribution for the transition to Succeed, if selected. The time for the transition to *Fail* is not of interest here so no random seed is associated with it.

G_{int} *(Start) = {Succeed,Fail}* the subset of nodes that are immediate successors of node *Start*, and $s' = \delta_{int}$ *(Start,* γ*,* μ*) = (SelectPhase* G_{int} *(Start,* γ*),* Γ *(*γ*),* μ*)*, where the latter uses the random number seed γ to select *Succeed* with probability P_{Succeed}, and *Fail* with probability $1 - P_{Succeed}$. *ta(Succeed,* γ*,* μ*) = (SelectSigma* G_{int} *(Start,* γ*,* $\Gamma(\mu)$*)* which selects the time required to succeed from the given distribution, τ_{succeed}, and λ is the time selected for the time advance.

Serial and parallel compositions in Figures 9 and 10 are defined using the standard DEVS coupled model specifications [33]. As illustrated in Figure 11, the temporal behaviors of the compositions are directly derived from those of the components and the coupling specified by the respective composition.

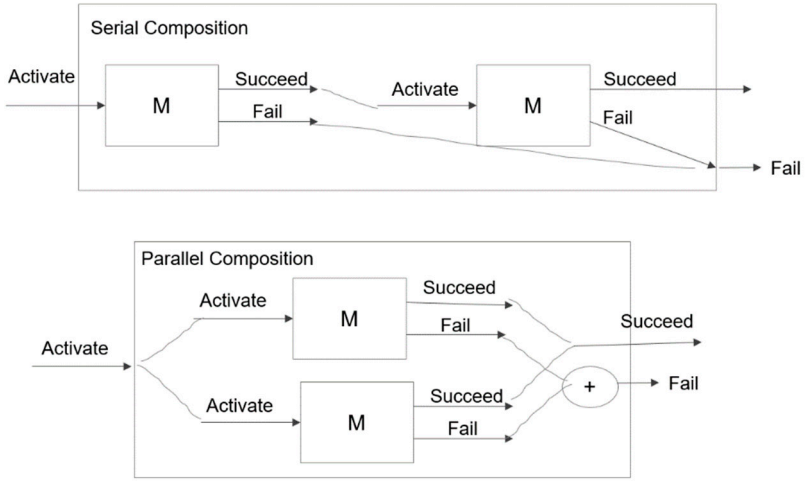

Figure 9. Serial and parallel compositions of Markov DEVS Success/Fail models.

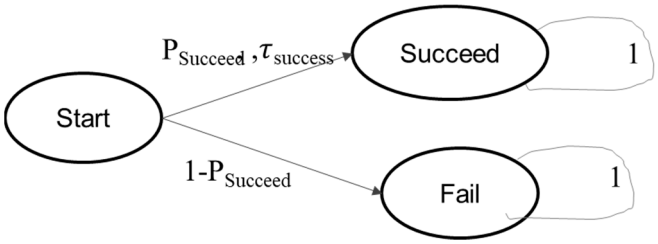

Figure 10. Probability and time transition structure of the DEVS Markov model.

In the serial composition, the Activate input is shown setting the first (top) model, M into state Succeed with an output after time *ta*. The latter is determined by the random sampling process just described and shown as a threshold value for the elapsed time, *e* to achieve. This output, Y is coupled to the input of the second component (bottom) model, M′ and causes it to output a final Success after ta′ for a total response time of *ta + ta′*.

In the case of the parallel composition, the Activate input starts both models simultaneously and results in a Success output from the quickest model at time *min{ta,ta′}*.

These paired configurations are easily generalized to finite numbers of components where, for the serial composition, components are placed in a sequence with the Success output port of one connected to the Activate input port of the next, and for the parallel composition, all components receive activation simultaneously with all output Success ports coupled to the overall output Success port. The desired outcome of the simulations of the compositions is the probability distribution of time needed for success. In the serial case, a sampled value of this outcome is the sum of the time samples from each component since all have to succeed for the whole to succeed. In the parallel case, a sampled outcome is the minimum of the sampled durations of the components since overall success is achieved by

the first to succeed. Analytic solutions such as those by Rice [38] are possible given analytic input distributions, but stochastic simulation is needed otherwise.

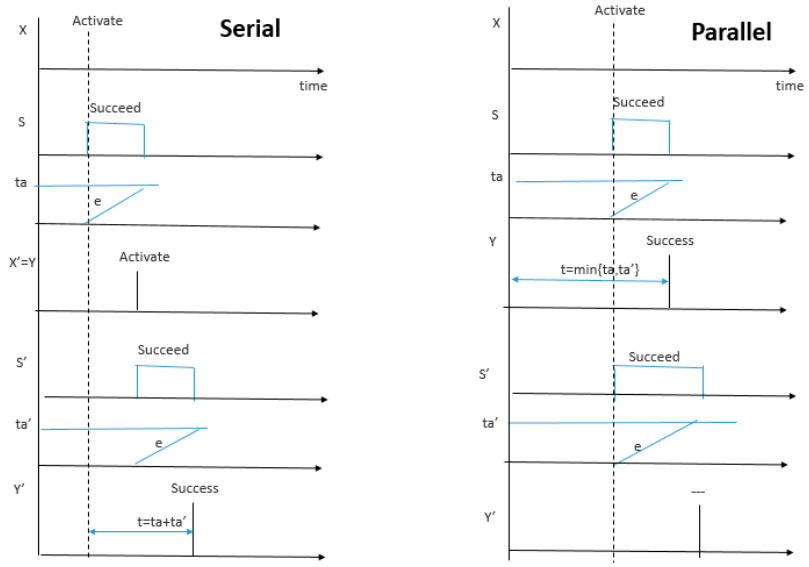

Figure 11. Temporal behaviors of serial and parallel compositions.

Computation Time Required for Serial and Parallel Compositions

In application to serial and parallel compositions, the number of components determines the depth of the tree, n. The temporal distribution of each component is assumed to be known and represented by a discrete probability density over an interval divided into G segments, where G is called the number of granules and determines the accuracy of the computed outcome. In the following, we simplify the discussion by considering only the case where the probability of failure is zero.

Tree expansions for the series and parallel compositions in Figure 12 evolve with G branches stemming from each node. For the serial compositions, with the first model at level 1, each of the G branches from the root is labelled by the time advance corresponding to the granule represented by that branch. For each of the nodes generated by such branching, the second model's response is represented by the branching of G nodes at level 2 labelled by the time advances corresponding to each. Response times, $t = ta + ta'$, for the composition are accumulated in the nodes terminating the paths labelled by the pairs of branches. In the case of parallel composition, the only difference is that the minimum operation is applied to the pair of time advances to be stored in the node terminating the corresponding path.

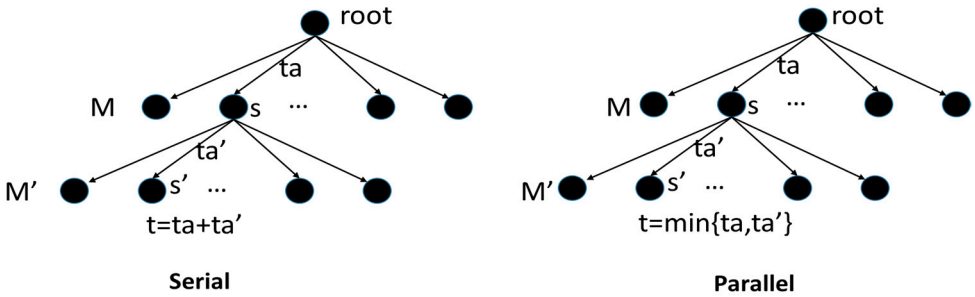

Figure 12. Illustrating tree expansions for series and parallel compositions.

Therefore, we see that in both serial and parallel compositions, the unmerged tree expands with G^n nodes at depth n. However, as the tree front expands, applying the merging process to nodes at the same level greatly reduces the number of nodes that must

be considered as the depth increases. Merging in the case of **serial** composition only adds G nodes at each level, thus reducing the growth in nodes to nG. This is so since at each successive level the range of sum ta + ta′ is bounded above by $max\{ta\} + max\{ta'\}$. Thus, after merging, only G new nodes are added to that level. Moreover, at each level, the number of operations is at most nG^2 since the nG nodes are combined with the G granules to create the next level. Thus, the incremental computation time is nG^2, and the computation time required should grow as $O((nG)^2)$, i.e., as the square of depth and number of granules.

Merging in the case of **parallel** composition does not suffer *any* tree expansion since the combined range of a minimization is the original range, i.e., range of min{ta,ta′} is bounded above by min{max{ta},max{ta′}}. Thus, by the reasoning above, the number of nodes grows as n*G and the operations grow as nG^2. So, the computation time required for depth n should grow as $O(nG^2)$, i.e., linearly with the depth and square of granules.

6. Related Work

DEVS has served as a basis for the formalization [38,39] and study of multiresolution constructions underlying multifidelity simulations [40–45]. Also, DEVS has been employed as a basis for the simulation of Markov Decision Process (MDP) models employing its modular and hierarchical aspects to improve the explainability of the models with application to optimization processes such as financial, industrial, etc. [46–52]. Capocchi, Santucci, and Zeigler [53] introduced a DEVS-based framework to construct and aggregate Markov chains using a relaxed form of lumpability to enhance the understanding of complex Markov search spaces. However, the methodology is limited to selecting optimal partitions according to a metric that compares Markov chains based on their respective steady states. The practical application is limited since these are not generally available in problem specification. In contrast, paratemporal and cloning simulation techniques are intended for application to stochastic simulation in general and offer opportunities for parallelism and cloning of state information. However, they have not demonstrated the ability to overcome the combinatorial explosion of branching arising from multiple choice points. The absence of such scalability presents a major hurdle that must be overcome to implement such techniques. Nutaro et al. [31] showed that the speedup of tree expansion methods is limited by the exponential growth of the tree with increasing depth. Zeigler et al. [54] introduced the merging of states based on homomorphism concepts to mitigate against such growth. Here, we demonstrated that homomorphic merging of states can be formally characterized using DEVS Markov modeling and simulation theory to show examples where such merging can achieve a reduction from exponential to polynomial computational effort.

7. Conclusions and Further Work

We have developed a formal framework covering conventional and proposed tree expansion algorithms for speeding up stochastic simulations while preserving the desired accuracy. Based on the theory of modeling and simulation, we showed how a reduced deterministic model with random inputs can be derived from such a stochastic model. This reduced model represents the results of cloning state and transition information at branching points. The reduced model was shown to be a homomorphic image of the original based on a correspondence restricted to non-deterministic states and multi-step deterministic sequences mapped into corresponding single-step sequences. An example was discussed to illustrate the tree expansion framework in which the stochastic model takes the form of a binary tree, allowing us to derive the computation times for baseline, non-merging, and merging tree expansion algorithms to compute the distribution of output values at any given depth. The results show the remarkable reduction from exponential to polynomial dependence on depth effectuated by node merging. We related these results to the reduced computation of binomial coefficients underlying Pascal's triangle.

Applications of node merging tree expansion algorithms are currently being studied in simulations of space-based threat responses to estimate the probability of successfully

identifying, tracking, and targeting hypersonic missiles within tight deadlines [38], as well as to attrition modeling employing stochastic interactions between opposing forces [55–60]. In such models, temporal duration outcomes in the form of probabilistic temporal distributions play a major role, and homomorphic merged tree expansion enables much faster computation of outcome distributions when analytic solutions are lacking.

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Appendix A

Please refer to [61,62] for a detailed exposition.

We define the behavior of a system formally as a function mapping input segments to output segments (Figure 6). We seek a DEVS model at the state description level that generates the defined behavior and then try to show it is a minimal realization or attempt to reduce it to one that is minimal.

We briefly review the approach to deriving a minimal realization from an input time function description. Figure A1a shows the behavior of a modulo 2 adder, and the minimal realization is in Figure A1b. The latter has two states corresponding to the two distinct nodes with transitions reflecting and alternating pattern exhibited by the derivatives of the behavior β in the tree. The alternating pattern is manifested by noticing that $\beta_0(\omega) = \beta(0\omega)$ and $\beta_1(\omega) = \beta(1\omega)$ so that the state "0" transitions to itself under input 0 and transitions to the state "1" under input 1.

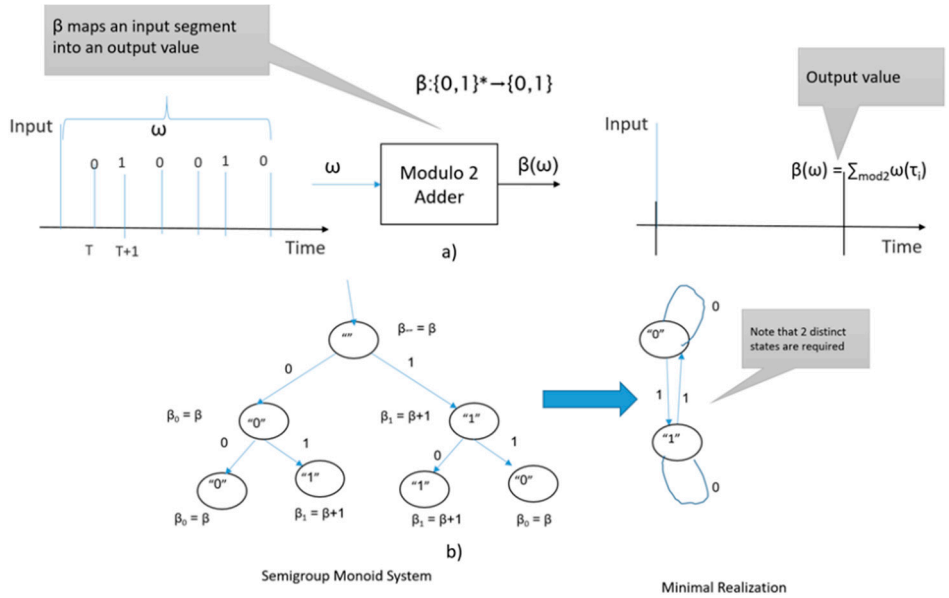

Figure A1. (**a**) Mapping input segments to output segments, (**b**) states reduction and minimal realization. Note: {0.1}* denotes the set of all finite strings over {0,1}.

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systems

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Synchronization and Patterns in Human Dynamics

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Abstract: We examine couplings, synchronization, pattern formation, and transformation in human dynamics. We consider intraindividual and interpersonal relations as coevolution dynamics of heterogeneous mixed couplings, synchronizations, and desynchronizations. They form the dynamic patterns of the embodied Self and organize intersubjective dynamics. We critically review various models with differing levels of complexity and degrees of freedom. The Fokker–Planck equation clarifies the balance between determinism and stochasticity. The HKB and Kuramoto models describe complex synchronization and pattern formation dynamics. Chimera states are ubiquitous in the mixed networks of human dynamics. Coupling, synchronization, and patterns form and transform, with gaps in between. We propose a formal model for these complex, mixed, and heterogeneous dynamics. Multidimensional theoretical models can represent the specific nature of human interactions and the dynamic structure of the embodied Self. The embodied Self emerges during a developmental process and retains its dynamical nature by continuously adapting to the ever-changing landscape of affordances of daily life.

Keywords: synchronization; biosemiotics; pattern; information; cognitive neuroscience; psychology; emotions; chimera states; statistical dynamics; coupling

1. Introduction, Complex Human Dynamics

The progress of studies on synchronization and coordination dynamics in mammals and humans has created a platform for an integrated science of human dynamics [1–4]. On this basis, further studies on intersubjective synchronization have shown that complex human systems operate through sophisticated coordination mechanisms governed by interconnected biological and semiotic networks. Semiotics studies signs, symbols, and meaning-making processes that are fundamentally integrated with human biological processes [5]. Research demonstrates that coordination occurs across multiple scales, exhibiting stability, instability, and change patterns throughout these systems. These systems display diverse patterns from molecular biology to social dynamics [6]. Unique patterns emerge, evolve, and adapt through coupling and synchronization, filling functional gaps. The dynamic organization of complex systems relies heavily on synchronization and pattern formation processes [7]. Synchronization manifests as time-organized activities that coevolve with spatial patterns, while spatial configurations and boundary structures can influence various forms of synchronization. Information flow within these systems saturates new patterns until transitions occur. The relationship between morphology and

synchronization is particularly evident in biological systems [8]. Neural network architecture supports the rhythmic firing of neurons. Concurrently, synchronized activity can lead to new patterns, as evident in developmental processes where coordinated cellular movement contributes to the formation of intricate structures. Within neural networks, synchronized neuronal firing generates oscillatory patterns essential for cognitive functions, such as memory and perception. The connectivity patterns within these networks significantly influence the emerging functional patterns. Similar principles apply to other biological systems. One example is the coordinated contraction of heart muscle cells, facilitating adequate blood circulation. Language plays a crucial role in scaling synchronization dynamics, functioning both as a synchronization medium and a regulatory tool across different communication levels [9]. The study of information dynamics reveals how information flows through these systems over time, including its generation, transfer, storage, and transformation. Considering internal and external interactions, this framework helps explain the emergence, stabilization, and transition of coordination patterns in human dynamics [10]. These complex patterns and interactions are fundamental to understanding human systems across multiple disciplines, from materials science to neuroscience and biosemiotics. Integrating these elements creates a comprehensive framework for studying human dynamics and underlying mechanisms. Integrating diverse expertise in human dynamics is essential for achieving significant advancements in this emerging field of dynamical systems research [11].

The notion that the embodied Self is a complex dynamical system has gained attention in various fields, including cognitive neuroscience, psychology, and philosophy. It suggests that the Self can be understood and described using the principles of complex systems theory [12–16]. Complex dynamical systems refer to systems that exhibit emergent behavior arising from the interactions between their components. Nonlinearity, feedback loops, sensitivity to initial conditions, and self-organization are characteristics of these systems. They often demonstrate adaptability, resilience, and the capacity to transition through phase changes while maintaining system cohesion. When applied to the embodied Self, considering it a complex dynamical system implies that it emerges from the interactions between its various sub-systems, such as neurodynamics, thoughts, emotions, memories, beliefs, social influences, actions, physiology, and biological foundations. These configurations interact with each other in dynamic ways, with a high degree of freedom, leading to the emergence of self-organization and self-regulation. Considering the Self as a complex dynamical system offers a framework for understanding the intricate interplay between internal and external factors, the constant adaptation to environmental change, and the emergent properties that arise from the system's interactions. A formal model of the embodied Self can ground human dynamics in complexity science. We will explore theoretical and empirical research leading to a robust and parsimonious model.

Emotions are particularly relevant in the dynamical integration of the embodied Self. They constitute the bridging matrix that integrates "biological and mental" regions of the PsycheSoma with a pertinent history of theoretical and empirical research [17–19]. An emotional sense of personal identity provides a foundation in everyday life. William James [20,21] defined this nucleus of our Self-identity as "the very sanctuary of our life." In parallel, our biological selves continually regenerate as cells are constantly replaced, while the immune system ensures that our biological identity persists and evolves [22,23]. This view of the integrated nature of the body and the Self echoes Maurice Merleau-Ponty [24,25]. The proto-self may be dynamically centered in a critical brain area, specifically within the center-medial diencephalic midbrain areas, such as the Periventricular and Peri-Aqueductal Gray (PAG), and nearby tectal and tegmental zones [19]. Walter J. Freeman extended this

core to other brain areas [26,27], as he located the emotional primary Self within the network of the limbic system. The limbic system, often called the paleo-mammalian cortex, is a collection of brain structures on either side of the thalamus, just below the medial temporal lobe. It works with emotions, intentional behaviors, long-term memory, and olfaction. It is a system that integrates sub-units with different functions, all relevant to the primary Self. Its systemic structure entails neuro-psychological pattern dynamics between areas and functions. Freeman considered the neural populations that compose the limbic system to be the key to understanding the biology of intentionality as the principal agent of action in space and time [27]. Studying and modeling human synchronization and pattern formation can provide crucial insights into the dynamical organization of the embodied human Self.

2. Materials and Methods, Synchronization and Pattern Formation

Terry Marks-Tarlow [28] further developed a perspective of the Self as a dynamical system. In this way, we can understand how the Self is a process of patterns continually formed, destroyed, and reconstructed by local interactions occurring at multiple levels in the brain, emotions, attachment relations, and narrative culture. The Self is an open system, a dissipative structure characterized by metastability, which requires a continuous flow of energy, matter, and information. Marks-Tarlow emphasized its self-organization, degrees of freedom, and continual regeneration while open to the environment. Independently, Tschacher and Rössler [29] conceived the Self as a self-organized system whose attractor-like homeostasis is maintained through repeated calibrations, such as in empathetic social exchange. David Pincus proposed that the Self has an interconnected fractal structure based on self-organization dynamics [30,31]. This complex and dynamic organization fosters systemic resilience.

The self-organizing Self is grounded in relational coordination dynamics. Building on Bowlby's observations [32,33] regarding attachment behavior, psychobiologists explored the mother-infant bond as a significant coupling organization primarily governed by inner emotional signals from its early stages of development. Myron Hofer and other developmental biologists revealed numerous hidden regulatory mechanisms in studies of rodents and primates [34,35]. These concealed factors influence various sensory channels: nutritional, olfactory, tactile, thermal, visual, and vestibular. Evidence for entrainment and coupling in physiological and semiotic domains holds at the emotional level. Research on infants suggests that not only are the emotions and responses of the mother or other primary caregiver critical in shaping the developing baby's sense of self, but the reverse is also true. There is a bidirectional influence, or mutual co-regulation, between the infant and the caretaker, through which they are coupled in coordination dynamics within a bipersonal field. These early dynamics provide the matrix for developing the primary embodied Self.

Most regulatory mechanisms remain hidden from a passive third observer outside the bipersonal fields and can be discovered in controlled settings. Similar hidden regulatory mechanisms in humans persist into adulthood; however, other emotional, cognitive, and social factors also influence their functioning. The interactions between the Self and its primary relations regulate the psychosomatic balance, and the reciprocal influence can be modeled by nonlinear dynamical theory [36,37]. Non-reductionist models delineate complex feedback systems marked by multiple layers and directions of causality. Extensive work on the neurophysiology of development highlights the embodied entrainment and mixed synchronizations between mother and child [38,39]. Emotions are placed as the crucial area of embodiment [40]. They are also shaped through active adaptation to culture, which serves to maintain, regulate, and sometimes challenge the cultural environment

to which they are tuned. Multilayered coupling is evidence of a reciprocally interactive relationship between culture and the embodied selves [41]. Each subsystem appears to contain interaction patterns across partially open boundaries and feedback loops operating in bottom-up and top-down directions. This perspective is also taken in the field of network physiology.

The process that supports human selfhood is integrating the PsycheSoma as a biosemiotic complex system. Hoffmeyer presents a semiotic interpretation of biology, suggesting that organic relations are grounded in meaning [5,42,43]. He combines the work of Charles Peirce and the Umwelt theory of Jacob von Uexküll to demonstrate how the interaction, exchange, and development underlying biological order are fundamentally semiotic processes. When animals perceive patterns in their surroundings and use them to guide their actions, they respond to stimuli and interpret signs, coupling with their environment, making it their *Umwelt.* James Gibson referred to this as 'affordance' in his theory of direct perception [44]. Affordance transcends the subjective-objective dichotomy, enabling us to understand the integration of biopsychosocial couplings. An affordance points both ways, to the environment and the subject. Thought exists within us, yet we exist within thought; just as our minds produce language and rely on the brain's mechanisms, we are immersed in language, which predates each of us and shapes our growth and learning. Furthermore, unless we are immersed in language, our brain cannot generate it, and vice versa: if our brain were incapable of developing language, we would not be immersed in it [45]. The conclusion is that the embodied Self is a biosemiotic process that emerges from and within a web of patterns. The PsycheSoma appears to be predisposed to achieve selfhood. Reciprocal and circular causal relations between multiple pattern levels are autopoietic, enabling recovery, repair, and reorganization within the threefold distinction of time scales proposed by Francisco Varela [12,46]. These include the elementary scale (varying roughly from tens to hundreds of milliseconds), the integrative scale (ranging from about 0.5 to 3 s), and the narrative memory scale (exceeding 3 s). Varela characterized these dynamics as having self-generating operational closure. Varela used the term "operational closure" in its mathematical sense, referring to a recursive process not isolated from interactions. Varela's notion of a selfless Self is consistent with Kelso's notion that there is no Self as a substantial controlling agent within the pattern. Our sense of a personal 'I' can be construed as an ongoing interpretative narrative [47] that emerges from the complex coordination of interacting patterns. This way, the embodied Self can be coherent, flexible, and metastable. The uncertainty, consonance, and information entropy levels depend on the fluctuations of synchronizations within their coupling fields. Pattern formation, transitions, and creative destruction and reconstruction processes generate cycles of hybrid, multiscale coupling and decoupling [48,49]. These transitions challenge the systemic flexibility and resilience of the Self. The Self can be categorized as fragile, robust, or antifragile based on its capacity to endure systemic stressors and maintain pattern formation processes [50,51]. Phase transitions between patterns yield free information entropy until a new organization forms into distinct patterns. The coupled inter-subjective organization can withstand temporary states of heightened entropy accompanying decoupling or pattern dissolution and transitions leading to new morphogenesis. Associated risks, such as uncertainty, dissonance, distress, or surprise, may arise, creating challenges and opportunities for positive self-organization. Recent research by Tschacher and Haken [52,53] presents an intriguing view grounded in the Fokker–Planck equation, also called the Kolmogorov forward equation. The Fokker–Planck and Kolmogorov forward equations are mathematically equivalent. While Fokker–Planck developed their version [54,55] to explain Brownian motion, the Kolmogorov forward equation was derived [56,57] to describe random processes. The

equation is often referred to as the Fokker–Planck equation in physics and the Kolmogorov forward equation in probability theory.

$$\frac{dP(x;t)}{dt} = \frac{d}{dx}(k(x - x_0)P(x;t)) + Q\frac{d^2P(x;t)}{dx^2} \quad = \mathrm{D} + \mathrm{S} \tag{1}$$

The one-dimensional Fokker–Planck equation encapsulates these concepts: the temporal change in the probability of a state variable x (i.e., the left-hand side) can be modeled by a deterministic term, D, and a stochastic term, S, which contributes to this change. The state variable x may represent a characteristic property of the system of interest. We assume that x is interval-scaled, allowing for the computation of statistics such as averages, variances, and correlations on x. We note that the S term contains d squared; this indicates that we are considering the second derivative of probability P, specifically the diffusion (the variance) of $P(x)$. Q represents the diffusion coefficient parameter, which models the increase or decrease in variable x's variance over time. The D term describes the first derivative, meaning the change in the probability of a given value of x, or $P(x)$. In this context, k and $x - x_0$ represent factors that directly influence P. If a system has a stable equilibrium state (i.e., an attractor), k defines the force that drives the system state x toward this equilibrium state. k is the force that restores equilibrium whenever the system is pushed outside its attractor due to random fluctuations, external forces, or actions. In the Fokker–Planck equation, x_0 typically represents the initial state or condition of the system, serving as the starting point at time $t = 0$ for the probability distribution function $p(x, t \mid x\_0, t\_0)$. This initial condition is crucial for solving the equation, providing the boundary value necessary for a unique solution. The Fokker–Planck equation suggests that behavior change, i.e., the temporal change in the probability of the state variable, depends on the system's current state and time and is commonly a mixture of stochastic and deterministic processes.

Deterministic (causal) and stochastic (random) factors influence human relationships. Deterministic processes establish boundary conditions, while stochastic processes facilitate the exploration of states and possibilities within the interpersonal field state space. Using stochastic dynamics, relational experiences can transcend a limited range of disharmonic, perceptual, and emotional experiences. Stochastic dynamics are associated with the emergence of uncertainty, dissonance, distress, novelty, surprise, opportunities, and sometimes playful humor [58]. In complex systems, the interaction between different causal factors often creates situations where multiple sufficient explanations exist for observed phenomena. This creates emergence, where system-level properties arise from multiple underlying mechanisms that could independently produce equifinality and similar outcomes. It relates to the challenge of attribution in complex causal networks, where numerous causal pathways, all affected by stochastic determinants, can lead to the same system state or behavior. The relationship between indeterminism and overdetermination presents an interesting scientific tension in our understanding of causation in the behavior of complex systems. Indeterminism is the absence of definitive causal determination, where future states cannot be precisely predicted based on current conditions. In quantum mechanics and complex systems, uncertainty and probability play essential roles. Conversely, overdetermination involves multiple sufficient causes for a single outcome, where each cause could independently produce the result. This creates a situation of causal abundance rather than causal uncertainty. In complex systems, these concepts often intersect in subtle ways. A system might exhibit indeterministic behavior at one level while showing overdetermination at another. Understanding overdetermination, equifinality, and indeterminism has essential implications for scientific methodology in challenging the so-called Laplace demon. It suggests that seeking single, definitive causal explanations in complex systems may be less

productive than understanding the multiple sufficient pathways through which phenomena can emerge and the multiple opportunities for change. This perspective has influenced approaches to studying everything from climate systems to neural networks [59–61].

3. Results, Modeling Human Dynamics

As a dynamic duo, synchronization and pattern formation are crucial for emerging new structures within the embodied Self. Modern research in synchronization and pattern formation can lay the ground for robust models of the embodied Self. Synchronization refers to the coordinated behavior of multiple individual components. It can also drive pattern formation, as synchronized activity can lead to the emergence of new patterns. Pattern formation, the process of creating organized structures from initially disorganized systems, often serves as a foundation for further dynamics, with patterns typically providing a framework for synchronization. Neurons can fire synchronously, forming oscillatory patterns that underlie cognitive functions such as memory and perception. The connectivity patterns within neural networks influence new emerging patterns [62–64]. For instance, the organized movement of cells during development plays a role in creating intricate structures, such as the alignment of neural networks. Understanding pattern formation and transformations during phase transitions is crucial across diverse disciplines, including materials science, condensed matter physics, chemistry, ecology, biophysics, neuroscience, and biosemiotics. Simultaneously, patterns within individual subjects reflect integrated, complex, and multidimensional networks [65–68]. Patterns in language are involved in scaling synchronization dynamics. A language's sounds are organized into patterns known as phonemes, expressed in morphemes. These patterns can be analyzed in terms of their features, such as voice, place, and manner of articulation. Morphemes form patterns of informational structures, which are studied in information combinatorics [69]. Syntactic patterns of word combinations to form sentences follow specific syntactic rules. These rules can be analyzed in terms of phrase structure, dependency relations, and grammatical categories. The meaning of words and sentences is determined by their semantic relationships, which can be interpreted in terms of semantic features, fields, and networks. The body's physiological processes, such as heart rate, breathing, and hormone levels, exhibit rhythmic or cyclical patterns, including coupling and decoupling, synchrony, and desynchrony, all of which alternate in different yet interconnected streams. Patterns are scaled in pathways, motifs, modules, and networks within the psyche-soma [70].

Scott Kelso suggested that unified coordination dynamics should be seen as a collaboration between established small- and large-scale synchronization models. The former relies on principles from synergetics and nonlinear dynamics, exemplified by the extended Haken–Kelso–Bunz (HKB) model [71,72], while the latter draws from statistical mechanics in groups of many oscillators [73]. Most studies backing the original HKB model have focused on the coordination of two interacting elements, whether two joints of a single limb or two individuals interacting.

$$\dot{\phi} = -\alpha \sin \phi - 2b \sin 2\phi \tag{2}$$

This is the original HKB interaction dynamic. ϕ is the phase or anti-phase synchronization in a dyadic interaction; a, b are coupling parameters.

In contrast, Kuramoto illustrated the statistical mechanics of large-scale coordination among numerous oscillators. Mathematicians such as Steven Strogatz and Art Winfree quickly adopted Kuramoto's model as a framework for understanding large-scale coordination in complex living systems, which encompasses phenomena ranging from the

synchronized flashing of fireflies to the functioning of heart cells and neurons, as well as the behavior of concertgoers [74–76]. This modeling and empirical research indicate that these integrated patterns maintain a dynamic framework of synchronization and coordination, along with multistability and metastability.

$$\frac{d\theta_i}{dt} = \omega_i + \frac{K}{N}\sum_{j=1}^{N} sin\left(\theta_j - \theta_i\right),\ i = 1 \ldots . N, \tag{3}$$

The system comprises N limit-cycle oscillators with phase θ_i and coupling K.

Kuramoto and Battogtokh's subsequent research [77] revealed limitations in their initial model, which had assumed uniform synchronization patterns in large groups of oscillators. Their empirical investigations demonstrated a more nuanced reality: networks of identical, nonlocally coupled complex systems of oscillators often exhibited simultaneous coherent and incoherent states. Prior research had established that non-identical coupled oscillators could display diverse behavioral patterns, including frequency locking, phase synchronization, partial synchronization, and incoherence. The prevailing assumption had been that identical oscillators would follow a simpler pattern, either achieving complete phase synchronization or maintaining an incoherent state. However, their groundbreaking discovery showed that even oscillators with identical coupling and similar natural frequencies could develop distinctly different behaviors under specific initial conditions. This phenomenon manifested as a stable state, where some oscillators achieved synchronization while others remained incoherent, challenging the previous understanding of oscillator dynamics.

Kuramoto and Battogtokh later pointed out that their previous model depended on the assumption of perfect homogeneous synchronization within large groups. However, empirical studies frequently reveal that coherence and incoherence can coexist, even among networks of identical, nonlocally coupled oscillators [78]. Coupled oscillators that are not identical are already recognized for demonstrating a range of complex behaviors, including frequency locking, phase synchronization, partial synchronization, and overall incoherence. It was anticipated that identical oscillators would either achieve phase synchronization or drift incoherently. They demonstrated that oscillators with identical coupling and comparable natural frequencies can exhibit diverse behaviors depending on their initial conditions. Some could synchronize, while others maintained a stable, incoherent state.

$$\frac{\partial}{\partial t}\phi(x,t) = \omega(x) - \int G\left(x - x'\right)\sin\left(\phi(x,t) - \phi\left(x',t\right) + \alpha\right)dx' \tag{4}$$

where ϕ is the phase of the oscillator and ω is the natural frequency, with $\omega(x) = \omega$ for all x. This equation corresponds to the continuum limit of the Kuramoto model, with x corresponding to subscript i. The integral kernel $G(x)$ describes the nonlocal interaction, and the phase constant α in the phase-coupling function is related to the original parameters.

Abrams and Strogatz introduced the term "chimera state" to describe this phenomenon of mixed synchronization [79]. Just as the mythological chimera was a creature of different animal parts, this mathematical state describes a system where synchronized and unsynchronized behaviors coexist. Their work provided theoretical foundations for understanding how and why this complex behavioral pattern emerges in oscillator systems. Chimera states are ubiquitous: coupling, synchronization, and patterns emerge and dissipate, with gaps in between. Chimera states were later discovered in limit-cycle oscillators, chaotic oscillators, chaotic maps, and neuronal systems. Initially, chimera patterns were observed in nonlocally coupled networks; subsequently, these states were identified in globally and locally coupled networks and modular networks. The usage of Markov chains

for mapping couplings and chimera states was also explored [79,80]. C.R. Laing studied chimera states in heterogeneous networks, examining the influence of mixed-coupling strengths. Of further interest for human dynamics is the emergence of chimera states in multiscale networks that result from coupling different networks [81], a phenomenon commonly observed in biosemiotic dynamics. The dynamic Self emerges from networks of synchronized oscillators linked within fields that include mixed biosemiotic domains [82]. A simplified general mathematical model for heterogeneous mixed chimera networks can be expressed as follows:

$$\frac{dx_i}{dt} = F_i(x_i) + \sum_j K_{ij} G_{ij}(x_i, x_j) \quad (5)$$

where:

x_i represents the state vector of the i-th oscillator.
$F_i x_i$ denotes the intrinsic dynamics of the i-th oscillator, which may differ for various oscillators.
K_{ij} indicates the coupling strength between the i-th and j-th oscillators.
$G_{ij}(x_j, x_i)$ is the coupling function between the i-th and j-th oscillators, which can also differ among distinct oscillators.

This equation is a coupled differential equation, often referred to as an interaction-based differential equation. It represents a generalized version of a coupled nonlinear dynamical system. The overarching structure suggests a system in which each component evolves based on its internal dynamics while being simultaneously influenced by interactions with other components. The coupling enables interaction among multiple variables, each affecting the others while maintaining distinct dynamics. The rate of change relies on both the intrinsic behavior of each variable and its interactions with other variables [83,84]. The prevalence of chimera mapping in synchronization and its diverse typologies has broadened the original definition to encompass phenomena such as human nonidentical coupling oscillators in hybrid networks and multiscale networks that display chimera-like dynamics even before this definition was proposed [10]. Essentially, hybrid chimera networks emphasize the diversity of coupling within a single oscillator type, while heterogeneous mixed-nodes chimera networks delve into the complex interactions among different oscillator types. The dynamical integration of patterns will encompass both rapid and gradual synchronization dynamics. For instance, rapid physiological responses can be observed in emotions, movement, neuro-mediators, breathing, and heart rate, whereas slower responses involve neurotrophic factors, hormones, and attachment dynamics. Speech and cognition can range from rapid to slow, ideally positioned within a mesoscopic dynamic area [85].

4. Discussion: The Dynamics of Self-Organization and Patterns

The coexistence of synchronized and desynchronized behavior within the same network is counterintuitive, as one might expect the oscillators to either synchronize or stay desynchronized. Instead, we can find a coexistence of order and disorder. Chimera states emerge when symmetry in the system breaks down, even when the oscillators are identical and the coupling is uniform. These states are more frequent in human dynamics, where there is coupling between different types of oscillators with varying strengths of coupling and network topologies. Chimera states can be stable or transient, depending on the system parameters and initial conditions.

Chimera states offer numerous systemic advantages, including enhanced resilience, robustness, fault tolerance, and adaptability. By combining synchronized and desynchronized regions, these states improve a network's ability to withstand disturbances and failures. When one part of the network is disrupted, other sections can maintain func-

tionality, preserving overall system stability. Transitioning between synchronized and desynchronized states enables the network to adapt to environmental changes, such as input signal shifts or network topology alterations. This synchronization blend facilitates a reliable information flow across different system components. Synchronized clusters ensure consistent communication, while desynchronized regions provide flexible pathways for alternative signal routing [86,87].

Research on heterogeneous synchronization in the brain reveals complex dynamics across different regions responsible for emotional, motor, and verbal functions. Synchronization patterns play a crucial role in cognitive processing, which requires a delicate equilibrium between neural segregation and integration. The brain's specialized regions efficiently perform segregated computations, while integrated neural systems ensure coordinated performance across multiple areas. Studies indicate that focused cognitive states primarily utilize shorter, local neural connections, whereas integration depends on subcortical regions and cortical hubs that maintain diverse connections throughout the brain [88,89]. Understanding chimera dynamics provides valuable insight into the complex synchronization patterns that emerge during critical cognitive processes. These patterns are particularly relevant when the brain must balance integration and segregation to support adaptive cognition and social interactions [10–12]. The emergence of chimera states in neural networks appears to be influenced by various types of neuronal interactions, including different synaptic mechanisms, varying connection speeds, and neuro-modulatory processes within the nervous system. As distinct brain regions collaborate to execute neurocognitive tasks, they generate variable patterns of partial synchronization. These chimera states manifest repeatedly across various intersubjective interactions, underscoring the complex nature of neural coordination in human cognitive processes. Self-organization, a phenomenon where overall order emerges from local interactions, plays a crucial role in creating spontaneous order in complex systems. This process can occur naturally when adequate information or energy is present without requiring external control. It is frequently initiated by random fluctuations amplified through positive feedback mechanisms. The resulting structure is entirely decentralized, with the organization distributed across all system components. Consequently, this organization is highly adaptable, resilient, and capable of withstanding or self-repairing even after significant disturbances.

The first Kuramoto model is deterministic in its classical form. However, it can be made probabilistic by adding noise terms or considering random initial conditions and coupling parameters. The intrinsic variability in coupling and synchronization patterns across the oscillator population can be regarded as effective stochastic behavior, even without explicit noise terms. The spatial heterogeneity in coupling creates local fluctuations that functionally resemble stochastic effects on system dynamics. Stochastic dynamics can be incorporated into the Kuramoto chimera model by adding noise terms. The most common approach involves adding Gaussian white noise $\xi_i(t)$ to each oscillator's phase equation as multiplicative or additive. The multiplicative noise term can introduce state-dependent fluctuations, while the additive noise term can provide background perturbations independent of the system state. This combination would account for richer dynamics and can lead to noise-induced transitions in the chimera states [90–94].

The Fokker–Planck and Kolmogorov equations are fundamental for studying stochastic processes and statistical dynamics enmeshed with deterministic processes. They describe how probability distributions evolve in systems subject to random fluctuations. These equations can also be used to analyze mixed synchronization states, particularly in systems where noise or stochasticity plays a role, which is the case in basically all real-life contexts. In systems with coupled oscillators, noise plays a significant role in the emergence and

stability of chimera states. The Fokker–Planck equation effectively describes the probability distribution of noise-influenced oscillator phases. For example, noise can disrupt synchronized regions, causing transitions between coherent and incoherent states. The Fokker–Planck framework facilitates the analysis of the noise effect on the coexistence of synchronized and desynchronized groups within chimera states. The backward Kolmogorov equation facilitates the study of the probability of transitions between various states in a system, including shifts between synchronized and desynchronized areas in chimera states. This approach is especially valuable for grasping the stability and duration of chimera states in the presence of noise. Noise can cause transitions between coherent and incoherent states, and the Fokker–Planck equation can describe the probability distribution of these transitions. The Kolmogorov equations can be used to study the stability of chimera states by analyzing the likelihood of transitions between different dynamical regimes [56,62].

5. Conclusions

Human dynamics present network states characterized by the simultaneous presence of multiple distinct synchronization patterns. Subsets of nodes exhibit different degrees or types of phase-locking relationships while maintaining stable global network dynamics. Fundamental advancements in empirical and theoretical research on human synchronization and coordination dynamics pave the way for an integrated complexity science of human dynamical systems.

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Complexity in Systemic Cognition: Theoretical Explorations with Agent-Based Modeling

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Abstract: This paper presents a systemic view of human cognition that suggests complexityis an essential feature of such a system. It draws on the embodied, distributed, and extended cognition paradigms to outline the elements and the mechanisms that define cognition. In doing so, it uses an agent-based computational model (the `TS 1.0.5`Model) with a focus on learning mechanisms as they reflect on individual competence to gain insights on how cognition works. Results indicate that cognitive dynamics do not depend solely on macro structural elements, nor do they depend uniquely on individual characteristics. Instead, more insights and understanding are available through the consideration of all elements together as they co-evolve and interact over time. This perspective illustrates the essential role of how we define the *meso* domain and constitutes a clear indication that cognitive systems are indeed complex.

Keywords: systemic cognition; the meso domain; complex systems; agent-based modeling

1. Introduction

This article is concerned with the seemingly odd concept that human cognition is *systemic*. This idea is not new; in fact, it was first introduced by [1] and then explored more recently in [2–4] (Chapter 12).

The main tenet of this perspective is that cognition is distributed [5,6] across enabling resources [7] and that their interactions constitute the basic foundation of a system. In a cognitive system, resources are all those elements that allow performative actions. For example, the act of speaking with someone involves the activation of specific neural patterns, an engagement with the body—utterances require a very precise exercise of the mouth, tongue, and related muscles—anchoring to the words that are spoken as a way of feedback onto what comes next and, not last, the explicit/implicit reactions of those who listen. To this, we can add several more elements. In fact, it is not irrelevant to think of the context in which this dialogue happens (e.g., a cafeteria, a bar, a public square, a classroom), nor is it secondary to think of other bodily engagements, such as hands or other movements (of the speaker and the listeners) that may elicit and support what the sentences refer to.

There are many assumptions underlying the idea that cognition is systemic. Two are considered as being constitutive in this article and should be referred to explicitly. On the one hand, the application of a system's framework to cognition highlights the intertwined and co-evolutionary dynamic patterns that can be observed among elements. This means that it becomes very hard to split the system and consider each element separate from the others. This seemingly simple (and rather obvious) assumption is not at all simple (nor is it obvious). It is not simple because it sets the ground for an understanding of cognition that is based on dynamics rather than elements and static properties. Furthermore, the heterogeneity, (in)stability, variance, sometimes ambiguity, and uncertainty of the interactions among elements make it very difficult to predict how cognition will unfold. On the other hand, the claim is not obvious if one reflects on the fact that, for many years, cognition has been studied as a function of the human brain, where any performance (e.g.,

language) is dissected and treated as information processed computationally. This tradition has roots in the very beginning of the cognitive science field [8,9] and has influenced some areas (e.g., linguistics) for decades [10,11].

One implication of the above is that it is the study of the combined effects of cognitive resources that allows for a deeper and better understanding of cognitive life. However, how this is achieved is yet to be defined. From the considerations exposed thus far, it is apparent that the study of cognition would benefit from applications of analytical tools from complex systems science. Given how blurry the boundaries of the elements involved are, and how much the system is capable of re-configuring itself giving rise to unpredictable patterns, variability of end states, and emergent properties, it is fair to consider a complexity assumption. This assumption complements (sometimes disrupts) previous traditions and is the focus of this article. Specifically, the article uses an agent-based computational simulation model (already presented elsewhere [12]) to explore and define the elements that make cognition a complex system. In doing so, it makes particular reference to the *meso* domain of interactions (see below for further details).

The following section is dedicated to providing a theoretical background to the claims above, while Section 3 presents a computational exemplification of the concepts outlined in Section 2. We then draw implications and conclusions in the last Section 4.

2. Background

A systemic take on cognition places emphasis on the fact that cognition revolves around the flexible, adaptive activity of agents. Agents possess more or less stable traits, such as competences, skill-sets, or other kinds of dispositions. For instance, Goodwin [13] shows how so-called 'professional vision' can develop in highly specialized and professional contexts, whereby cognitive agents become predisposed to see certain things that others would not. For example, utility company workers use professional vision to spot a leakage underneath a pavement in the winter. This is possible because the snow melts in the area due to the hot water leaking underneath it (see, [14]). From a sensorimotor enactivist perspective, Noë [15] makes a similar point. He appeals to so-called 'perceptual understanding,' which effectively interrelates with an agent's practical understanding whereby one skillfully deploys concepts in plain perceptual encounters. In terms of the importance of such an understanding, Noë provides the following example:

> "It is difficult to tell, looking at the entrance to the Taj Mahal, which bits of squiggle are mere ornament, and which are writing in Classical Arabic. You can have this experience, it is available to you, only if you are not fluent in Classical Arabic, or in this style of Arabic script." (p. 3, [15])

Under this angle, a disposition like one's practical understanding effectively enables the skillful agent to competently pick up on certain relevant environmental cues (e.g., affordances, symbols, etc.) and make effective use of these in a manner that the unskilled agent is not able to. In fact, expertise is not merely a matter of being able to use a tool or an instrument correctly but it can also include the perception of practice-relevant aspects of one's surroundings. This is precisely why human systemic cognition unfolds in the context of socio-material practices, which function in the realm of what Hutchins [16] terms the human *cultural-cognitive ecosystem*. Importantly, as Hutchins notes, specific skills develop by means of engaging with practices and by the fact that different practices interrelate. For example, the ability to project a trajectory onto a spatial arrangement allows for diverse activities such as queuing or navigating an airplane across practical contexts. As Hutchins puts it, the "relationships among practices in the cognitive ecosystem can create possibilities for generalization of skill across activity systems" (p. 42, [16]).

Thus, skills are not strictly local or situational, but rather flexible in the sense that they can be used to engage with cognitive resources across situations, practical arrangements, and even practices. These skills and their enabling practical understandings are just some of the elements that make cognition work as a system. Since a systemic take on cognition is fundamentally anti-Cartesian, it follows that cognition is not viewed as

unfolding strictly through intra-cranial processes that are somehow tightly affiliated with the workings of a mind or an intellect. The brain is also dismissed as the primary locus of cognitive behavior. Instead, cognition spreads across agents, the environment, tools, etc.; as argued in Gahrn-Andersen et al. [2], this means that different ontologies are at play. Indeed, human systemic cognition is precisely 'systemic' because it enmeshes phenomena that traditionally would have been attributed to particular stand-alone ontologies (e.g., the cognitive, the linguistic, the biological, the social, etc.) (p. 90). Precisely because no explanatory weight is placed on representational mental content, it follows that cognition unfolds in actual agent-environmental relations. This means that cognition is relationally constituted and effectively cuts across inner-outer dichotomies related to the mental:

> "While ideas can emerge in silence under a furrowed brow, thinking more typically arises as people battle with an invoice, look for the foreman or choose to trust a web site. Though people can think alone, they also do so when looking at X-rays, drawing geometrical shapes or, indeed, talking with others. In all cases, brain-side activity is inseparable from world-side events." (p. 256, [1])

However, it is not enough to recognize the importance of factors pertaining to the micro-level of agent–environment relations; we must also recognize that systemic cognition is socio-practical by nature. This means that it unfolds in a practice-constitutive fashion amongst interacting agents and, hence, it constitutes *a meso domain*. This is not a new concept. In fact, other domains have effectively utilized the concept of the *meso* when discussing systems. For example, Dopfer's interpretation of Schumpeter's attempt to reformulate the traditional micro–macro dichotomy into a *micro-meso-macro* framework redefines evolutionary economics [17]. This in-between domain is connected structurally to the macro and procedurally to the micro, in a way similar to what we claim it does in the cognitive sphere. Another prominent example comes from the change management literature as it meets complexity [18–20]. Here, the *meso* is used as explanatory "rules that arise from some dominating assembly that facilitates macro structures and processes (that result in behaviour) through their actualisations" (p. 1339, [20]).

From the perspective taken in this article, the meso domain involves the interplay of various socio-practical elements such as tools, individual and collective skills, and understanding, where cognitive processes are distributed across different aspects of the socio-material environment. Placing emphasis on the meso underpins the role of community, collaboration, and shared practices in shaping and sustaining cognitive activities, further demonstrating that cognition cannot be fully understood without considering the broader socio-practical context in which it occurs:

> "The domain comprises any action that connects up how individuals perform daily duties such as, e.g., working a machine, arguing a point in a meeting, writing an email, or simply chatting with a colleague in front of the coffee machine. All such activities require some part of the biological organism (e.g., brain, body), an interpretation of or sensitivity toward (awareness of) organizational superstructures (e.g., norms, cultural expectations), and the actual resources through which cognition is enabled (e.g., a colleague, a computer)." (p. 4, [2])

In meso-domain interactions, cognition typically revolves around some sort of task orientation. Indeed, as Brentano envisaged, cognition involves an intentional directness towards the surroundings, and while Brentano was a mentalist and prone to emphasizing the solitary 'thinker' as the cognizing agent, a systemic approach pushes the basic Latourian and Heideggerian counterpoint: the agent and their directionality cannot be seen apart from the socio-practically saturated world they exist in and engage with. In this sense, it is the *local* situational context that matters. This allows us to recognize the importance of task orientation which is distributed across the system. It also makes the fact that there is a strong collaborative element to what characterizes the task orientation of agents more apparent.

Perry [21] places emphasis on agents' abilities of transforming a particular practical problem or task domain by means of their skills and competencies, the availability of resources at hand, the dispositions of other agents, etc. Specifically, he points to the fact that a distributed cognitive system need not be characterized by fixed rules and procedures and, hence, amount to a tightly coupled system (although this was how they were originally envisaged by [5]). Rather, it unfolds in a more *loosely coupled* manner whereby the system itself is characterized by a high degree of flexibility, adaptation, innovation and, last but not least, *plasticity* as to its structure [22,23]. Effectively, this means that important constitutive elements such as agents' roles, rules and procedures, goals, the functionality of tools, etc. are not strictly preconditioned but rather emerge from how agents organize at the meso level.

Indeed, loosely coupled systems may still very much be characterized by the presence of so-called macro-domain phenomena such as culture-defining norms and Standard Operating Procedures (SOP). Yet, the crucial difference here is that such phenomena are heavily or consequently enforced (p. 158, cf. [21]). This entails that the system in question exhibits a high degree of self-organization, precisely because (a) it has the freedom to do so and, (b) it is organized around sets of complex tasks (or problems) which are complex and thus do not lend themselves to straightforward solutions based on the successful resolving of tasks in the past, fixed training regimes, or SOP.

Since the resulting organization has no center, there is a strong focus on how control evolves. Indeed, as Hutchins argues, "centers and boundaries are features that are determined by the relative density of information flow across a system" (p. 37, [16]). In other words, it is the observer who decides on the extent of the boundaries of a system, and given that the observer him/herself cannot be fully taken out of the equation, we necessarily come to accept that systems exhibit incompleteness, both theoretically and in practice (pace, [24]). Nevertheless, in spite of this, we find that it is a foundational characteristic of self-organizing systems that some of their elements impose a degree of control; Cowley and Vallée-Tourangeau put it thus:

> "In a species where groups, dyads and individuals exploit self-organizing aggregates much depends on cognitive control. At times, this is more demand led; at others, it is looser and individual-focused. Control thus depends on management of the body, various second-order constructs, and lived experience. Not only is systemic output separable from actions but, just as strikingly, we offload information onto extended systems." (p. 269, [1])

While recognizing that cognition is systemic and, hence, that it unfolds across aspects of agents and their environments, Cowley and Vallée-Tourangeau also highlight the importance of individual agents who, in Batesonian-inspired terms [25], should be recognized as those differences that effectively allow for the unfolding of the cognitive system in question. This is because individual agents exhibit partial control through their skillful engagements with their surroundings. Here we must keep Hutchins' point in mind that even though individual agents might be the locus of control, the control remains partly determined collectively. For as he reminds us, "In some cultural contexts, people seeking service arrange themselves in a queue as a way to control the sequence of access to services" (p. 39). So, going back to their point concerning the trans-practical (or eco-systemic) skill of 'projecting a trajectory onto a spatial arrangement', we find that skills such as this are also constrained, in part at least, through macro-level constraints that are reified or brought into relevance on the level of meso, through the manner in which agents coordinate amongst one-another. It testifies to Secchi's point concerning the fact that organizations seem to "create the condition for distributed cognitive mechanisms" which give rise to certain kinds of behavior, thus allowing the organization to be "a cohesive unity of individuals despite being also a complex [, unpredictable] and adaptive social system" (p. 176, [26]).

3. A Computational Example

In order to explore the theoretical propositions presented in the first part of this paper, we employ a computational simulation methodology. We use an agent-based model that represents teams working to perform specific tasks and, in doing so, they use the cognitive resources available, especially their own and other people's expertise/competence. In the following pages, the model is briefly introduced, and then the method of analysis is presented together with a selection of the most relevant findings.

Before engaging with the model and its features, it is relevant to indicate why agent-based modeling is an appropriate method in this case. This technique has been developed [27] and used to study complex systems [28,29] and it has been argued it could and should be applied to the study of cognition, especially under embodied, distributed, and extended perspectives [4]. These models make it relatively easy to study interactions among elements, what affects them, and how they behave under a set of evolving circumstances (e.g., stresses, shocks, or unchanged conditions). Hence, through the study of such models, it is possible to unearth the mechanisms leading to emergent patterns [30] and, in general, enquire on the causes of systemic complexity, especially in social systems [31].

3.1. The `TS 1.0.5` Model

The `TS 1.0.5` Model was developed after an ethnographic study concerning a large Danish utility company operating unmanned aerial technology (i.e., drones) to detect leakages in the hot water pipe system. The focus of the model is the maintenance department and the structure of its three teams. They are organized around a flexible structure that allows employees to work across teams, depending on the type of leakage repair and on their personal preference (sometimes grounded in competency attributes). Hence, performance is defined in relation to the way in which the employee-agents are able to deal with leakages and to provide a "fixing" of the problem.

This model is programmed and implemented using `Netlogo 6.3.0`.

3.1.1. Agents and Environment

The full description, aim, and capabilities of the `TS 1.0.5` Model are presented in [12]. Since the purpose of this paper is limited to understanding the elements that make cognition work as a system, the description of this model is limited to the features that are actually used in the current study.

The model has three types of agents: managers, employees, and leakages/cases. Agent-managers and agent-employees share three characteristics: (a) *disposition to listen* (L_i) to information coming from other agents, (b) *disposition to share* (S_i) information with them, and (c) a degree of *competence* (c_i), that is the professional ability to deal with the tasks at hand. These values are attributed to the agents at the beginning of the simulation using a normal distribution such that a random number generated is by $\approx N(0, 0.5)$ for managers and $\approx N(1, 1)$ for employees for both dispositions to share (S_i) and to listen (L_i). Competence is, instead, attributed using a random-normal distribution $\approx N(1, 0.5)$ constrained such that $0 \leq c_i \leq 2$. Agent-leakages have characteristics such as (a) *size*, indicating the extension of water dispersion on the ground, and (b) *importance*, that is the extent to which a leakage needs to be dealt with, (c) *complexity*, that is the range of expert knowledge necessary to deal with them, and (d) *type*, that is whether the information on the leak comes from a drone scan, a call from a customer, an alarm, or something else. Furthermore, these agents become `cases` when their importance is higher than a threshold, controlled by the modeler on the interface.

All agents are randomly assigned a place in the environment, and agent-persons establish relationships with other agents in their surroundings, according to parameter *relationship range* (ϕ).

The simulation is set to run for 260 time units. One unit represents a week and, assuming there are 52 working weeks in a year, this number corresponds to 5 years.

3.1.2. Mechanisms

Once the agent-employees and the agent-managers are placed in the environment, they start to connect to each other depending on spatial proximity. This means that two agents may cooperate to perform a task if they establish a connection. The agent-leaks appear in the environment gradually, as the simulation time goes by. Some of these agent-leaks would pass the threshold and become "cases", meaning that they can be dealt with by any agent-employee that is close enough and interested.[1] Once the connection between an agent-employee and an agent-leak is established, the procedure works as follows:

1. If competence is such that $c_i \geq 2$, then
2. The agent checks that the materials necessary to fix the leakage is available, and
3. If the material is available, then the case is solved
4. Otherwise there is some lag between the time of the connection and the time the case is solved.

If point 1 of the procedure does not hold, then the agent-employee "asks" the other agents to which it is connected, in an attempt to gain the additional competence that is needed to perform the task. However, this social aid mechanism materializes as follows:

1. If competence of the agent-employee is such that $c_i < 2$, then
2. The agent-employee asks for help to their network
3. It receives help in the form of competence increase δ_c if
   a One's own disposition to listen is more than average, and
   b The helper's disposition to share is more than average.

From the above, it is apparent that a case may never be solved and remain hanging in the system for the entire duration of the simulation. Furthermore, it is possible that a case is distant from employees and managers and this secures it being undetected and/or impossible to deal with.

3.2. Analytical Approach

The original simulation had four organizational structures and it compared them to understand which one would lead to the highest proportion of cases fixed, on which terms, and in what time. It had a main computational experiment with a 4608 parameter space that needed more than 100,000 simulations to be analyzed appropriately. The analysis indicated that, under most conditions, the "hybrid" structure designed after the ethnographic data was almost always the slowest to reach an average number of cases fixed but, once it did that, it also progressed to become the most successful of the four structures. This is only observable when the entire lifespan of the simulation is considered. The previous study focused on macro patterns as they are informed by the initial and ongoing settings of the simulation. However, it does not tell much about the internal processes that shape and are shaped by the way in which the system is configured. This is what this article is set to do.

Starting from a configuration of parameters that lead the "hybrid" structure to become the most successful,[2] this article zooms in on one simulation run by downloading all possible data related to the agents, their characteristics, and the links, both those with a "social" (i.e., with other agent-employees or agent-managers) and those with an "operational" scope (i.e., with leaks/cases).

Once this is conducted, we downloaded 260 datasets, one per week, and created a large dataset with all the information necessary to define teams and their dynamics over time. We used several packages from `R Version 4.3.1` and worked on `R-Studio Version 2023.06.1+524`.

3.3. Findings

The first aspect to look at is team composition. The team number is associated with the agent that originates from the informal network (each agent has a unique numerical denomination, starting from 0). For example, *Team 0* is the team around agent-manager 0, *Team 27* is the team of agent-employee 27. When the team network originates from

an employee, this is constituted by informal work relations that connect various other agent-employees. The management teams are instead more formal networks and are also made of agent-employees. Figure 1 shows the various different networks, established for the sole purpose of dealing with cases that cannot be solved otherwise. The first aspect to notice is the wide variety of team members; there are a few that peak, with the 21 members of *team 3* and a few with very low numbers, such as *team30* with only 2 members. The average number of team members is 9.77 with a standard deviation of 5.35.

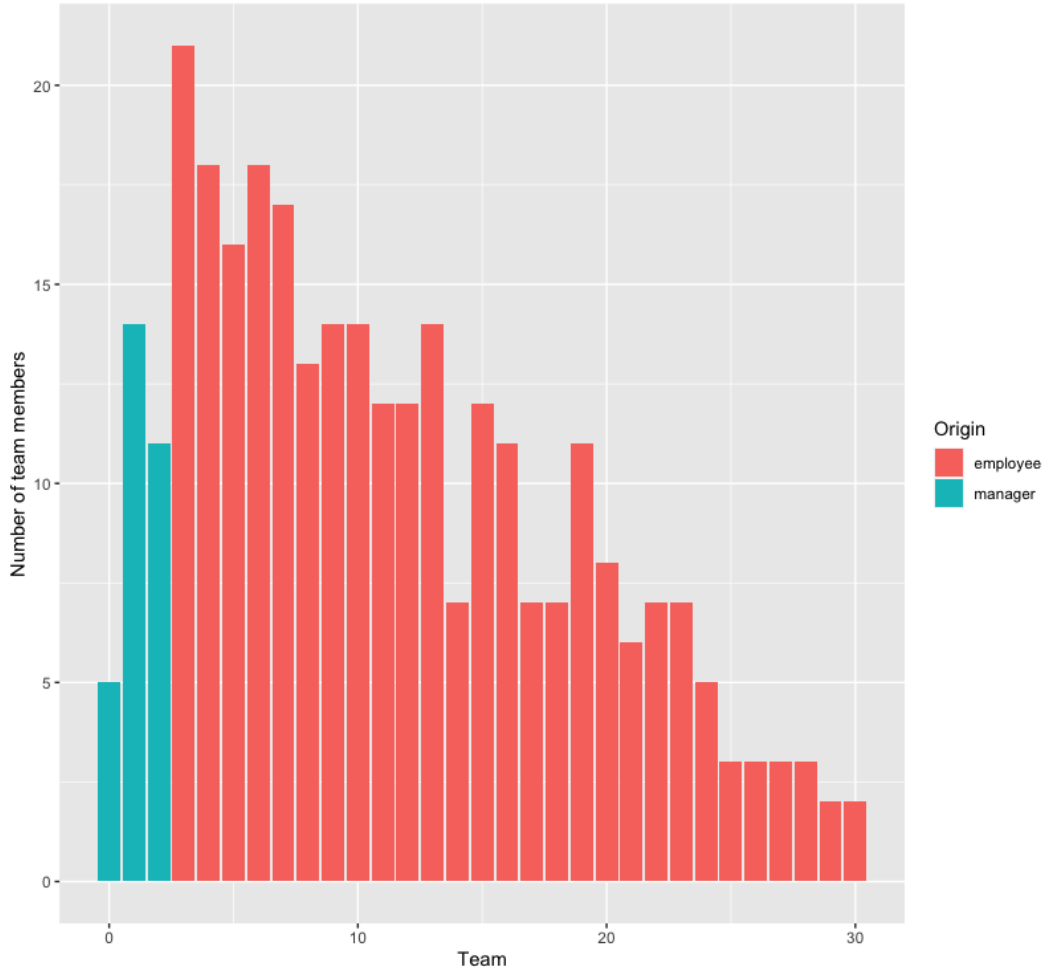

Figure 1. Number of members in the informal work teams originating from employees and managers.

3.3.1. Social Network Analysis

A more appropriate visualization is perhaps offered by social network analytical tools. Figure 2 shows the intricate informal network connecting all the agents in the simulation. The three managers stay at the margins of the networks, as if they serve as facilitators for others to connect. Hence, and even without calculations, it is already apparent from Figure 2 that managers are not central to the operations. They may still have to make decisions, but they are not at the core of daily operations.

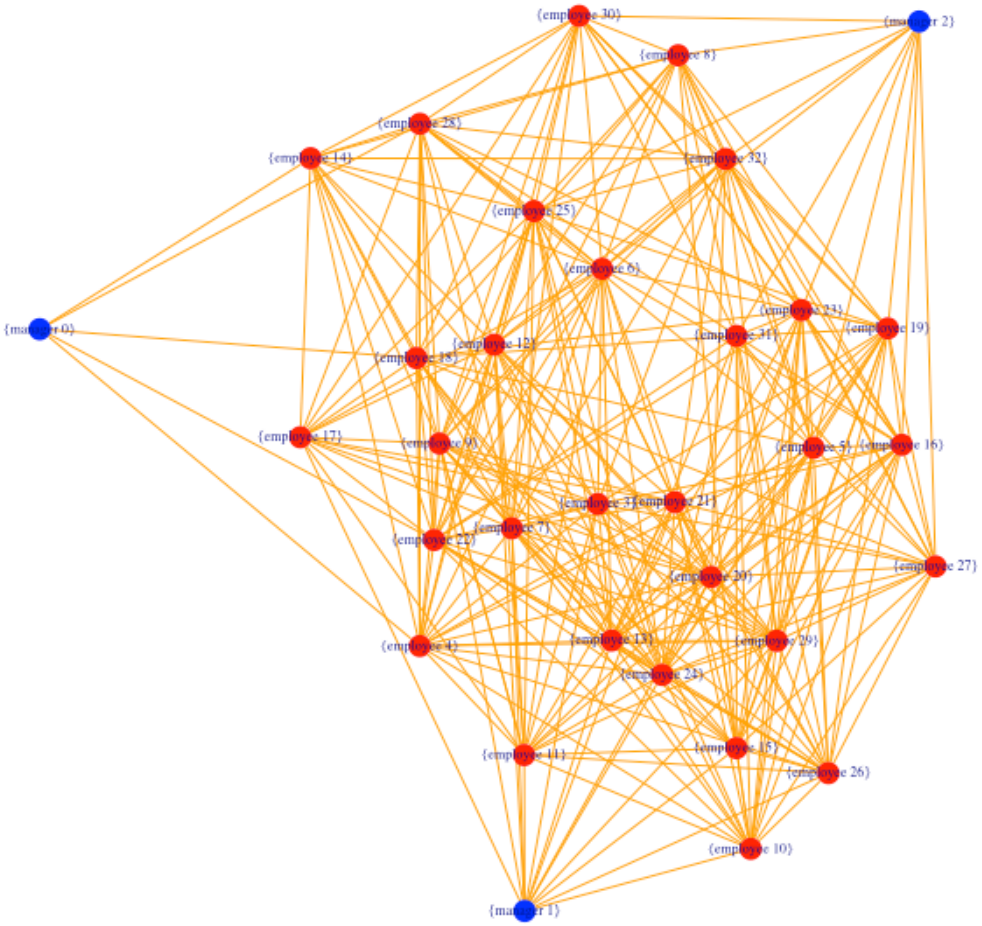

Figure 2. Social network of the work teams. (blue nodes: managers; red nodes: employees).

The three measures presented in Table 1 certify the considerations above by reporting the values of three of the most relevant centrality indices related to each agent. *Eigenvector* centrality is a measure of influence, and it is calculated by weighting the node's connections as opposed to every other node in the network. *Betweenness* centrality relates to the times the node is part of a path connecting two other nodes. Finally, *closeness* centrality is a measure of the shortest paths that allow getting to the node from any other node in the graph, on average; it is calculated as geodesic distance.

Table 1 ranks the teams according to influence (i.e., eigenvector); however, apparent from the other two indices, agents ranking high in one are likely to score high in the other indices as well. The information confirms what is visible in the visualized network (Figure 2), that is *agent-managers* 0, 1, and 2 are ranked 33, 32, and 25. Given their location at the edges of the network, it is rather obvious that information does not pass across them, hence *betweenness* is low to very low—it ranges from 0 to 1.5 (max value for this index is 15.62 from *team 22*). This limits their influence, with an *eigenvector* ranging from 0.17 to 0.62 (max = 1). The third index, *closeness*, also scores particularly low, with the longest path of 0.5 associated with *agent-manager 0*. The agents that show better indices are not necessarily those with larger informal teams. For example, the two agents with the highest *eigenvector* values are *agent-employee 13* and *agent-employee 24*, with, respectively, 14 and 5 team members. In fact, *agent-employee 3* has the highest number of team members with 21; it ranks high in the list but it is noticeable that other nodes/agents have more influence and overall centrality. Another interesting consideration concerns those agents that score the highest in *betweenness* but are neither influential nor close. For example, *agent-employee 18* has one of the highest *betweenness* values (i.e., 11.74), due to its position in the network, but scores very low in the other two indices. The highest *betweenness* value comes

from *agent-employee 22* that, with 15.62, is very much away from the average of 6.96. One might think that the highest values depend on how many networks (i.e., informal teams) an agent-employee is part of. That is, however, not the case. In fact, *agent-employee 22* is part of 15 teams, including the one that originates from it. The highest value pertains to *agent-employee 29*, part of 21 teams. *Agent-employee 18* is part of only 10 teams, similar to the 11 of *agent-employee 13*—the first in the overall ranking—and unlike the agent with the second position in the ranking table, *agent-employee 24*, part of 20 teams. In other words, there is no correlation between the number of teams an agent is part of and *betweenness* centrality values.

Table 1. Eigenvector, betweenness, and closeness centrality of the agents.

#	Agent	EV	B	C	#	Agent	EV	B	C
1	13	1	10.077	0.800	17	25	0.800	8.518	0.727
2	24	1	10.077	0.800	18	9	0.787	5.021	0.711
3	20	0.964	9.224	0.780	19	15	0.739	5.128	0.696
4	29	0.925	7.575	0.762	20	5	0.709	6.496	0.696
5	3	0.924	8.294	0.762	21	32	0.706	7.763	0.696
6	21	0.894	6.414	0.744	22	23	0.703	6.445	0.696
7	7	0.868	7.508	0.744	23	27	0.700	4.220	0.681
8	6	0.840	9.658	0.744	24	31	0.655	5.727	0.681
9	12	0.816	6.872	0.727	25	1	0.622	1.507	0.615
10	4	0.816	13.230	0.727	26	28	0.602	9.920	0.681
11	11	0.812	5.077	0.711	27	17	0.596	3.745	0.653
12	26	0.811	4.312	0.711	28	8	0.579	6.516	0.667
13	10	0.811	4.312	0.711	29	30	0.578	7.106	0.667
14	16	0.811	7.475	0.711	30	18	0.574	11.740	0.667
15	22	0.811	15.626	0.744	31	14	0.545	5.679	0.653
16	19	0.810	7.184	0.711	32	2	0.411	1.554	0.582
					33	0	0.174	0	0.508

Note. *EV: eigenvector centrality; B: betweenness centrality; C: closeness centrality.*

3.3.2. Cognitive Dynamics

The question to ask in relation to the results above is whether those agents with higher centrality are also those that receive better or improved effects in cognitive terms. Put differently, the position in the network can be an indication of the way in which they develop their competence—aptitude towards the problem or task they are dealing with—and is reflected in their performance (leaks/cases fixed).

Competence

The idea is to compare competence change for agents at the top with those at the bottom of the ranking Table 1. The trends for (log) competence in each team leader (or originator) are presented in Figure 3, where linear regressions summarize the general patterns. Competence can only increase when an agent fixes a case and this can happen either because the agent has enough competence or as a result of cooperation with other agents. The two most central agents are 13 and 24; both experience a relative increase in competence, especially if compared to the one experienced by agent-managers (i.e., 0, 1, and 2). Some agent-employees—25, 27, 28, 19, and 11—do experience minimal competence growth. When compared with the information in Table 1, it is quite surprising that *agent-employee 29*, ranked 4 for influence, experiences a decrease, on average, of competence (Figure 3).

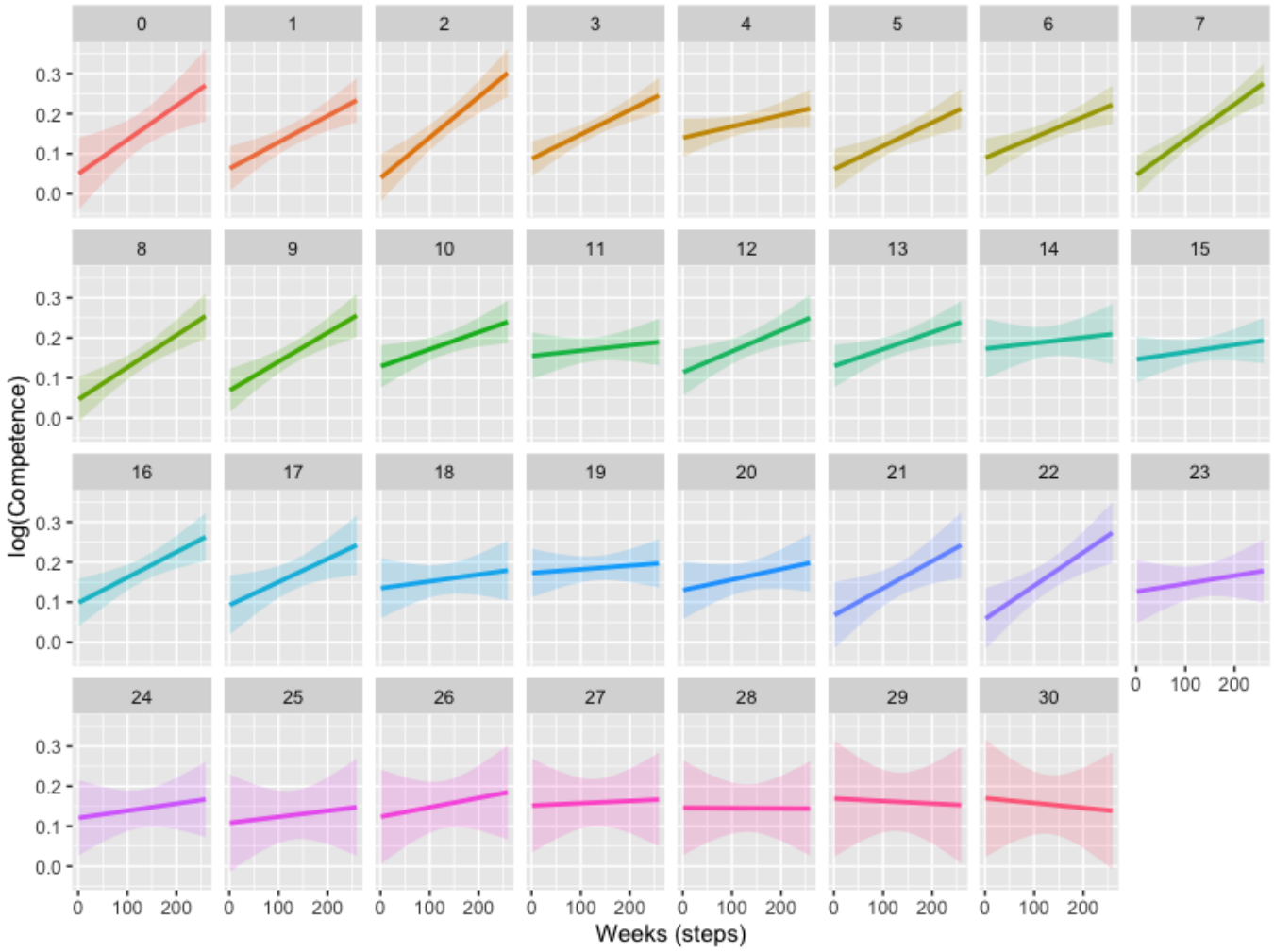

Figure 3. Competence (log) for each informal team leader (linear regressions and confidence intervals).

From the above, it is apparent that a simple analysis of the structure of informal networks as well as of the most influential nodes does not explain cognitive dynamics, in the sense that competence—i.e., learning from a combination of cognitive resources—is not completely dependent on these aspects.

Dispositions

The following step in the analysis is that of trying to understand competence through cognitive dispositions. As mentioned above, each agent has a *disposition to listen* (L_i) and a *disposition to share* (S_i) information. Thus, it becomes essential to understand whether these two are able to predict a modification in the learning mechanism leading to competence variability among agents.

Probably one of the simplest ways to isolate this effect would be that of using a linear mixed-effect regression model [32] that takes care of the longitudinal nature of the data (its evolution over time) while, at the same time, taking the groups (i.e., teams) into account. Thus, we created a model that regresses the agent's competence on time, and disposition to share and listen to both the agent and the others in the team.

The first result is that almost all variance $\approx 99\%$ in the dependent variable (i.e., competence) is explained by differences within teams rather than by those between them. The grouping is meaningful. Concurrently, the effect of time seems to be irrelevant, reporting an estimate $\beta_t = -0.0000175$ $(s.e. = 0.00007)$, $p = 0.8091$. On the contrary, the effect of the *disposition to share* of the other shows the highest effect, with $\beta_{S_{e2}} = 0.071$ $(s.e. = 0.003)$, $p < 0.0001$, where S_{e2} is the disposition to share of the other end of the connection in a given team. The *disposition to listen* of the agent also has an effect on competence increase, with $\beta_{L_{e1}} = 0.021$ $(s.e. = 0.004)$, $p < 0.0001$, where L_{e1} is the disposition to listen of the node from where the link originates. The coefficients are to be interpreted as the average increase the selected independent variable has on the dependent variable at each time step. If observed from this perspective, in spite of the apparent low number of the estimate, the effect is actually extremely powerful, given we have 260 data points in time.

The other two variables considered are the *disposition to share* of the agent, and the *disposition to listen* of the other agent. Now, from a purely rational perspective, these seem to be irrelevant in that competence should be a function of the information gathered by the agent, and not that transferred to other agents. Results support this assumption only partially. On the one hand, a positive attitude of an agent towards sharing information has a positive effect on its own competence, with an estimate that has the highest effect in the regression, with $\beta_{S_{e1}} = 0.175$ $(s.e. = 0.003)$, $p < 0.0001$. This is surprising and it probably indicates that the exchange needs to be bidirectional to actually work. In other words, cognition needs to be considered a system in order to work (more on this below).

On the other hand, it is surprising to see that the disposition of the agent at the other end of a connection to listen affects the development of competence of the agent at the origination point negatively, with an estimate of $\beta_{L_{e2}} = -0.023$ $(s.e. = 0.004)$, $p < 0.0001$. Again, this is probably related to a systemic effect that is discussed in Section 4.

Figure 4 is a visual representation of these regression results. However, this is conducted by crossing these results to the findings of the structural network analyses above. In order not to overestimate any of the centrality indexes presented in Table 1, we have created a Composite Centrality Index (CCI) that is a simple weighted average of eigenvector (EV), betweenness (B), and closeness (C) centrality:

$$CCI = \frac{1}{3} \times EV + \frac{1}{3} \times C + \frac{1}{3} \times (B/max(B)). \quad (1)$$

We then categorized the data points into three influence groups, split by the 1st and the 3rd quartiles. Data are organized around these three groups in the panes shown in Figure 4. The *y axis* is the logarithm of *competence* for the team leader, the *x axis* is the *disposition to listen* (L_{e1}), and colors represent the *disposition to share* (S_{e1}) of the team leader. The plot shows that competence is higher when CCI is high (right pane vs. left and middle pane), indicating that structural elements of the network do have an effect. However, at the same time, these effects can only be seen in combination with the two cognitive dispositions, that need to be relatively high in order for competence to occupy higher positions in Figure 4.

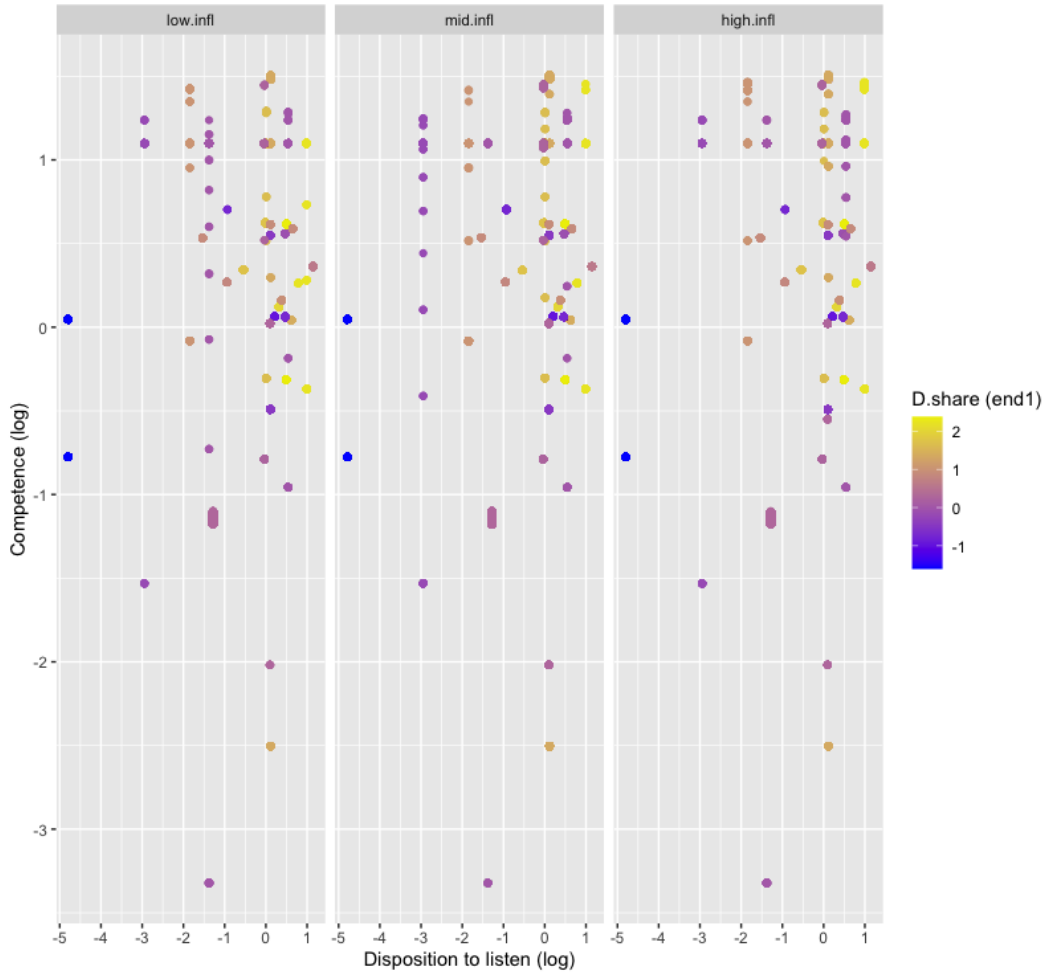

Figure 4. Competence (log) for each informal team leader explained by (log) disposition to listen to the agent. The data points are colored using the disposition of the team to share leader. Each pane is split over a centrality index that combines the three measures in Table 1.

4. Implications and Conclusions

This article started by presenting the assumption that cognition is systemic, it has provided the theoretical arguments to support this claim, and it has then used a computational simulation as an example to observe and to reflect on cognitive dynamics.

The analysis of the agent-based `TS 1.0.5` Model is oriented towards unearthing cognitive dynamics that relate to agents' learning mechanisms that ultimately affect their competence in dealing with the task at hand. The analytical approach has been incremental and started from the structural elements to then assess the dynamics emerged within teams. Implications are organized into two areas: (a) the workings of the *meso* domain (i.e., the *elements*), and (b) the importance of the distributive *processes*.

4.1. Systemic Elements

The analysis of the data from the simulation shows that competence is nested within teams. In part, this derives only indirectly from how the simulation was developed. In fact, the simulation model makes it such that competence increases from cases that are successfully solved. This allows agents to acquire new knowledge and develop their competence further. In principle, agents with high levels of competence are more likely to successfully deal with the task at hand and they may learn from this activity. When competence is not developed enough, the informal network of other agents comes into play. Furthermore, in this case, the solution to cases only depends on successful exchanges with other connected agents. The simulation does not give "preference" to these social

interactions, in the sense that parameter values are distributed normally around means and standard deviations and the procedures split the agent population in two, by using the mean as a threshold. Nevertheless, the vast majority of agents in a team do develop their competence as a result of being embedded into such teams.

This means that the social elements of cognitive dynamics lie more at the core than those claimed by both traditional cognition [8,11] and distributed cognitive scholars [5]. It is the formation of social relationships around each agent that constitute the basis for "learning" to happen, as reflected in competence development. In light of this feature, we have called this phenomenon *social organizing* elsewhere [3,33]. This also means that a "center" of such a system is very difficult to isolate and standard measures of centrality (see Table 1 above) do not fully capture cognitive dynamics. They do provide information on positions and roles in a (nested) structure of informal networks, but the knowledge that can be gathered from them is about the potential of each node. In this article, social network analysis has been pivotal in understanding that more information was necessary in order to analyze the dynamics of the cognitive systems. Furthermore, there are as many cognitive systems as there are teams, although these are, as anticipated, nested—the same agent is part of multiple teams.

The *fluidity* with which agents develop competence is another element that emerges from the analysis. This means that, in spite of their centrality and initial parameter values, it is very difficult to predict where the cognitive dynamic of each agent is going to evolve, or is going to end when observed from the start of the simulation. Some of them may develop competence as a result of an emergent process, leading to unexpected outcomes (i.e., the final competence level) [28].

4.2. Systemic Processes

Structural aspects—the teams in our simulation example—are very relevant in the understanding of cognitive dynamics. At the same time, they are incapable of providing a full explanation. A structure needs to be understood in the dynamics originates in it generates. The elements—social and other resources—of a structure interact to give rise to configurations that cannot be understood by an isolated analysis of it. This is why the elements of a system must be understood in connection to their actual and potential capabilities. This, in turn, may affect structure itself, among other aspects.[3] For this reason, the mechanisms with which agents interacted in the simulation were not fully in line with the results of the social network analysis.

Cognitive dispositions play a significant role in any cognitive system [4,34]. However, what emerges from the simulation results is that they have to be considered in a systemic perspective. This means that cognition has no actual "center", but its distributive features make it very difficult to understand how, when, and why an element is central. The rather surprising result that the competence of *agent x* depends on the disposition to listen of another *agent y* points to this proposition. Furthermore, the other result that indicates that the disposition to share of *agent x* affects its own competence development negatively is also supporting of this proposition. If we reinterpret results by thinking systemically about them, then a candidate (apposite) explanation is that it is the combination of all the elements together and their interactions that affect cognition. In light of this perspective, sharing may redirect resources over others and it can be thought of as an investment (a cost) to pay to build trust and other relationships. In other words, it is a negative effect that creates other, more powerful, positive effects. Again, it is the system that matters, not the role of the individual element.

4.3. Concluding Remarks

This article started with the proposition that cognition is systemic. Building on it, the claim is that the type of system that should be considered to understand, define, and analyze human cognition shows features typical of complexity. As a way to define more precise boundaries of this proposition—i.e., that human cognition is better described

as a complex system—we have used an agent-based computational simulation model. We zoomed in on a particular configuration of parameters of the `TS 1.0.5` Model to study the cognitive dynamics behind competence development. In the model, as well as in most observed cognitive systems, competence constitutes a body of knowledge that is applied to specific domains to perform tasks, solve problems, or to perform one's job, more generally. Traditionally, just like cognition, competence has been considered as something pertaining to the individual. We have come across something that departs quite significantly from this perspective.

There are at least two major remarks that can be drawn from the theoretical background and the example presented in this paper. One is that the type of complexity we have outlined is very much in line with systems that adapt, self-organize, reconfigure, show resilience, weaken dependence on initial conditions, and are extremely difficult to predict. The assumptions made in the `TS 1.0.5` Model are fairly simple. Agents are not characterized by standard features of human beings; they only have characteristics that are strictly functional to the task to be performed. These characteristics are also in line with the social environment in which the agents operate. In spite of this abstraction, the results discussed in this article clearly indicate that cognition clearly shows dynamics that can only be characterized in the realm of complexity. Furthermore, the point here is that, if such a simple abstract representation already produces a fair level of complexity, there are good reasons to believe that complexity can be found also when the model (the observed system) increases the complex characteristics of its agents (human beings, in the observed system).

The other consideration reflects the elements that make this complexity. The theoretical concept presented in the first part of the article that states the importance of social mechanisms in understanding and analyzing cognitive dynamics is probably the kernel of what we have shown in this article. The mechanisms of cognitive distribution that allow agents to learn, and thus increase their competence, are, in essence, social interactions. These happen in a given frame and with given characteristics of the agents, yet their dynamics are such that they can shape (or re-shape) the system. Neither the frames (e.g., the network structure) alone nor the individual characteristics (e.g., competence, dispositions) alone can explain cognitive dynamics. This supports the original proposition that the *meso* domain is central in understanding complex systemic cognition.

The portion of the `TS 1.0.5` Model presented in this paper is a relatively simple snapshot of a broader version that has been used to analyze the effect of team structures on performance. Future research may look at sensible extensions of this model to move the inquiry further. Amongst the many, a modified version of this model that develops characterizations of agents by including historical information, expertise, skill levels, and a more nuanced account of informal relations among agents would benefit our understanding of the making of the meso domain as well as define the system in more detail. Another version of the model could compare different perspectives of competence in an attempt to understand when and if a more traditional (isolated) account matches the explanatory power of the distributed account presented here. Finally, the model could be extended to include more dynamic perspectives of agents leaving a team and joining another, or a hiring/firing process. In this case, adaptation would play a role and it could be interesting to understand how big a role it could have.

Perhaps we can end the article with a call for cognition scholars, on one side, and to complex systems scholars, on the other. The former should consider an a-centric complex system perspective when studying human cognition; such a perspective makes it possible to increase the explanatory power of the analyses while, at the same time, providing a more accurate representation. We would like to invite the latter to consider the domains across and between micro and macro—what we called *meso* here and elsewhere—when studying complex social systems.

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Notes

1 This simply means that the *type* of agent-leak is consistent with the area of competence of the agent-employee.

2 Apart from the parameter values indicated in the text, the simulation also fixes the *case importance threshold* at 0, *competence increase* $\delta_c = 0.02$, and *relationship range* $\phi = 15$ (its maximum).

3 This was not possible to observe through the simulation, because we have selected a relatively static version of it to analyze in this article. However, this could be a good topic for future research studies.

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Emergence in Complex Physiological Processes: The Case of Vitamin B12 Functions in Erythropoiesis

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Abstract: In this paper, we will explore the relation between molecular structure and functions displayed by biochemical molecules in complex physiological processes by using tools from the philosophy of science and the philosophy of scientific practice. We will argue that biochemical functions are weakly emergent from molecular structure by using an account of weak. In order to explore this thesis, we will consider the role of vitamin B12 in contributing to the process of erythropoiesis. The structure of the paper is the following: First, we will consider biochemical functions and why they cannot be easily reduced to their chemical realisers. We will suggest weak emergence as an alternative while also accounting for the relevance of the context, in our case, systemic and organisational. The paper will conclude by considering (1) how the usage of tools from the philosophy of science, such as weak emergence, can aid our understanding of the relations between the components of complex phenomena, such as erythropoiesis, and (2) how the philosophy of scientific practice sheds light on the explanatory role of processes that are dynamically stabilised and the different levels of organisation implied.

Keywords: biochemical functions; weak emergence; robustness

1. Introduction

Biological and life scientists use the concept of function in reference to a variety of structures and processes that concern living organisms. And even more so, it is noted that one of the differences between the living and the inanimate is that biological systems display functions, but how these functions arise from physical-chemical components is still the object of discussion and seems to lack scientific explanation. This question becomes even more complicated to answer if we consider functional ascription to entities such as biochemical molecules, which operate as a key link between chemical processes in organisms and biological processes.

Biochemical molecules, such as vitamins, proteins, or nucleic acids, are commonly ascribed functions, however, they are chemical compounds and not the standard target for functional ascription [1–4]. This opens questions on the relation between the structure that these molecules display and their (attribution of) functionality. Specifically, one can ask whether it is possible to reduce the functionality of these molecules to their chemical structure or not. In this paper, we will explore the relationship between molecular structure and functions displayed by biochemical molecules in complex physiological processes by using tools from the philosophy of science. We will argue that biochemical functions are weakly emergent from molecular structure by using the account of weak emergence suggested by Franklin and Knox [5] and Bellazzi [6]. According to this account, a given phenomenon can be considered weakly emergent if it is novel and robust. Novelty implies that the postulation of the phenomenon allows for novel explanations compared to only postulating the entities from which it emerges. Robustness implies that the phenomenon is stable within given perturbations, which we will consider in terms of multiple realisability [6–8].

In order to explore this thesis, we will consider the role of vitamin B12 in contributing to the process of erythropoiesis. The structure of the paper is the following: First, we will consider the status of the controversy and why the biochemical functions of vitamin B12 cannot be easily reduced to their chemical realisers. Mostly this is because of the relevance of the evolutionary history of erythropoiesis, which is relevant to identifying which chemical properties of the molecules are contributing to the process. Given that reduction is not feasible, we will suggest weak emergence as an alternative to reductionism, as in the account mentioned above. While building up on Franklin and Knox [5] and Bellazzi [6], we will also present a novel contribution to this account by considering the relevance of the context, in our case evolutionary, to weak emergence. The paper will conclude by considering how the use of tools from the philosophy of science, such as weak emergence, can aid our understanding of the relations between the components of complex phenomena, such as erythropoiesis. We will also specify how the philosophy of scientific practice sheds light on the explanatory role of processes that are dynamically stabilised and the levels of organisation that are present in such processes.

2. Biochemical Functions: Erythropoiesis and Vitamin B12

Vitamin B12 is a vitamin functional for different life and physiological processes, among which erythropoiesis, the renovation of red blood cell. This vitamin comes in four forms: vitamers of cobalamin-compounds: cyanocobalamin, methylcobalamin, hydroxycobalaim, and adenosylcobalamin. This characterisation of vitamin B12 shows that this kind is not characterised only by structural chemical properties but also by the function that these groups of compounds display: it is a functional kind, like "acid". Vitamins are not defined by their composition (alone), but by the behaviour they display in given physiological and biochemical processes [9]. Given the core role that the functional properties play for this kind, it is then important to ask: What does it mean that this vitamin has a function? How does it relate to its structural components?

Functional ascription at the molecular scale has been the object of discussion in recent literature (see [10,11]). This is because, while on the one hand, functions are regularly ascribed at the molecular scale, on the other, there is tension regarding whether evolutionary or etiological views of functions can be applied to such cases because of both "socio-linguistic arguments" and "ontological arguments" (as in [4,12]). The first wants to underline that scientists do not ascribe functionality to molecules by thinking of evolutionary-selected functions. The second instead focuses on whether molecules can be the right ontological target of evolutionary selection. These considerations can lead instead to using a chemical view of function for biochemical molecules, akin to the causal theory of functions [13]. The shortcoming of this approach is that biomolecules seem to have functionality in terms of their contribution to specific biological processes rather than having a different chemical reactivity profile. A way to keep together the considerations while accepting genuine functional ascription to molecules can be found in Bellazzi [4], according to whom a correct analysis of functions in biochemical systems needs to comprise both their chemical and biological characterisation. This can be conducted by identifying which chemical components of the molecule contribute to the process under consideration, via which chemical reactions, and how this contribution is process-specific. This offers us the following account of biochemical functionality:

BC-function: Biochemical functions are associated with a set of chemical properties that lead to a specific effect within biological processes. These biological processes are a product of evolution, and, as such, the relevant chemical properties are indirectly evolutionally selected [4].

This account of function, while it individuates a specific realization basis for biochemical functions, does not reduce such functions to their chemical components, as the individuation of them is not specific enough to analyze the contribution that biochemical molecules make. This view accordingly builds on a casual contribution view of functions a-la-Cummins [13], for which a function is a causal contribution to a given process.

However, this view is also different from it as it adds and specifies that the evolutionary context is the one picking up the relevant chemical processes for the biological process (and not the interest of the scientists)[1]. Moreover, this account of functions is compatible with the organizational account of functions, which has proved successful in the analysis of other cases of relations between different parts of given systems [14,15]. According to an organizational account of functions, functions have to be understood as inherently related to the idea of the self-maintenance of biological systems. This view works well with the proposed account of functions, as biochemical functions are seen as specific causal contributions to an organizational system or process that are contributing to life. In this sense, a biochemical function can be seen as realized by those chemical properties of the molecule that contribute to a higher or organizational process that maintains life. At the same time, this account does not want to present a unique view of functionality and can be seen as compatible with forms of function pluralism, for which we can ascribe functions in different ways in different contexts (as in [11]). In this regard, the account is compatible with using a causal contribution view of functions in some contexts, a biochemical view of functions in others, and an etiological evolutionary view of functions for others as well.

Let us consider an example to make the case more precise: erythropoiesis[2]. Erythropoiesis is the process that produces new erythrocytes in order to allow for the renovation of red blood cells and the destruction of the old ones that are needed daily to keep blood healthy. In order for this process to proceed properly, different biochemical molecules are needed, and in particular, the role of folic acid, vitamin B12, and iron has been underlined. Specifically, vitamin B12 is needed for the proliferation of erythroblasts during differentiation. A lack of this vitamin can lead to severe dysfunction in erythropoiesis, which can result in erythroblast apoptosis and anemia. As a result of this brief overview of the considered physiological processes, we can notice that erythropoiesis is a complex process that requires the interaction of different components that need to be integrated for the process to continue appropriately. In this paper, we focus on the biochemical function of vitamin B12 in this process. Following the account aforementioned, the biochemical function of vitamin B12 (**BF-B12**) corresponds to the specific set of chemical dispositional properties that are manifested in "the transfer of a methyl group from 5-methyl-THF to homocysteine via methylcobalamin, thereby regenerating methionine" [16].

Accordingly, we can unpack B12 vitamin function as those chemical dispositional properties that react in a specific way during the regeneration of methionine required in erythropoiesis (following the account presented in [4]). The action of the chemical powers of **BF-B12** depends on the right biological context for their contribution and on the presence of the right process to which the molecules can contribute. This can be seen within the framework of an organisational account of function: the organisational process of erythropoiesis needs to be happening, also thanks to cell regulatory mechanisms and the action of various enzymes and co-factors, for the **BF-B12** to be realised. Given the organizational account of function that works well in this context, it is important to stress that this functional contribution relates to the well-functioning of a process that is *evolutionarily selected*. The role of evolutionary selection is important in identifying which processes and contributions of vitamin B12 result in functional erythropoiesis in a way that is beneficial to the self-maintenance of the organism.

This consideration rules out the possibility of fully reducing biochemical functions to their chemical realizers. This is so because the organizational and system considerations that pertain to the process of erythropoiesis are needed in order to identify the specific contribution that relates to the biochemical function. How can we then characterise the relationship between chemical components and the biochemical function realised in erythropoiesis, if not via a reductive strategy? An answer can be provided by weak emergence.

3. Weak Emergence of Biochemical Functions: Erythropoiesis and Vitamin B12

Emergence is a useful tool to characterise the relationship between dependent but different or autonomous components of a given system [17]. The discussion on this notion

is wide in terms of conceptions, applications, and topics, and it is important to clarify where we stand in this regard. Emergence can firstly be characterised in terms of epistemic or ontological emergence, where the first (epistemic) refers to the relation between the entities or phenomena within theories and relations of explanations/computation and the second (ontological) regards some ontological or qualitative difference that the emergent entity has in comparison to the lower level. In the case of epistemic emergence, a given entity is considered emergent in relation to whether that emergent property or entity cannot be *derived*, *computed*, *or predicted* on the basis of the theories, laws, or postulated properties that realise them [18]. In the case of ontological emergence, instead, a given entity is considered emergent in relation to *whether that entity displays some novel or causally specific features that makes them qualitatively and ontologically* different from the lower-level [18,19]). In this paper, we are concerned with *ontological emergence*[3]. A second important distinction that one can draw within the sphere of ontological emergence is the difference between weak and strong emergence[4]. A given phenomenon is considered weakly emergent when it is "realised by the lower-level ones" in a genuine way, even if every token of the property of the emergent phenomenon is identical with *some* lower-level feature at the time considered [19]. A given phenomenon is instead considered strongly emergent when it is realised by the lower-level entities, but at least one token of the properties of the emergent phenomenon is novel compared to the lower-level at the time considered [19].

In this paper, we will consider ontological weak emergence and follow this characterisation: a given phenomenon can be considered weakly emergent if it is novel and robust [5,6]. Novelty implies that the postulation of the phenomenon allows for novel explanations compared to only postulating the entities from which it emerges. Robustness implies that the phenomenon is stable within given perturbations, which we will interpret in terms of multiple realisabilities. This account presents a combination of epistemic and ontological criteria in that it considers both the contribution that considering a given entity makes to explanations and the stability displayed. Moreover, it acknowledges the relevance of robustness, a feature of biological systems that plays a crucial role in the discussion in the biological sciences [7,21].

In detail, the defining properties of the phenomenon under consideration are considered emergent when they are characterised by two features:

- Novelty: "it is possible to identify the emergent property in a distinctive way[5] from the properties held by the lower-level entities, and the consideration of such a property improves explanations, leading to new ones" [6]; see also [22]). Novelty is a useful criterion to identify emergence as it captures the epistemic component that the postulation of emergent phenomena can bring. Specifically, it allows us to see that there are explanations that can be provided by applying emergent phenomena.
- Robustness: the emergent property displays stability within a certain range of perturbations and relatively to some lower-level properties, which we will interpret here in terms of multiple realisations [5,8]. While novelty is mostly epistemic, robustness is the ontological feature of this account. In this paper, robustness is interpreted in terms of multiple realisability, as in Boone [7] and Bellazzi [6], where a phenomenon can be considered multiply realisable when it can be realised by different lower-level entities.

Weak emergence, so formulated, can be a fruitful conceptual tool when considering the relations between chemical structure and biochemical functions. This view combines a form of dependence, allowing for the identification of the specific chemical components that contribute to the physiological processes, with the ontological autonomy and relevance of the functional contribution. This allows us to maintain the specificity of the biochemical functions while keeping them distinct from the chemical features from which they are realised. Moreover, as we will clarify in the next section, this account allows for good compatibility with scientific practice, as the weak emergence of biochemical functions in the right context can be an *explanans* for their stability and relevance in erythropoiesis. Specifically, it is legitimate to ask about the relationship between novelty and robustness and the weak emergence of the phenomenon. On the one hand, we can interpret novelty

and robustness as our means to track and have access to the weak emergence of the phenomenon that we are considering. On the other hand, weak emergence represents the ontological reason or principle why the phenomenon displays novelty and robustness (see also [21]).

Let us now apply this account to the case study considered. As we said in the previous section, vitamin B12 has **BF-B12** in erythropoiesis, and this can be identified with the specific chemical properties of the vitamin B12 molecules that are responsible for the transfer of a methyl group from 5-methyl-THF to homocysteine via methylcobalamin. These properties are relevant because of the evolutionary history of erythropoiesis, which evolved in order to interact specifically with the chemical properties of given chemical compounds. Can **BF-B12** in erythropoiesis be considered weakly emergent?

The first step is to consider whether **BF-B12** in erythropoiesis satisfies **(a) novelty.** Novelty is defined as the capacity to lead to new explanations once the property is distinctively identified and it is possible to identify a distinctive causal profile of such property. This criterion is mostly epistemic and tells us that the postulation of the property considered provides more explanatory power than simply postulating the lower-level entity from which it emerges. In the case considered by this paper, it means that postulating **BF-B12** in erythropoiesis is more explanatorily powerful than considering the simple cobalamin as a chemical compound and its functional profile, i.e., its reactivity profile. We argue that this is the case for two reasons. The first is that, as we said, the consideration of the merely chemical properties of the compound is not specific enough to tell us which properties are contributing to erythropoiesis and thus does not give us enough explanatory power. Specifically, the reactivity profile of the various cobalamin compounds comprises a variety of reactions the molecules can undergo, and this differs from the more specific contribution vitamin B12 makes to erythropoiesis. In terms of explanations, the consideration of **BF-B12** as a biochemical function allows us to consider the specific functional role that the vitamin plays as a vitamin and not as a series of chemical compounds. This provides us with more specific explanations. Moreover, it allows us to see the contribution vitamins make to a specific physiological process. In a nutshell, considering BF-B12, it explains the functional role of the vitamin in a more specific and focused way than its chemical counterpart, thanks to the specificity of the function and its role in the context. The second reason for which the consideration of **BF-B12** is novel in this sense can be found in the multiple realisabilities that this function displays. As we said, multiple realisability can be defined as the capacity of a given type to be realized by different lower-level ones. Vitamin B12 can contribute to erythropoiesis in its four vitamers form; that is, four different chemical compounds can contribute to erythropoiesis thanks to specific relevant interactions. This allows the **BF-B12** in erythropoiesis to be multiplied by the four vitamers. Why would this matter for our explanations? The answer is that the consideration of **BF-B12** as such, compared to the chemical properties of each vitamer compound, allows us to consider the contribution of vitamin B12 to erythropoiesis while screening off chemical differences. Accordingly, the consideration of the biochemical function in itself (without considering the details of the realisers) can allow us to improve our explanatory power in terms of making a more direct and simpler explanation compared to the one that would consider each vitamer on its own (following a chemical explanation only) compared to a biochemical systemic one.

Moreover, the account of biochemical functions presented is compatible with an organisational view of functions (as in [15]). The analysis of the function from the point of view of the organizational system can boost our explanatory perspective as it allows the identification of the level of biochemical complexity that generates a particular physiological phenomenon, namely the regeneration of erythroblasts, and the contribution that B12 makes to this process. The introduction of **BF-B12** in erythropoiesis can thus be considered novel. Moreover, this novelty remains particularly interesting because it allows considering the explanatory role that biochemical functions have, despite their manifestation and causal role being, by definition, context-dependent. The context dependency of biochemical phenomena can be used either in favor of or against their ontological, that is, existent,

status (as in [3,23]). In the account proposed, it is the fact that biochemical functions are context-dependent, that is, within an organizational systemic setting, that allows for their novelty to be explanatorily relevant.

Let us now turn to **(b) robustness**. The literature on robustness is wide in scope and relevance, as we can identify different kinds of robust behavior. Nevertheless, robustness can be seen as a useful "bridging notion" that allows for the integration of practical and theoretical aspects of a given phenomenon [24]. Generally, we can define robustness as the capacity of a given phenomenon to remain stable within given perturbations. This interpretation of robustness is well captured by the expression of Giuliani, for which robustness relates to the "die-hardness" of a phenomenon: this phenomenon can resist variations at the lower level [8]. In the context of biological cases, we find that an interesting application of this can be seen in terms of multiple realizability (as in [6,7]). In this case, a phenomenon is "hard to die" when there are different phenomena or things at the lower level that can realise it.

Let us unpack this further. Multiple realisations can be seen as having the same type of entity; in the case discussed, a given biochemical function is realised by different types of entities at the lower level, that is, the chemical properties of different cobalamin compounds [7,25]. Moreover, according to this understanding of multiple realisations, at the given time *t* every token of the property considered will be realised by some specific token features of the realising feature. For example, in a given instance of erythropoiesis, the contribution of **BF-B12** to erythropoiesis can be realized by a set of token molecules of cyanocobalamin (one of the vitamers of vitamin B12), and in another instance, it can be realized by instances of metyhlcobalamin. This makes the function **BF-B12** multiply realised, while maintaining the possibility that, in given instances, the token functions remain singularly realised.

Given the definition of robustness in terms of multiple realisability, the fact that **BF-B12** can be realized by different molecules while maintaining the efficiency and organizational stability of the process of erythropoiesis is sufficient ground for its robustness. Again, the multiple realisability and robustness of such functions can only be properly understood if we consider the organizational context around such functions, that is, the process of erythropoiesis and its evolutionary history. It is thanks to this organizational structure that the contribution that given chemical components bring to erythropoiesis can remain robust, despite being realized by different vitamins of vitamin B12.

In conclusion, while there is a relation between the chemical structure of vitamin B12 and its functional contribution, we have grounds to interpret such a relation in a non-reductive way, specifically by interpreting such functions as weakly emergent. **BF-B12** can display novelty because the postulation of biochemical functions understood as organizational and specific functions can improve our explanations of erythropoiesis. This is so because the notion of function used is causally specific and allows for the context and organizational dependence that these phenomena maintain. Moreover, **BF-B12** can display a form of robustness as well as stability, as the function is multiply realizable because vitamin B12 can be composed of four different vitamers. Accordingly, **BF-B12** is weakly emergent as it displays novelty and robustness within erythropoiesis.

4. Scientific Practice and Weak Emergences

Why is the consideration of weak emergences relevant for scientific practice, and what are the benefits that their consideration can bring?

As we said above (Section 3), novelty and robustness are our means to track the weak emergence of the phenomenon that we are considering. On the other side, weak emergence represents the ontological reason or principle why the phenomenon displays novelty and robustness. Emergence is, in a way, the feature through which we can both postulate the existence of something and its knowledgeability (as in [6]). So, when in scientific practice we are studying an emergent phenomenon, we can know that it is such because it displays novelty and robustness; we have epistemic access to its emergence thanks to its being novel

and robust. But, from an ontological point of view, the phenomenon can display novelty and robustness because it is emergent and so existent in the first place[6].

Let us consider this more precisely. Novelty has been defined as what captures an epistemic dimension of scientific practice, allowing the identification and explanation of a new stable dynamic process, i.e., of a phenomenon that is context-dependent. The emergent property or phenomenon offers an *explanans* for these new dynamics. More precisely, the weak emergence of BF-B12 allows for explaining why vitamin B12 contributes to erythropoiesis in the specific way considered. However, this is also possible because the emergent property has an explanatory power by virtue of its stability, that is, its robustness: we are able to track the contribution of BF-B12 in a way that is stable and that "screens-off" the fact that these molecules are multiply realisable.

This suggests considering the role that robustness has in this account and its relevance for scientific practice. On the one hand, robustness is a feature of the phenomenon that indicates (epistemically) the presence of a weak emergent phenomenon; on the other, robustness is also an ontological feature of the phenomenon because it brings in multiple realisabilities. This is so because the emergent property can be understood independently from the system's constituent at the lower levels and can acquire a proper ontological status: it is something different from its realizers. In scientific practices, this allows the emergent entity to become an *explananda*, and an object that can then be identified, tracked, and explained.

We can notice that, thus, a weakly emergent phenomenon can be both an *explanandum*, as something that explains a specific contribution, and an *explananda*, by becoming a self-standing phenomenon and thus an object of scientific inquiry. This duality allows us to see that at the crossroads of functional accounts and robust explanations, there is an issue of philosophy in practice that regards how different levels of explanation are identified and inquired about. What, in fact, becomes relevant is accounting for, on the one hand, the specific causal contribution that the emergent entity has while, on the other hand, how much such entity can be explained once it is identified as a core contributor to the phenomenon. In the case considered, BF-B12 has a given causal specificity in erythropoiesis that is novel, allowing for better explanations, and remains robust; at the same time, the function of BF-B12 remains something to be explained in scientific practice, justifying its investigation in scientific terms. How can we then have something that is both *explanans* and *explanandum*?

As Giuliani wrote [8], one of the core features of biological systems is that they operate with different *levels of organisations* that are connected by specific nodes, such as, for instance, biochemical molecules. Moreover, this paradigm allows for the detection of a clear "signature of robustness", i.e., the ability of a system to keep different scales of response to environmental stimuli separated.

The consideration of different levels of explanation can allow us to see how emergent phenomena can play this double role in scientific practice. Erythropoiesis can be divided into "biochemical" and biological "level". The first is the system of biochemical reactions needed in the regeneration of methionine for erythroblasts. In this case, the emergence of BF-B12 allows us to explain (being an *explanans*) the contribution made by vitamin B12 thanks to its robustness and novelty. The second is the biological level, which allows us to see how the production of new erythroblasts contributes to the organism. At this level, the stability of BF-B12, given its robustness, allows it to be a target of the relevant evolutionary explanations that still need to be further investigated. This interplay allows us to see how, within given levels of organisation, we can see the relevance that weak emergence brings.

This is possible because the account of weak emergence used considers robustness, which allows us to identify the ability of a system to "keep separate different scales of response to environmental stimuli" (as in [8]). The robustness of BF-B12 represents a bridge between the two levels of explanation, the biochemical and the biological, and this can be further used within scientific practice.

This reflection can be further expanded by considering the relevance that robustness plays across other levels of organization. Robustness is the *explanandum* for inquires from an ontogenetic or phylogenetic point of view, and it is the *explanans* for evolvability or higher-level biological phenomena. In this sense, robustness is a target of natural selection and can be listed among the features that enable evolutionary change. This is an example that Huneman [26] labels with the term "explanatory reversibility" [24]: "Thus, with respect to evolution, robustness may be seen as an aspect to be explained by (*explanandum*) or as a feature that explains (*explanans*) evolutionary change and/or the particular evolutionary trajectories that are discovered in the history of life. Robustness as an *explanandum* connects with other evolutionary *explananda* such as complexity, modularity or evolvability". The context dependency (e.g., embodied topological features of the system) can be understood, in this sense, as the "invariance through continuous transformation" exhibited at the network level (Huneman, ibidem). This is something that we can apply to BF-B12, and it will allow us to further see the duality of *explanans* and *explanandum* that its weak emergence plays. Biochemical functions remain stable while changing the specific vitamer considered and while maintaining the contribution to the network involved in erythropoiesis. The function to be explained is no longer an attribute of a piece of matter but of that piece of matter (molecules) in a given network. This allows it to be something that explains a specific contribution but also something that has to be explained within the evolutionary history of the network of relations involved in erythropoiesis.

Concluding that weak emergence is so characterised allows us to see how the consideration of weakly emergent phenomena can contribute to scientific practice, specifically when there are different levels at play[7]. The consideration of biochemical functions provided framed them as fundamentally dependent on the network in which they operate. Network approaches allow us to account for biological regulation in terms/trough weak (but robust) emergent properties and allow us to link the components of our analysis. Giuliani wrote that this allows for the detection of a clear "signature of robustness", i.e., the ability of a system to keep different scales of response to environmental stimuli separated [24][8]. This offers two different sides of the explanation. On the one hand, the emergent phenomenon is a source of explanation for the biochemical level considered; on the other, the emergent phenomenon can become a target of explanations thanks to its robustness.

5. Conclusions

The characterisation of the relationship between structure and function in biochemical systems and molecules is still an object of discussion. This characterisation is even more relevant if we consider that biochemical functions operate as a key link between chemical processes in organisms and biological processes. In this paper, we have argued that the use of the philosophical tool of weak emergence can allow us to characterise the relation between structure and function in a way that is interesting for scientific practice as it considers the levels of organisations involved. Specifically, we have built up on an account of weak emergence (as in [5,6]) by considering how the context, in our case systemic and evolutionary, can allow us to frame weak emergence in a way that can aid the consideration of different levels in scientific practice. This is so because weak emergence can allow us to shed light on the different explanatory roles that are present in processes that are dynamically stabilised and the levels of organisation that are present in such processes. Specifically, we concluded by considering how the emergent phenomenon can be both explanatory and explained, thanks to the crucial role that it plays as the connecting link between biochemical and biological processes and its robustness.

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Notes

1 For a more detailed analysis of the relation between this view of functionality and Cummins' account can be found in [4].

2 The main reference for erythropoiesis is [16]. Moreover, parts of this section rely on the discussion on biochemical functions published in Bellazzi [4].

3 As suggested by the reviewer, it is important to notice that sometimes weak emergence is referred to as epistemic emergence, while strong emergence refers to ontological emergence (as also in [18]). In this paper, we are considering ontological weak emergence, which considers the features of the emergent entity as qualitatively different from the lower-level, but still dependent on it and not presupposing any form of non-physicalism. Moreover, this account wants to be compatible with forms of epistemological or methodological reductionism, allowing for scientific research to advance in a way that allows a reductive methodology or explanation of the emergent features, without changing their ontological status (as in [5,6]).

4 The distinction between weak and strong emergence can also be framed within epistemic contexts. For instance, Chalmers [20] defines weak emergence as the case in which the "high-level phenomenon arises from the low-level domain, but truths concerning that phenomenon are *unexpected* given the principles governing the low-level domain" and strong emergence as the case in which the "high-level phenomenon arises from the low-level domain, but truths concerning that phenomenon *are not deducible even in principle* from truths in the low-level domain".

5 In a "distinctive way" indicates that the emergent property possesses a specific causal profile compared to the entities realising it, that is leading to specific effects.

6 The difference between the epistemic and ontological aspect of our argument is important to underline why the characterisation of emergence proposed is not circular. Specifically, weak emergence is what makes the phenomena novel and robust in the moment in which we want to track them, but it is precisely the manifestation of these features that allows us to see that weak emergence is in place.

7 As suggested by one of the reviewers, a further implication of this paper could impact how we can conceptualise the distinction and interplay between pragmatic systems biology and systems-theoretic biology. While this represents an interesting further development, it goes beyond the scope of this paper and remains to be explored in future work.

8 Segue: For Giuliani, the biological way to robustness in an ever-changing environment is the presence of a network in which elements self-organize, by the only effect of their location in the network, in differentiated roles, so as to ensure both high sensitivity to environmental stimuli and the maintenance of an invariant structure.

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Systems Precision Medicine: Putting the Pieces Back Together

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Abstract: Systems precision medicine is an interdisciplinary approach that recognises the complexity of diseases and emphasises the integration of clinical knowledge, multi-omics data, analytical models, and the expertise of physicians and data analysts to personalise the care pathway in complex diseases, such as cancer or diabetes. The aim is to gain a comprehensive understanding of diseases by analysing individual components and identifying relevant aspects for therapy and diagnosis. Key components, their interactions and emerging patterns can be studied using statistical, mathematical and computational tools. The combination of data analysis and clinical evaluation is crucial to effective decision-making, emphasising the need for an integrative approach rather than relying on data alone. Therefore, the crucial point discussed in this paper is that the "computational" part and the "artistic" part (i.e., the physician's intuition) cannot be separated, and therefore, systems precision medicine can be configured as a collective work of art, involving not only different medical professionals but also, and above all, professional data analysts. The work is "artistic" because data and mathematics alone, without medical knowledge of the context, are not enough. But the work is also "collective" in the sense that it must be the place of cultural integration between the professional intuition of the physician, which cannot be translated into mathematical formulas, and the ability to extract information from multi-omics data of the data analysts, who instead use formal and computational mathematical methods. However, to drive the medical revolution and reassemble a patient's parts, data analysts need to be involved in the hospital context, and precision medicine physicians should embrace data analytical perspectives. This will require ongoing dialogue, new languages of communication, and education that promotes continuous learning and collaboration between professions, fostering a new level of interdisciplinary collaboration for personalised care.

Keywords: systems medicine; precision medicine; interdisciplinary medicine; data medicine; systemic approach; biological big data analysis

1. Introduction

Systems precision medicine is a multidisciplinary approach that involves quantitative biotechnologies, information systems for data management, and methods for their analysis and interpretation. Ongoing and recent efforts and projects are playing a crucial role in advancing its implementation. Two notable examples are the 1000 Genomes Project and the European Health Data Space. The 1000 Genomes Project is an international collaborative effort to create a comprehensive catalogue of human genetic variation. The European Health Data Space is a European Union (EU) initiative that aims to facilitate the sharing of health data between EU Member States. Both initiatives are essential to the implementation of systems precision medicine.

Moreover, data quality, assessment, standards and good practices are vital components of effective data management forsystems precision medicine. They contribute to the reliability, integrity and usability of data, enabling organisations to make informed decisions, conduct meaningful analysis and derive valuable insights. Organisations can optimise the value and influence of their data assets by adhering to established standards and best practices, thereby ensuring data quality is maintained.

However, the success of this approach depends not only on large databases, advanced technological tools and the formation of interdisciplinary groups but also on the integration of heterogeneous data, ranging from patient records and multi-omics data to the identification of pharmacological targets [1]. This twofold integration is an incredibly difficult task, which in fact requires a long series of human and technological ingredients largely not seen in clinical practice. Instead, we see the intrusive presence of high-tech hucksters selling miraculous algorithms with fancy names. Meanwhile, in just a few years, the algorithm as such has become the new philosopher's stone, precisely because, like the philosopher's stone, it is thought to be able to do the following [2]:

- Provide data analysis methods capable of curing any disease (elixir of life);
- Acquire omniscience, or absolute knowledge of the future, through artificial intelligence and machine learning (the philosopher's ingredient);
- Transform data (base metals) into information (gold).

Unfortunately, the temptation to delegate therapeutic decisions to some distant, cold and calculating deity is an ancient human temptation that transcends time and space, as we turn to an "elsewhere" when we no longer feel able to solve our problems here at home. Artificial intelligence and all its esoteric offshoots now occupy the Olympus of fashion. Just think of the "neural networks", which have been given this suggestive name simply because they are inspired by the functioning of biological neurons, but they actually have nothing in common with biology [3,4]. To understand the inappropriate and dangerous association, just think of a network of tanks connected by tubes, which could legitimately be called a "urological network", inspired by the functioning of the bladder and urethra. Or a doll that cries because it wants a dummy could be called an "artificial baby" because it is inspired by human behaviour. And what about the dishwasher? The vacuum cleaner? Words are important because they define contexts of meaning in collective perception. If I call "Sleepwell" a pillow-shaped sweet that does not make me sleep well, I cannot say that I was inspired by the pillow; I am making an improper use of words and, in this case, a very dangerous one for people's health. Of course, neural networks are data analysis tools that are potentially very useful, even in medical applications, but it is important not to associate their functioning with that of a biological brain because this operation, as I said, is not only inappropriate but also very harmful in terms of the false expectations it can create in the patient.

Systems precision medicine as such puts its finger on the wound by clearly and unambiguously showing that treatment is an "earthly" matter and that it is not necessary to rely on in silico divinities but rather on flesh-and-blood people with the right interdisciplinary approach. We are all aware of the problem of integrating medical knowledge not only with data and analytical models but also, and above all, with physicians' intuition, because their deep, unstructured knowledge, which is not organised in schemes that can be captured by universal algorithms, is the most valuable resource for the true personalisation of the care pathway. The road is still long and arduous, and the reason is simple: if, on the one hand, "tearing apart" a patient is an operation that we can perform with great efficiency and accuracy, the same cannot be said when it comes to reassembling the overall picture to highlight the most relevant aspects for therapeutic purposes, diagnostics and treatment [5]. Therefore, let's leave the algorithms in their place in our toolbox and start discussing the path indicated by the systems view.

In precision medicine, the concept of a "system" refers to a set of "objects", such as molecules, cells or tissues, that are interconnected at different levels of aggregation, either physically or through functional and regulatory relationships [1]. The first step in a systems approach is, therefore, to identify the key components and their interactions. The next step is to examine the consequences of these interactions and observe emerging patterns or the system's behaviour. The ultimate goal is to understand the determinants that contribute to the birth and development of a disease using statistical, mathematical and computational tools that support each phase of the systems approach. The problem, however, is that while the physical and engineering sciences have a long history of using

these approaches, medicine has unique characteristics that make this work much more complex to put into practice.

Identifying and quantitatively measuring the parts that make up the system is an unavoidable first step: we can only start with data, i.e., "measurements" of some kind, and the biotechnological tools available today allow us to "see" more and more deeply, i.e., more and more details. Put simply, the parts of the system are becoming smaller and smaller and more numerous. While, on the one hand, we can unpack a patient in an increasingly fragmented way, on the other hand, the problem of putting the pieces back together is becoming more and more difficult. The incredible development of molecular biotechnology brings with it the price of a patient that is fragmented into ever thinner powders that become ever larger clouds. And there is still no agreement, even minimally, among researchers on how to integrate data and skills into a unified and coherent vision that can be applied in clinical reality.

In this article, I try to summarise, from a very personal perspective, the salient points of the historical and cultural development of the systemic approach in precision medicine and the challenges/opportunities it presents. In particular, I support the idea that, while the definition of the parts is now an uncontrollable and irreversible process that has been underway for decades, their integration into a unified framework cannot be based solely and exclusively on data and their analysis—as all approaches labelled as "data-driven" or "digital driven" suggest—but must build its foundations on the harmonious interaction of data, data analysts and clinicians. In other words, we also need a cultural integration that goes through the personal experience of each professional involved. This is why the path of diagnosis and treatment in systems precision medicine is strikingly similar to a collective work of art. The problem is not one of human "supervision", but of incorporating multidisciplinary technologies and skills into the same process of diagnosis and treatment.

I begin by identifying the turning points of systemic thinking and its first successes, which are making a huge impact in all areas of medicine, but particularly in what is known as "precision medicine", i.e., medicine based on molecular data that can identify the specific therapeutic targets of a given patient. Finally, the limitations of this single-target approach will lead us into the unexplored territory of defining new strategies that are not yet on the horizon, but which will certainly have truly revolutionary characteristics because, like all true revolutions, they will change the lives not only of patients but also of doctors and data analysts, who will increasingly work together in ways and forms that we could define as "artistic" rather than strictly "scientific".

2. Descartes' Dream

The idea of a world in which science represents the ultimate knowledge of reality, where truth coincides with certainty and where rationality is the only guide in the midst of life's chaos, was born in a most daring way on 10 November 1619. This occurred in a small room in Ulm, a Bavarian town on the banks of the Danube, which many years later would prophetically witness the birth of Albert Einstein. For weeks, young René would remain locked up in this poorly heated room, trying to solve the terrible problems that had plagued mankind since the dawn of time and that our "humble" friend, now only 23 years old, was pursuing relentlessly and with titanic determination and perseverance. It was very cold that evening and he fell asleep in the faint heat of the stove.

The first dream was of a ghostly whirlwind that tossed him here and there, making him pirouette three or four times on his left foot as he felt himself falling towards nowhere. Then, the wind stopped, and he woke up. But immediately he fell asleep again, and the second dream took him suddenly. He heard thunder and saw sparks flying around his room. The second dream ended and immediately began the third, the most disturbing and foreboding (at least according to him). Here, everything was extremely quiet, calm, the atmosphere serene, meditative. There was a table with a book of poems: he chose a page at random and read a verse: "What path will I take in life?" Then, another apparition, a stranger, recited another verse: "Yes and no". Then, he told the stranger that he had a

more beautiful book than the one he had just read, but as soon as he finished, everything disappeared: the table, the book and the stranger. He woke up. René was shocked and began to pray. When he recovered, he felt that he had had a supernatural experience. In fact, he had good reason to because his interpretation of the dreams and visions he had that fateful night showed him nothing less than the way to unify all human knowledge by means of the "method of reason"; the Spirit of Truth had wanted to open to him the treasures of all sciences through this dream. And it took René eighteen years to write a book containing this ominous result: the "Discourse on the Method" of 1637, published in French by a publisher in Leiden, Holland. René's great idea was the certainty of the existence of a precise instrument capable of unifying all the sciences, from metaphysics to physics and then all the other sciences (including biology, of course): the instrument was mathematics. In fact, according to him, the very essence of reality is mathematical, echoing and reviving the Pythagorean and Platonic visions. It is precisely this identification of mathematics as the essence of the world that allows it to be applied to reality, all reality, from the physical to the metaphysical, without any limitation. In short, René was one of those who, in the end, did not care much for experiments because theory, i.e., abstraction, is a guarantee of reality, as Plato believed.

René is fascinated by the procedures of mathematics, where, starting from very simple objects and properties, it is possible, by applying a few rules, to arrive at extremely complex knowledge, a bit like the elements of Euclid, who, starting from concepts such as point and line, built structures and discovers wonderful and complex properties. Why not extend this approach to the whole of reality? On the other hand, if everything is mathematics, it is not clear why we cannot use its wonderful methods to analyse it. Descartes' dream was indeed the total and absolute mathematisation of the world of objects and thought. For example, René argued with a priori arguments that boiled water brought back to room temperature freezes at a lower temperature than unboiled water. Too bad he did not conduct an experiment!

But let us see what these rules are that allow us to "learn to distinguish the true from the false, to see clearly in my actions, and to proceed with confidence in this life". There are only four of them, but they are very important because they have shaped (and will continue to shape) profound scientific and technical thinking. We must not forget that these rules are used, in a more or less recognisable form, in every scientific and technological enterprise. They are as follows:

- First rule: never accept anything as true without clearly knowing it to be so; that is, do not judge anything that does not present itself to reason so clearly and distinctly as to leave no doubt.
- Second rule (top-down): divide any problem into as many parts as possible to make it easier to solve.
- Third rule (bottom-up): organise your thoughts in an orderly way, starting with the simplest and easiest things to know, and working your way up to the most complex knowledge.
- Fourth rule: make such perfect enumerations of all cases and such complete reviews that you are sure nothing has been left out.

The second and third rules are the ones that we can consider to be very current in data analysis. The second rule corresponds to what is known as "top-down" reasoning, i.e., the need to break down any object or problem into its parts in order to reveal its internal structure. This procedure is reminiscent of the reductionist approach, which, as we shall see, is found in the development of the medical sciences and the paradigms of health and disease that have followed one another over time, starting with the organs as "carriers" of some "dysfunction", then the individual cells, right up to the current paradigm that goes in search of the "faulty" protein, DNA or RNA in order to define a cure. But also, the analysis of the data, as in the universal intentions of René, represents a phase of classification and characterisation of the pieces of reality that are available, namely, the data, which are obviously the only elements that should define the picture of the disease, that is,

the division into many parts, down to the simplest (from the organism to the molecule in our case).

The third rule is definitely the most fascinating of all because even today, no one knows exactly how to achieve it in biology and medicine, even though it has been successfully applied in many cases. We are talking about the "bottom-up" approach, that is, the phase of reconstructing reality (or the problem, but for René, the laws of physics and thought were the same), which allows us to obtain an "overview" of the phenomenon that interests us. In other words, the third rule should enable us, after identifying the trees, to see the forest as a whole again. But the third rule could wait because medical science has progressed rapidly on the basis of the second rule only, which is the one that children like to use when they take apart a toy they have just been given.

3. Patients Torn to Pieces

Historians of medicine have identified several stages in the development of ideas about disease. The first phase is magical and religious, as in the Egyptian civilisation (around 2700 BC), where illness was seen as a magical phenomenon, of supernatural origin, a real divine punishment [6]. The phase that we can consider "pre-modern" is the one that began in Greece in the fifth century BC with Hippocrates of Kos, whose oath is still taken today by the new doctors of medicine and surgery. In the purely rationalist style that characterised the Greek worldview, disease was considered to have a natural origin, without the intervention of the gods. In fact, Hippocrates believed that illness was caused by an imbalance in the four basic "humours" (blood, phlegm, yellow bile, and black bile). It is interesting to note how the disease was "delocalised", i.e., seen as a problem of the whole body, to which a "sick person" corresponded as a whole [7]. Even the method of Hippocrates is worthy of Dr. House, at least in the initial phase when all the symptoms are carefully evaluated to find the cause of the disease, and therefore, the therapy. In fact, many centuries before Hippocrates, traditional Chinese medicine considered disease to be an imbalance of the forces of nature, of yin and yang, and therefore, also characterised by the disturbance of a balance that affects the whole organism and not just a part of it. The common characteristic of illness, therefore, regardless of the different cultures, is that it is a property of the person and not of a single part, as we have seen. The patient as a whole was the object of study for the physician, who, therefore, had to treat the person with a particular disease and not the disease in isolation [8].

The irony of fate is that today, 2500 years later, we are back where we started: modern medicine is desperately searching for a way to put the pieces back together, to have a characterisation of the disease that is not simply a collection of the results of many tests or analyses at various levels, from the functionality of an organ to its molecular profile. In fact, the aim is to "reconstruct" the patient in order to see the disease as Hippocrates did, i.e., at one with the body, the social environment and lifestyle. The effect of Cartesian scientific reductionism in medical practice can be linked to the conception of disease as something separate from the sick person and, as such, analysed with increasingly sophisticated analytical tools. In the seventeenth century, for example, the English physician Thomas Sydenham, one of the fathers of English medicine and a profound expert on the manifestations and course of smallpox and scarlet fever, wrote the following: "it is necessary that all diseases be reduced to definite and certain species with the same care which we see exhibited by botanists in their phytologies" [9], as reported in [10]. In other words, the idea affirmed by modern medicine is analogous to the work of the botanist, who collects the plants he finds during his explorations and classifies them in a precise and systematic way, in the style defined by Linnaeus.

The history of pulmonary tuberculosis [10] is a perfect example of the transformation that Descartes and many others brought to medicine over time [11]. Tuberculosis has existed for at least 15–20,000 years and was described by Hippocrates as "an ulcer of the lungs, chest and throat, accompanied by cough, fever and destruction of the body by pus". Until the nineteenth century, tuberculosis was incorporated into the medical

classification of "consumption", which was based on a mixture of hereditary characteristics, occupation, social status and personality traits. It was not until the precise assessment of the tuberculous lesions in the lung tissue that the disease was clearly defined, and its symptoms brought into a single category. It was William Stark, in his observations published by James C. Smith 18 years after his death [12], who proposed the evolution of the pulmonary nodules into ulcers and cavities, thus justifying the different manifestations of the disease in a single location of the lesion. These lesions were further studied in microscopic detail until, in 1882, Robert Koch identified the microbiological cause, the bacillus *Mycobacterium tuberculosis* [10]. In this exemplary case, Descartes' second rule is clearly seen in action, from the whole organ to its lesion, down to the microscopic level where the cause of the disease is evident.

We must not forget that this process of reducing the disease from the whole patient to its parts, organs and tissues, and then to microbiology, allowed for the development of streptomycin and other antibiotic therapies. However, this great success of the Cartesian method hides serious limitations. During Koch's time and in the years that followed, many other scientists and clinicians realised that apart from special cases, no therapeutic advance could ignore the totality of the patient's condition [13]. Despite the doubts, the impact of such a clear and simple story could not fail to fascinate the most refined scientific minds, leading them to try to repeat this approach for other diseases, not only for their diagnosis but also for patient care.

4. "Go, Catch, and Kill"

The process that led to the discovery of the cause of tuberculosis and its cure was in fact simple, elegant and very seductive. Identifying smaller and smaller parts of our body down to the individual molecules that make it up, in perfect accordance with the Cartesian method, suggests the possibility of digging all the way down to find a hidden cause, in perfect analogy with the search for a diamond in a mine. The reductionist/Cartesian approach has been very effective in all areas of science and technology, and still supports all those visions of disease that point inwards, from the macroscopic to the microscopic, in the belief that by curing the microscopic, the macroscopic will automatically be cured. Unfortunately, this is not always the case; in fact, the opposite is more often the case, in the sense that the cause of a disease cannot always be considered at the "lowest" level, i.e., the DNA, because many other factors, at different levels, influence the effect that a mutation of a gene can have on the organism as a whole. In addition, external factors, such as the environment and lifestyle, have a huge impact on many diseases, such as hypertension, cancer and diabetes. This is why doctors often recommend lifestyle changes and the elimination of environmental stressors in addition to medication. In any case, the basic idea introduced into medicine by the spectacular success of tuberculosis treatment is still with us and has immense implications. Medicine's job is to identify the causes of disease at the microscopic level and find another target to hit. In the words of the Pulitzer-Prize-winning Indian oncologist Siddhartha Mukherjee, medicine today is based on this simple sequence of events: You have an illness and you go to the doctor. Then, you take the pill he prescribes, and that pill kills something [14] (not just bacteria or viruses, but individual proteins or whole cells).

The "go, catch, and kill" paradigm underpins all of modern medicine and pharmacology and has deep roots in the success stories of tuberculosis and antibiotics. Drugs produced by pharmaceutical companies all have the same characteristics: once introduced into the body, these molecules can find their target, lock it up, make it unable to function and then throw away the key. Over the last hundred years, we have tried in every way to replicate this model for all diseases, from diabetes to cancer, from cardiovascular disease to autoimmune disease, and with great success, so much so that we have given it a truly suggestive name: the magic bullet paradigm. But how did we get there? We need to take a step back and talk about the extraordinary intuition of a great German doctor, avid cigar

smoker, Nobel Prize winner in 1908 for his studies in immunology and passionate reader of Sherlock Holmes: Paul Ehrlich.

5. Paul's Magic Bullet

He had a very annoying vice. He scribbled drawings and formulae on every conceivable surface: laboratory walls, tablecloths, napkins, and even the soles of his shoes and the shirts of his colleagues. And finally, his most important contribution to medicine came in the form of a crazy and breathtaking idea. In 1900, he published an article entitled "On Immunity with Special Reference to Cellular Life", in which he explained his theory of the immune response, which he called the "side chain theory". In modern terms, Ehrlich's idea is that potentially dangerous foreign molecules (antigens) bind to receptors scattered on the cell wall. Receptors are very localised areas on the membrane or within the cell itself that interact with molecules of different types (for example, hormones, small molecules or chemical messengers). The receptors stimulate the cell to produce more receptors of the same type and to release the excess (antibodies) into the extracellular fluid.

Ehrlich called these antibodies "magic bullets" that targeted single antigens. This model of immune response was completely out of the box and provoked furious and disbelieving reactions from the scientific establishment of the time. The point that was difficult to digest was actually surprising: the foreign body, the antigen, finds a receptor on the cell surface that binds it perfectly and uniquely, without ever having encountered it before! But what was the point of having so many receptors, most of which would be useless? And was there enough space on the cell wall? In fact, these observations were very sensible, though Ehrlich's proposal was not entirely correct. However, his idea of an antibody that binds solely and exclusively to a specific antigen was absolutely correct and was the basis for subsequent models of the immune response. But for our history, another unexpected development of this idea would lead to the birth of pharmacology and the "go, catch, and kill" model that pervades modern and future medicine. Ehrlich himself had called antibodies "magic bullets" in the search for target antigens. He was probably inspired by Emil Fisher, who had proposed a "key-lock" model for the workings of enzymes.

Paul's intuition was to reapply the "magic bullet" model he had imagined for the way antibodies worked, and thus, to develop the concept of a chemical that binds to another and blocks its function, thus selectively killing microbes (as in the case of tuberculosis) or even cancer cells (as in chemotherapy). The importance of this intuition cannot be underestimated [15].

Ehrlich's powerful metaphor became a central element of re-organisation of twentieth-century medicine and its depiction as the "golden age". The image of the "magic bullet" depicted institutional medicine as being able to control and defeat diseases. The new biomedical paradigm able to identify a specific cause and cure, with its strong links with laboratory science and new biotechnological apparatuses, has been the central pivot for the rise of the status of medicine.

The "heroic" nature of his scientific endeavour is well expressed by the historian of science Fritz Stern [16]: "And perhaps more than anyone else, Paul Ehrlich has shown how much an individual can achieve on his own: thanks to his laboratory discoveries, clinical doctors have been able to save an incalculable number of human lives".

6. Four Senators and Descartes' Third Rule

How far do you have to go to dismember a human being? Indeed, the so-called "omics technologies" have reached an impressive level of detail and have managed to measure an incredible number of elements of an organism down to the molecular level. Of course, it is very difficult to know a priori what is "necessary" for a complete characterisation of a disease in a given patient. The reason for this is that each pathology is very different from the others, and what may be enough for one person to see their doctor may not be enough for another. In other words, we know with certainty that we do not know, and that is why

biotechnologies have entered into a whirlwind of technological innovations that allow us to measure new molecules or entire organisms (for example, the microbes that live in our intestines) every day in the hope that "the more data we have, the better". This approach, although understandable and even sensible in principle, must never lead us to forget that data is not information, and therefore, having many, many rivers, floods, tsunamis of data does not guarantee that useful information is somewhere in this immense sea. However, the quantity and quality of data that can now be obtained from biotechnology have grown so rapidly that it requires an epochal turning point in medicine, defining what is now commonly called the era of "big data medicine". However, the appropriate use of big data is not only a problem for medicine; in fact, completely different sectors are struggling with very similar problems, from which it is possible to learn to avoid falling into the same traps.

All major film and TV production companies, such as Netflix or Amazon, need to know which projects to make and which to drop. The future of the company depends on these decisions and, of course, the head of the executive, who cannot afford to miss a beat. But these companies have an ace up their sleeve: when we watch a show, they watch us, and they can obtain a huge amount of data about the behaviour of millions of viewers. There is a lot of heterogeneous data that can be obtained. For example, for each user, you can record when they press play; when they pause; and when they continue watching, perhaps the next day. But you can also know which parts are skipped or re-watched: basically, all the actions we carry out on the screen, from the terms we use in searches to our favourite programmes; our ratings (thumbs up, thumbs down); and our preferences in terms of producers, directors, actors and so on. So, for each user, there is a lot of data that characterises their behaviour and should, therefore, allow us to assess the "fate" of a series project, i.e., whether it will be successful, at least in probabilistic terms. The interesting thing—as Sebastian Wernicke reports in a very successful TED talk [17]—is that this is how it actually worked. And indeed, in April 2013, after collecting an impressive amount of data, Amazon's content executive and his data analyst staff conducted their analysis and all the necessary calculations until the data produced an answer: "Amazon should produce a series about four Republican senators in the US". They made this series, called "Alpha House". The result? A mediocre IMDB score [18] of 7.5 out of 10. Keep in mind that a real success should get a score above 8.5 (for example, Game of Thrones attained a score of 9.2 and Breaking Bad attained a score of 9.5) to be in the top 5% of all shows ever made. Around the same time, another executive at a competitor like Netflix is tackling the same problem using "big data" extracted from the user mine. Again, the stakes are high: the goal is to find a "hit show" rather than a mediocre product like many others. Same problem, same type of data, but in this case, the analysts hit the mark: they produced "House of cards", which is a popular series that scored an 8.7.

How is it possible that two groups of expert data analysts, two companies with great and long experience and decisions based on the same "ingredients" produced such different results? In fact, it seems that an approach based on a lot of qualified data must always work, i.e., the collection of immense amounts of data and high quality must somehow "guarantee" a good decision, or at least the possibility of defining a good TV programme. But if there is no guarantee, even for a television programme, what should we think about much more "delicate" applications, such as those relating to health? It is really worrying, but it is too big of a problem to underestimate. But back to the point. What was the difference between the two approaches taken by Amazon and Netflix? Both have followed the "Cartesian method" to the letter, i.e., they have "torn apart" the problem of trying to understand viewer behaviour on the basis of many small individual actions: without this data, these many small aspects, they could never have a realistic idea of what is happening in the mind of a user watching a series. Data is, therefore, extremely important to define the parts or "pieces" of a problem and to characterise them quantitatively so that the various statistical algorithms for data analysis can be used. However, the "reverse" process, the practical application of Descartes' third rule, in which the solution to the original problem is reconstructed from the many small pieces (the synthesis of data), was quite different.

The decision that led to the production of Alpha House was based on data alone. Instead, as Wernicke recounted in his TED talk, the decision to create the "house of cards" was made by the executive and his staff on the basis of considerations independent of the data. In other words, the data were used in the first phase of analysis, i.e., in determining the detailed "constituent" elements that were considered relevant to define the overall problem, but the final decision was not based solely on the available data, but on a collective choice of the working group, which shared its assessments and came to an agreement. If the human brains can do anything good collectively, it is to put the pieces together, to make sense of incomplete and partial information.

7. Networks

A very promising way to put the pieces together in systems precision medicine is to use networks. As a matter of fact, phenotypic outcomes result from the intricate interplay of molecular components orchestrated by biological networks. Homeostasis represents the delicate balance and dynamic equilibrium of network states that maintain proper physiological function. However, perturbations in these networks can lead to pathological disease states. Understanding the dynamics of biological networks and their role in shaping phenotypic outcomes can provide a valuable framework for putting the pieces back together and designing effective interventions [19]. Moreover, the use of networks in systems precision medicine may also have the role of a "lingua franca" that can be used to break down the barriers between precision physicians and multi-omics data analysts [20].

A "network" is a "cognitive schema", an abstract framework of concepts that helps us make sense of the complex world of life. It is not a tangible entity, but rather a representation of relationships and connections between concepts. The characterisation of a network involves cores (concentrated areas) connected by edges (representing pathways or connections) in a less dense environment. However, when applied to protein–protein interactions, for example, this concept recognises that interactions are not simply lines connecting points, but complex phenomena influenced by spatial and energetic factors.

By replacing proteins with nodes and their interactions with links, we create a metaphorical projection of the protein–protein interaction network onto the network diagram. This allows complex systems to be represented and understood using a simplified abstraction of the data. In essence, the network serves as a functional abstraction that allows us to understand complex systems by simplifying their representation, thereby facilitating dialogue between physicians and data analysts.

A network is a visual representation of data that focuses on the relationships (links) between elements (nodes), with more emphasis on the configuration of the links than on the specific characteristics of the nodes. The aim is to identify network patterns that can be applied metaphorically to biological concepts, creating a common language that bridges the gap between computational and clinical researchers. This will allow them to discuss and interpret the same reality from different perspectives.

Biological systems, such as cells and organisms, exhibit intricate organisation and function through the interplay of different molecular components. These components interact in a highly regulated manner, forming complex networks that control fundamental processes, such as metabolism and gene regulation. Understanding the different modalities of biological network organisation and considering their interactions on a larger scale has been shown to be of great value in understanding the functioning of living systems.

Metabolism, for example, refers to the totality of chemical reactions that occur within a cell or organism to sustain life. These reactions involve the interconversion of molecules, the production of energy and the synthesis of cellular components. Metabolic pathways form a network in which different molecules serve as substrates, products or intermediates, with enzymes acting as catalysts to facilitate the reactions. By analysing the organisation of metabolic networks, researchers can uncover key pathways, identify regulatory nodes and gain insights into how cellular metabolism is coordinated.

Another relevant example is gene regulation, where the control of gene expression enables cells to respond to internal and external cues. Gene regulatory networks consist of genes, transcription factors and other regulatory molecules that interact to modulate gene activity. These networks determine when and to what extent genes are activated or repressed, thereby influencing cellular processes and development. By studying gene regulatory networks, scientists can elucidate the mechanisms underlying cellular differentiation, disease progression and responses to environmental changes.

Considering the large-scale interactions of these biological networks provides a more holistic view of how different modalities of cellular organisation work together to achieve overall system function. By integrating data from multiple networks, scientists can identify novel regulatory mechanisms, predict cellular responses and uncover emergent properties that cannot be understood by studying individual networks in isolation. A comprehensive review that discusses the relevant applications of network science to the field of medicine can be found in [21].

Finally, networks can be used as a vocabulary generator, where different disciplines use the same "words" to refer to the same underlying concepts (cell behaviour, health, disease, etc.). Using this approach, researchers can continue to study their respective disciplines while engaging in interdisciplinary dialogue to advance systems precision medicine in a clinical setting.

8. Conclusions

Systems precision medicine, as an interdisciplinary approach, plays a key role in tackling complex diseases. This approach requires the integration of clinical knowledge, data and analytical models, as well as the in-depth knowledge of physicians and data analysts to personalise the care pathway. The challenge, however, is to reconstruct the whole picture of the disease after analysing the individual parts to identify the relevant aspects for therapy and diagnosis. Systems precision medicine focuses on identifying key system components and their interactions and studying the consequences of these interactions and the patterns that emerge. The use of statistical, mathematical and computational tools supports this approach but is not sufficient. The implementation of systems precision medicine presents unique challenges because it requires agreement between researchers on how to combine data and expertise into a coherent vision for clinical application. Cultural integration, including the personal experience of each professional involved, is essential.

Descartes' dream of unifying all the sciences through mathematics, after the initial spectacular successes heralded by the metaphor of Erlich's "magic bullet" for identifying therapeutic targets, is showing all its limitations. Systems precision medicine, on the other hand, seeks to consider the patient as a whole, which overcomes the reductionist approach that separates the disease from the patient, by integrating data, mathematical and statistical models, and active participation (not just supervision) of the professionals involved, from the clinician to the data analyst, in the diagnosis and treatment process. It is important to combine data analysis with an overview and collective evaluation in order to make effective decisions, because—as shown by the choice of TV series to be produced—the use of big data alone does not guarantee success but requires an integrative and collective evaluation.

Moreover, in the realm of biological research, it is crucial to differentiate between statistical significance and biological meaning when interpreting experimental outcomes. While statistical significance provides a measure of the reliability of an observed effect, it does not necessarily imply that the observed effect is biologically meaningful or relevant. This distinction emphasises the importance of sanity checking or critically evaluating research findings beyond purely statistical analyses. In fact, statistical significance alone does not provide insight into the magnitude or relevance of the observed effect. It is essential to consider the biological context and the practical significance of the findings. Biological meaning refers to the relevance, importance and interpretability of the observed effect within the context of the specific biological system being studied.

In addition, sanity checking involves scrutinising the experimental design, methodology and potential confounding factors that may influence the results. It is essential to consider factors such as the sample size, study population characteristics, experimental controls and the validity of the chosen statistical tests. Conducting independent replication studies or meta-analyses can further strengthen the reliability and generalisability of the findings. By incorporating sanity checking, researchers and scientists can ensure that their interpretations of statistical results align with the underlying biology and have meaningful implications. It helps to prevent unwarranted conclusions, misinterpretations and overgeneralisations based solely on statistical significance.

The recognition that complex phenotypic outcomes in biology are driven by chains of physically or functionally related activities of biological components highlights the importance of establishing causal relationships and associations. Statistical associations, while valuable, must be scrutinised in light of these connections in order to distinguish genuine underlying mechanisms from chance findings. By focusing on the interactions and relationships between biological components, researchers can gain a deeper understanding of complex biological phenomena.

The key issue for an effective implementation of systems precision medicine in a clinical setting is to encourage direct collaboration between precision physicians and multi-omics data analysts, which is an issue of great relevance to patients. However, this collaboration is blocked by the fashionable approach called "data-driven" or "digital-driven", where it is believed that the physician's role should only be that of an independent evaluator of the output of an algorithm. The idea that one can automatically extract useful information for patients using somewhat "intelligent" algorithms is deeply misguided and dangerous: data alone should never be trusted; it should always be put in the right context and in the more general perspective of the patient, which is an operation that can only be undertaken by an expert physician in the field. In other words, the message here is that there are no one-way roads from data to patients, but that a collective enterprise of integrating data and skills is needed. This means that the computational and mathematical approaches must coexist harmoniously with the more artistic approach of intuition and the physician's non-formalised knowledge of the patient's general context.

What is the rational basis or premise for this intuition? Physician intuition, often referred to as clinical intuition or clinical judgement, is the ability of experienced physicians to make accurate and rapid decisions based on their intuition or gut feeling, even in the absence of explicit conscious reasoning. It is an important aspect of medical practice, particularly in situations where time is limited or information is incomplete. The rational basis or premise of medical intuition lies in the accumulation of knowledge and expertise over years of clinical practice. Through extensive training, doctors develop a deep understanding of medical concepts, diseases and patterns of patient presentation. This knowledge is stored in their long-term memory and is readily accessible during clinical encounters. Doctors develop an intuitive sense of recognising patterns, picking up subtle clues and synthesising complex information. They learn to identify similarities between a patient's symptoms, signs and medical history and those seen in previous cases. This recognition of familiar patterns enables them to make quick connections and generate diagnostic hypotheses. Intuition can be seen as a form of pattern recognition that occurs rapidly and automatically, drawing on a vast repertoire of experiences. In addition, physician intuition is supported by the integration of both conscious and unconscious cognitive processes. While explicit conscious reasoning and analytical thinking are essential to medical decision-making, intuitive judgements involve unconscious cognitive processes that operate below the level of conscious awareness. These processes, including heuristics, mental shortcuts and pattern recognition, allow doctors to process information quickly and make intuitive judgments.

Biologists and physicians have a wealth of expertise in known biological pathways and systems. This expertise enables them to streamline the process of prioritising associations that are more likely to be mechanistically feasible based on the known biological context.

In doing so, they can effectively triage potentially spurious statistical quirks and focus on associations that hold greater promise for further investigation and understanding.

The path to diagnosis and treatment of a complex disease can be compared with a collective work of art, requiring not only competence but also the presence of the human element. It is necessary to combine the creativity of nature, which generates the disease, with that of human experts, who must create a unique path based on data. This requires cooperation between physicians and data analysts, with both contributing to the construction of the patient's story. It is crucial to involve data analysts directly in the hospital context and to enable precision medicine physicians to understand and benefit from the new perspectives offered by data analytics. The physician must be involved in the loop, there cannot be a direct, linear data–diagnosis–therapy pathway, but a circular activity of encounter/clash between data, analysis techniques and contextual medical knowledge. There is also an urgent need for continuous dialogue and new languages of communication, such as the language of networks [20], as well as education that promotes continuous learning and collaboration between both professions. This revolution in medicine requires a radical change in our conception of ourselves as physicians and data analysts, challenging us to welcome the other into our cognitive process. This challenge goes beyond algorithms, as "intelligent" as they may be, and requires a personal commitment to allow the "other" to enter and reach new levels of true interdisciplinary collaboration for personalised care.

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systems

MDPI

Review

Chemical Organization Theory as a General Modeling Framework for Self-Sustaining Systems

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Abstract: This paper summarizes and reviews Chemical Organization Theory (COT), a formalism for the analysis of complex, self-organizing systems across multiple disciplines. Its elements are resources and reactions. A reaction maps a set of resources onto another set, thus representing an elementary process that transforms resources into new resources. Reaction networks self-organize into invariant subnetworks, called 'organizations', which are attractors of their dynamics. These are characterized by closure (no new resources are added) and self-maintenance (no existing resources are lost). Thus, they provide a simple model of autopoiesis: the organization persistently recreates its own components. The resilience of organizations in the face of perturbations depends on properties such as the size of their basin of attraction and the redundancy of their reaction pathways. Application domains of COT include the origin of life, systems biology, cognition, ecology, Gaia theory, sustainability, consciousness, and social systems.

Keywords: chemical organization theory; self-organization; autopoiesis; resilience; reaction networks; sustainability

1. Introduction

Complex adaptive systems [1,2] are systems consisting of many interacting components that exhibit some degree of self-organization: coherent patterns of organization spontaneously emerge out of the network of interactions [3]. Most of the phenomena we are confronted with in real life are such complex adaptive systems: people, organisms, societies, ecosystems, markets, cultures, etc. Great progress has been made in understanding the dynamics of such systems by means of multi-agent computer simulations [2]. However, on a more abstract, theoretical level, our understanding of self-organization and adaptation remains rather superficial and fragmented.

Part of the reason is that the conceptual and mathematical building blocks of our theories are poorly fitted to describe emergence and interaction. Traditional scientific models start by reducing a system to its static components and the properties in which these components can vary. The values of these variables define the state of the system. The evolution of the system is then represented as a time-parameterized trajectory in the thus predetermined state space, governed by a static equation. This approach makes it intrinsically difficult to understand the fundamental changes that result in the emergence of new components, properties, systems, or dynamics.

An alternative approach is to start from a *process metaphysics* [4,5] or *action ontology* [6,7]. Such a philosophy assumes that reality is not constituted out of static objects but out of processes or actions, and that objects and systems are merely stabilized (networks of) processes. While this perspective fits in with our most recent insights into complex adaptive systems, the problem is to represent processes in a way that allows precise modeling of such emergent systems [3].

This paper wishes to introduce a formalization of processes, namely the reaction networks used in what has been called *Chemical Organization Theory* (COT) [8–10]. In reaction networks and COT, the relation between states and dynamics is turned upside down. The processes are primary, in the form of 'reactions', which are the most fundamental elements of a reaction system. States only appear in a second stage, as the changing concentrations of the 'molecules' that the reactions are processing into other molecules. The molecules therefore are not static objects, but merely raw materials that are constantly being produced, consumed, and recreated by the reactions. In that sense, reaction networks form perhaps the first formalization of a process ontology that is both general and practical [11,12].

The general character means that COT can describe systems and processes in the most diverse disciplines—from elementary particle reactions via systems biology and cognitive science to the political organization of society. Its particular strength is that it provides an elegant mathematical method to define and construct *organizations*, i.e., self-sustaining networks of reactions within a larger network of potential interactions. As such, it is eminently suited to describe self-organization, autopoiesis, sustainability, resilience, and the emergence of complex systems out of simpler components.

Next to its broad foundation in process philosophy, COT derives its power from its concreteness and simplicity: basically, you can represent any process in the real world as a combination of reactions between suitably chosen 'molecules' and then start analyzing the resulting reaction system for self-maintenance, closure, and other observable properties. Moreover, COT models are intrinsically modular: it is trivial to add or to remove molecules or reactions from an existing model and (somewhat less trivial) see what effect that has on the emerging organizations. This makes it possible to model systems of great complexity, where you start with a simple model in order to get an intuitive grasp of what is going on, and then gradually add more detail and sophistication in order to achieve a more realistic representation.

Finally, COT focuses on what are the most important questions about a complex adaptive system: to what extent is it sustainable and resilient, i.e., able to maintain itself both autonomously and in the face of external perturbations? To what degree does it grow, remain the same, or perhaps diminish and decay? If it is perturbed to such a degree that it cannot maintain its present organization, which new type of organization is it likely to evolve into? How do its components and processes co-evolve, mutually adapt, and become coordinated into a symbiotic system? In summary, how does it self-organize into a robust, coherent whole?

The latter is perhaps the most important question in the whole of science and philosophy, and their applications to society. Practically all the phenomena we are confronted with—including matter, organisms, ecosystems, societies, and minds—are the result of self-organization producing complex wholes out of simpler components. Any general theory that would help us to understand, model, and control that process is likely to revolutionize our worldview, while opening up an endless variety of concrete applications.

The present paper wishes to make the case that COT, together with its future extensions, provides an exceptionally promising foundation for such a general theory. It will do that first by pointing out how the COT formalisms avoids the pitfalls of earlier approaches, then by offering a survey of existing and potential applications of COT to a broad variety of issues. It will do this in a simple, non-technical way, emphasizing the basic formalism and the core new insights, while avoiding some of the (relatively) more complex mathematical techniques required for a full implementation of COT.

2. Reaction Networks

As its name implies, the COT formalism [8] is inspired by chemistry, and the way it describes how chemical reactions transform molecules into new molecules. Therefore, it has inherited much of its terminology from chemistry, while being similar in its conceptualization to the emerging domain of systems chemistry [13,14]. In order to widen its appeal and to convince other scientists of its potential for transdisciplinary unification, it

may be wiser to replace some specifically chemical terms by more broadly applicable ones (and perhaps even rename the whole approach to the more neutral 'Process Organization Theory'). The present paper will therefore replace some COT terms with new terms, while clearly pointing out the changes.

The basis of a COT model is a reaction network. It consists of two types of entities, which we will call *resources* ('molecules', 'molecular species', or 'species' in the traditional COT formulation) and *reactions*. A resource is an abstract representation of a specific kind of substance, entity, or, most generally, measurable phenomenon. Examples of resources are particular types of chemical substances, elementary particles, biological species, economic goods, human agents, messages, ideas, or decisions. All the resources in the model are assumed to be available in some shared container or workspace, which in COT is called the 'reaction vessel'. This joint presence allows any resource to interact directly or indirectly with any other resource. Reactions denote elementary processes that create or destroy resources. They typically produce combinations of new resources out of combinations of existing resources. Yet, the simplest reactions just create or destroy a single resource.

Formally, we will define a reaction network as the 2-tuple <M, R>, where $M = \{a, b, c, \ldots\}$ is the set of resources, and $R \subseteq P(M) \times P(M)$ is the set of reactions, where $P(M)$ denotes the power set (i.e., the set of all subsets) of M. Each reaction $r \in R$ maps a particular subset X of M onto another subset Y of M:

$$r\colon X \to Y\colon \{x_1, x_2, \ldots \mid x_i \in M\} \to \{y_1, y_2, \ldots \mid y_j \in M\}$$

Note that the sets X and Y can be empty. We will call X the *input set* and Y the *output set* of r and denote them, respectively, $In(r)$ and $Out(r)$. We will call the elements of $In(r)$ the *reactants* of r, and the elements of $Out(r)$ its *products*. Borrowing the chemical notation for reactions, a reaction is conventionally written as:

$$r\colon x_1 + x_2 + \ldots \to y_1 + y_2 + \ldots$$

The '+' symbol here represents a *conjunction* of the resources: x_1 and x_2 and ... all need to be simultaneously present in $In(r)$ for the reaction to take place, while the reaction simultaneously produces y_1 and y_2 and .... If $In(r)$ is empty, the reaction will be written as:

$$\to y_1 + y_2 + \ldots$$

Note that in traditional COT, it is assumed that $In(r)$ and $Out(r)$ are multisets. This means that the same element x_i can occur more than once (say n_i times) in $In(r)$. This is necessary to describe reactions of the form:

$$2a + b \to 3c + d$$

or more generally:

$$n_1x_1 + n_2x_2 + \ldots \to m_1y_1 + m_2y_2 + \ldots \quad \text{with } n_i, m_j \in \mathbb{N}$$

For simplicity, we will here just work with ordinary sets, i.e., resources that only occur once in a reaction. For a COT formulation in terms of multisets we refer the reader to [8,12].

2.1. Reaction Networks vs. Traditional Networks

The combined system <M, R> forms a network because the resources in M are linked to each other by the reactions in R that transform the ones into the others. But this is not a traditional network (i.e., a *directed graph*), in which a link connects a single element ('node', 'vertex') x to a single element y. A reaction connects a set X of elements to a set Y of elements. In mathematics, a network with this property is called a *directed bipartite graph*, or a *directed hypergraph* [15]. This appears to be the essential generalization that gives

reaction networks their power with respect to traditional network models. Let us try to explain how that happens.

A traditional network consists of nodes N and links L, with $L \subseteq N \times N$. Thus, <L, N> is a reaction network, but where the reactions $r \in L$ are limited to one input and one output:

$$r\text{: } x \rightarrow y, \text{ with } x, y \in N$$

A general reaction network provides much more richness and flexibility because it allows combinations of inputs to produce combinations of outputs, opening up an exponentially wider range of interacting processes. In a traditional network, the only way processes can 'interact' is by sharing input or output nodes, e.g.,

$$r_1\text{: } x \rightarrow y$$

$$r_2\text{: } x \rightarrow z$$

$$r_3\text{: } u \rightarrow y$$

Here, an initial state x can lead to y and/or to z via, respectively, r_1 and r_2. This immediately creates an ambiguity: are r_1 and r_2 both taking place, producing y and z simultaneously? Or does the process make a choice between r_1 and r_2, ending up in either y or z? Similarly, y can be produced via r_1 and/or r_3 from x and/or u. Do we need both x and u, or is one of them sufficient to produce y? The problem is that in traditional networks, there is no way to distinguish between conjunction ('AND') and disjunction ('OR') of nodes and links. Next to juxtaposition of links/reactions, there simply is no operator to express a different type of combination.

In reaction networks, we have an additional operator, denoted with '+', that plays the role of the conjunction. The juxtaposition of reactions plays the role of the disjunction. Consider the following reactions:

$$r_4\text{: } x + u \rightarrow y$$

$$r_5\text{: } w \rightarrow y$$

This expresses unambiguously that in order to produce y we need either (x AND u), OR w. Now, different processes can interact in many ways to produce complex organizations, as we will see in further sections.

2.2. Reaction Networks and Propositional Logic

Interpretation of COT operators in terms of conjunction and disjunction points us towards formal, Boolean logic, where propositions can be combined in terms of these operators, together with the operators of implication and negation. Implication is naturally expressed with the '$\rightarrow$' operator. This directly suggests the logical formalism of Horn clauses [16]. These have the following form:

$$a \,\&\, b \,\&\, \ldots \rightarrow x$$

This is to be read as 'if a and b and ... are true, then x is true', or 'x can be derived from the conjunction of a, b, ...'. The translation in terms of reaction networks requires a qualification, though, which is that if you derive the new proposition x from the conjunction of propositions on the input side of the inference, then the propositions on that side *remain* actual (they are not destroyed by the process). They therefore should properly be listed on the output side as well. This gives us the straightforward COT translation of a Horn clause:

$$a + b + \ldots \rightarrow x + a + b + \ldots$$

Note that in this interpretation, logical inference is a special type of reaction, namely one in which no 'resources' ever get consumed: inferences can only *add* true propositions to our knowledge, they cannot remove any. This is why logic is inherently static: nothing really changes by making logical inferences; at most, we become aware of additional statements that were already true implicitly, but had not been proven yet. That is the fundamental reason why attempts to express process, action, or time with logic have not been very successful, in spite of a plethora of formalization attempts such as 'dialectical logics', 'process logics', or 'dynamic logics' (see, e.g., [17–19]). Insofar that these logics describe genuine changes in the state of the world, they have left the domain of logic proper and entered the domain of dynamics, which is more properly described by a formalism such as reaction networks.

2.3. Competition and Cooperation

Unlike logic, COT does not (as yet) incorporate a negation operator. However, reactions can express an implicit negative relation between two resources a and b: increase in a implies decrease in b. For this, we need to introduce the quantitative level of COT, where a resource is determined not only qualitatively by its presence or absence, but quantitatively by its amount or concentration in the reaction vessel. We can then define the relation 'a inhibits b' as:

$$\exists\ r \text{ such that } a, b \in In(r), b \notin Out(r)$$

This means that a enables a reaction r that consumes, but does not produce, b—thus reducing the concentration of b. The opposite relation, 'a promotes b' applies when a enables a reaction that produces, but does not consume, b. The relations of inhibition and promotion can be (but need not be) symmetric, in which case a and b inhibit or promote each other. In the latter case, we might say that a and b are competitors, respectively, cooperators. Note, however, that the same resource can simultaneously inhibit and promote another resource via different reactions. In that case, we need to use the more detailed, quantitative model of the reaction network, which allows us to calculate the net production of the different resources by summing the contribution of all reactions, and thus to determine whether the overall effect of a resource on another one is positive or negative.

Inhibition is a negative causal influence; promotion is a positive one. An uneven number of negative influences connected in a cycle (from a via a number of intermediate resources back to a) determines a *negative feedback* loop. Negative feedback suppresses deviations from an equilibrium level, thus producing a stabilization or an oscillation of the concentrations of the resources in the cycle around that level. A cycle with only positive influences, or an even number of negative influences, determines a positive feedback loop. Positive feedback produces an exponential growth of the resources in the cycle, which stabilizes only when they reach the 'carrying capacity' of the system, which is determined by the amount of external resources entering the cycle.

Systems dynamics [20] is a simple and useful formalism for representing and analyzing networks of such causal influences, and the positive and negative feedback loops they form. Moreover, system dynamics analyses processes in terms of *stocks* (equivalent to resource concentrations) and *flows* that add to or subtract from stocks (equivalent to reactions). Compared to COT, however, it lacks the ability to combine different resources in a single reaction: a system dynamics network only allows one-to-one connections between stocks.

The interactions between reactions take place through their shared resources: the same resource can appear in input and output sets of different reactions. Because these resources are either consumed or produced by the reactions, a reaction can facilitate another one (e.g., when the one produces a resource needed by the other) or hinder it (when the one consumes a resource needed by the other). This creates a network of 'ecological' relationships between reactions. These include *mutualism* (mutual amplification, cooperation, or synergy), *competition* (mutual inhibition, conflict, or friction), *predation* or *exploitation* (growth of the one at the expense of the other), and *commensalism* (growth of the one facilitated by the other, but without loss or gain for the other) [21]. As we will

show further, the general logic of self-organization [7] explains why this complex non-linear dynamics tends to move towards a self-sustaining regime, as resources and reactions that do not fit in with the emerging system are eventually eliminated, while those that efficiently exploit the more abundant resources grow and take over. This is the origin of the 'organizations' that we will now define.

3. Organizations

The most important new concept introduced by COT is an *organization*. This denotes a reaction system that is fundamentally self-sustaining: the resources it consumes are also the resources it produces, and vice versa. This means that although the system is intrinsically dynamic or process-based, constantly creating or destroying its own components, the complete set of components (resources) remains invariant, because what disappears in one reaction is recreated by another one, while no qualitatively new components are added.

This property is part of the definition of *autopoiesis* ('self-production'), a concept that Maturana and Varela introduced to characterize living organisms [11,22–24]. The second defining property of autopoietic systems is that they produce their own topological boundary, such as the membrane that separates living cells from their environment. This property does not apply to organizations, and therefore organizations are more primitive than living systems. As such, they were introduced as a simple model for the origin of life out of interlocking cycles of chemical reactions [25]—and a generalization of the more common but more restrictive model of an *autocatalytic set* [26,27].

Consider a subnetwork $<M', R>$ of a larger reaction network $<M, R>$, i.e., $M' \subseteq M$. The formal definition of an organization is derived from three characteristics that such a reaction network $<M', R>$ can have:

- **Closure**: This means that nothing new is generated; the only resources produced by the reactions are those that were already in the starting set M': $\forall\, r \in R$ such that $In(r) \subseteq M'$, the requirement holds that $Out(r) \subseteq M'$.
- **Semi-self-maintenance**: This is the complementary condition that nothing existing is removed; each resource consumed by some reaction is produced again by some other reaction working on the same starting set: $\forall\, x \in M'$ for which $\exists\, r \in R$ such that $x \in In(r) \subseteq M'$, $\exists\, r' \in R$ such that $In(r') \subseteq M'$, and $x \in Out(r')$.
- **Self-maintenance**: This is a stronger form of the semi-self-maintenance condition, which states that each consumed resource $x \in M'$ is not only produced by some other reaction in $<M', R>$, but that the amount produced is at least as large as the amount consumed.

The determination of self-maintenance is more complex than the other two conditions because it requires the introduction of a quantitative dynamics in the reaction network, which specifies the rate at which resources are consumed and produced by the different reactions. The standard dynamics for chemical reactions is based on a mass action kinetics [28,29], which assumes that the rate of a reaction is proportional to the concentration of the reactants. However, COT also allows using different types of dynamics, depending on the domain being modeled. Knowing these rates is necessary to establish the long-term maintenance of the resource set M' [8,10] because the reactions producing x may be slower than the ones consuming it, so that the concentration of x eventually goes to zero. The rate of each of the reactions defines the *flux vector*. Note that even without knowing the exact rates in a given state of the network, we may normally assume that the rate of a reaction increases when the concentration of its input resources increases (because there are more reactants to 'feed' the reaction) and decreases when that concentration decreases (this is anyway the case if we assume mass action kinetics).

In order to calculate the balance of consumption/production, we need to determine the *stoichiometric matrix* [8]. For each resource-reaction pair, this matrix specifies the net number of the resource produced by that reaction. This number is 1 if the resource is produced but not consumed, -1 if it is consumed but not produced, and 0 otherwise (in the multiset version of COT, the absolute values of these numbers can be larger than 1).

The product of flux vector and stoichiometric matrix then determines the total net rate of production (production minus consumption) for each of the resources across all reactions.

The requirement for self-maintenance is that this rate is non-negative for all resources, i.e., all resources either increase or are conserved. The reaction network fulfils this condition if there exists a flux vector (i.e., list of reaction rates) for which this requirement holds. Note that if the constraints determined by the (qualitative) reaction network allow such self-maintaining flux vectors to exist, then it seems likely that the (quantitative) system will converge to the corresponding regime of self-maintenance. The reason is that resources that are consumed more than they are produced (no self-maintenance) will decrease in concentration up to the point that the reactions consuming them slow down enough so that production (which is normally not affected by the concentration of the products, only by the concentration of the resources consumed) compensates for consumption. For simplicity, we will not further discuss this quantitative aspect in the present qualitative description. Therefore, we will ignore the flux vector and the calculations that need to be performed on it in order to determine whether self-maintenance is possible for the given set of reactions, and just note that this requirement is easy to check computationally. Examples of how flux vectors are calculated can be found in [30], while [31] provides a detailed presentation.

We are now able to define the crucial concept of organization: a subset of resources and reactions <M', R> within a larger reaction network is an organization when it is closed and self-maintaining. This basically means that while the reactions in R are processing the resources in M', they leave the set M' invariant: no new resources are added (closure) and no existing resources are removed (self-maintenance). Note that this does not exclude an overall input (resources entering the organization) or output (resources exiting the organization). These can be represented as reactions working on the empty set (which is by definition a subset of M'), such as $\rightarrow a$ (a is injected into the organization) or $b \rightarrow$ (b diffuses out of the organization). The only requirement is that a and b maintain a non-zero concentration in the organization.

Being an organization may seem a rather uninteresting property: nothing really changes. Most theories, models, and formalisms are based on invariant elements, so what is novel here? The essential contrast with classical modeling frameworks is that we started by assuming that *everything changes*: all resources are in a constant flux, being consumed by some reactions, produced by others, but by default processed into something else. The concept of organization establishes that stability can arise even within such ceaseless flux of transformations.

An organization is an *emergent system* that sustains itself by reprocessing its components, and thus constantly rebuilding its own structure. This is the essential property of living systems that Maturana and Varela have tried to capture with their concept of *autopoiesis*. What COT adds is that the same kind of emergent organization can arise in a wide variety of other domains outside of biology, on the sole condition that we have a sufficiently rich network of reactions and resources [12]. Moreover, COT reformulates the rather difficult and confusing notion of autopoiesis as a simple mathematical property characterizing even simpler sets of resources and reactions [11].

3.1. Some Examples

The simplest organization would consist of the single resource a and the single reaction $a \rightarrow a$. This would be the description of a resource that just maintains itself without interacting with anything else. The organization becomes slightly more interesting when we add the reaction $\rightarrow a$ (empty input set, single element output set). Here, a is not just maintained, it is also created out of nothing. We can make it more interesting by adding $a \rightarrow$. This means that a is not only produced or added, it is also removed from the 'reaction vessel'. This would describe a situation where some resource flows in and out of the reaction vessel.

For the simplest non-trivial organization, we need two resources $\{a, b\}$ that interact. They define an organization when the reactions form a cycle: $a \to b$, $b \to a$. This can be extended with an unlimited number of intermediate stages:

$$a \to b, b \to c, c \to d, \ldots, z \to a$$

This is still too simple to be very useful, but we can make it more complex by considering reactions with more than one input or output, e.g.,

$$a + b \to c$$

$$c \to d + e + f$$

$$e \to a$$

$$d + f \to b$$

Here, an a and a b together are transformed into a c, which is then converted to d, e, and f, which again produce a and b, so that the cycle can start again. Let us make it more concrete by considering recognizable resources and reactions, in this case describing the organization of the Earth's ecosystem at an abstract level (this high-level view of Earth as an autopoietic system is similar to the Gaia hypothesis [32]).

$$\to sunlight$$

$$plants + sunlight + carbon\_dioxide + minerals \to plants + oxygen + heat$$

$$plants + animals + oxygen \to animals + carbon\_dioxide + detritus + heat$$

$$detritus + bacteria \to bacteria + carbon\_dioxide + minerals + heat$$

$$heat \to$$

This describes the recycling of oxygen, carbon dioxide, and minerals by plants, animals, and bacteria, fueled by the energy of the sun (which enters the system from the outside, which is why the reaction producing it has no input within the system), while radiating heat into space. This is subtler than a simple cycle, because reactions require several inputs while producing several outputs that are all needed to sustain the organization. But the system is properly self-sustaining, as it produces all its essential components: nothing that is needed to sustain the organization gets lost; nothing new is added.

Note that some resources (such as *bacteria* in the last reaction) appear in both the input and output of a given reaction. That means that they are neither removed nor added by that reaction. Yet, they are necessary for the reaction to happen. In chemistry, such resources are called *catalysts*: they enable a reaction, but are not themselves affected by it. In our more general interpretation, we may call them agents [7]: they act on the other resources in the reactions, processing them into something else. For example, the bacteria are the agents that turn detritus into the carbon dioxide and minerals that are needed by the plants. The plants are the agents that transform these resources, with the help of sunlight, into oxygen (and more plants). The animals act on the plants and oxygen, converting them to detritus and carbon dioxide, which then again function as 'food' for, respectively, the bacteria and the plants.

3.2. Extending the Model

This model of global recycling is of course much too simple. To start with, it does not specify the relative proportions of the different resources produced and consumed. For example, plants do not produce just oxygen, they grow, thus producing *more* plants. In the multiset version of COT, the additional amount could be specified, e.g., by writing '2 *plants* + *oxygen*' on the output side of the reaction. While this may clarify the relative proportions, the actual rate of production would need the full, quantitative version of COT, which includes the rates of the different reactions as expressed with the flux vector. We will ignore these complications in the present introductory survey, and continue focusing on the power of COT for qualitative modeling.

Qualitatively, the simple model could be extended by noting some additional processes, such as *plants* → *detritus* (plants die, thus producing matter to feed bacteria) and *animals* → *detritus* (animals similarly die). We may also want to specify that it is not only bacteria that break down organic matter, but fungi as well, thus adding *fungi* + *detritus* → *fungi* + *carbon dioxide* + *minerals*. But fungi are sometimes eaten by animals: *fungi* + *animals* → *animals* + *carbon dioxide* + *detritus*.

A different kind of extension may occur by making the general resource categories more specific. For example, we could note that not all animals eat plants or fungi, but that some are carnivores. This leads us to split up the category 'animals' into the categories 'carnivores', 'omnivores', and 'herbivores', each characterized by its own specific reactions. In this way, we can go on adding reactions and the concomitant resources until we feel the model is detailed enough to include everything that seems relevant for a realist description.

But the crucial question remains: is the resulting network an organization? By adding a particular reaction, we may create a 'source' or a 'sink' for a particular resource, either injecting it into a system in which it was previously absent (thus interrupting closure), or removing it from the system faster than it can be produced (thus interrupting self-maintenance). Let us then try to better understand how organizations emerge.

4. Self-Organization

An arbitrary subset of a reaction network will in general not be an organization: its reactions working on its resources will produce additional resources (non-closure). These additional resources may react with some already present resources, producing even further new resources. Thus, every addition may activate reactions that produce further additions. However, this process of growth of the resource base must come to an end when there are no further resources that can be produced by reactions working on the already present reactions. At that stage, all produced resources are already in the present set, and closure is reached. Thus, closure can be seen as an attractor of the dynamics defined by resource addition: it is the end point of the evolution, where further evolution stops.

Let us now apply the same reasoning for self-maintenance, starting from the previously reached closed set. Some of the resources present in that set will be consumed by the reactions, but not produced, or at least not produced in sufficient amounts to replace the amounts consumed. These resources will therefore disappear from the closed set. Note that this does not affect the closure, because loss of resources cannot add new resources. Without these resources, some of the reactions producing other resources will no longer be able to run. Therefore, the resources they otherwise produce will no longer be replaced if they are consumed by some other reaction. If no other reactions continue producing these resources, they too will disappear from the resource set, possibly triggering the disappearance of even further resources that depend on them for their production. Thus, resources disappear one-by-one from the set. However, this process too must come to an end, when the remaining resources do not depend for their production on resources that have been removed, but only on resources that are still being produced in sufficient amounts. Thus, self-maintenance too can be seen as an attractor of the dynamics defined by resource removal.

The process of resource addition ending in closure followed by resource removal ending in self-maintenance produces an invariant set of resources and reactions. This unchanging reaction network is by definition an organization.

This scenario for the spontaneous emergence of an organization illustrates the general *principle of self-organization* [33]: any dynamic system will eventually end up in an attractor (originally called 'equilibrium' by Ashby [33]), i.e., an invariant regime of activity defined as a subset of the system's state space that the system can enter but not leave. In the present qualitative formulation of COT, such an attractor is defined as a subset of resources that is self-sustaining and therefore invariant.

To model the quantity of resources present at a particular moment, we must specify a dynamical law governing the rate with which resources are produced and consumed (this typically takes the form of a system of ordinary differential equations). In COT, it has been proven that every fixed point (the simplest, 0-dimensional type of attractor) of such dynamics corresponds to an organization [34]. However, the opposite is not true: certain organizations cannot be realized as fixed points. Instead, we may encounter more complex attractors, exhibiting oscillatory regimes, limit cycles, and even chaotic behavior [35]. In [34], it was shown that these dynamically stable regimes correspond in most cases to organizations. This means that while the set of resources participating in an organization is invariant, the quantity of each resource can still vary according to some complex dynamics.

In the attractor regime produced by self-organization, the different components of the system (resources in this case) have mutually adapted [33], in the sense that the one no longer threatens to extinguish the other. They have co-evolved to a 'symbiotic' state, where they either more or less peacefully live next to each other, or actively help one another to be produced, thus sustaining their overall interaction [7]. This is the default state for an evolved ecosystem—such as a forest or a coral reef—in which the different species of plants and animals have adapted to the network of ecological dependencies they all constitute together [21].

While some of these species are competitors, or predators (exploiters) of other species, they will normally not consume more of their prey than what is produced from other resources in the ecosystem. Predation may actually regulate the population numbers of the prey. This can prevent the problem where the prey increases so much in population that they exhaust other species on which they depend, thus indirectly threatening their own survival. A classic example of this regulatory function is found in the wolves that were reintroduced as top predators to the Yellowstone natural reserve [36]: their presence reduced the number of deer, thus allowing vegetation that the deer were consuming to recover. This in turn helped other species dependent on that vegetation to increase in number, boosting the overall diversity and sustainability of the ecosystem.

As we noted about organizations in general, the population of a species (i.e., quantity of the corresponding resource) in such an ecosystem is likely to fluctuate over time—e.g., following the classic predator–prey dynamics that leads to periodic increases and decreases, or following a more chaotic dynamic. But on the qualitative level, each of the species should be able to be reproduced at a rate sufficient for it not to disappear altogether, because this would entail a potentially radical reorganization of the ecosystem.

The relations between the different resources and reactions in an organization form a similar web of exploitation, competition, and cooperation—or, more generally, ecological dependencies—that has stabilized into a self-sustaining network. Depending on the number and type of reactions, this network can be very complex. However, its defining features of closure and self-maintenance are easy to formulate mathematically and verify computationally by analyzing the reaction network and checking whether each resource can be produced at least as much as it is consumed, while no new resources are created.

5. Sustainability and Resilience

Organizations generally require a sufficient input to self-maintain. In environments with such an input, an organization is by definition a self-sustaining, and therefore *sustain-*

able, system. That means that it can maintain perpetually, without ever running out of the resources that it needs to function—because all resources are recycled through the inherent reactions and/or because there is a dependable input from outside the system (represented by reactions of the form: $\rightarrow a$).

Many organizations do not just maintain, they *grow*, because they produce more of certain resources than they consume. Such resources are said in COT to be 'overproduced' [37]. Organizations with overproduction fulfill the ideal of *sustainable development*: growth that can be sustained without exhausting its environment.

While this may seem paradoxical, we should note that the COT formalism does not a priori assume any conservation law for resources [25], as one would expect for material or energetic resources. That is because the formalism is intended to be more flexible than traditional chemical or physical models. This allows it for example to model informational resources, such as knowledge, decisions, or messages, which do not obey a conservation law, or hybrid material-informational resources, such as economic products. This also helps us to simplify our models by ignoring ever-present inputs (such as air or sunlight) or outputs (such as dissipated heat or waste). Still, it is possible to impose conservation on a particular set of reactions if that would help to make the model more realistic.

Ecosystems are normally sustainable with an approximately constant level of resources, externally supplemented by energy from the sun. Economic systems, on the other hand, although they grow, are often unsustainable: they consume more of certain resources than they produce. Therefore, they may collapse when the resource reserve is eventually exhausted. For example, our present economy is largely relying for its energy on fossil fuels that are in limited supply. Creating a sustainable economy means shifting to energy sources that are renewable through a dependable external input (e.g., solar energy) or through reprocessing within the network (e.g., energy produced from waste).

In this example, the cause of unsustainability is easy to identify as it resides in a single type of resource (fossil fuel), and therefore the solution is obvious: replacing this resource by other, renewable resources. More generally, sustainability is an emergent property dependent on the reactions between all the resources used, because a shortfall in one resource may be compensated by the increased production of another resource performing a similar function. It is here that we need the more sophisticated quantitative formalism of COT with its flux vector and stoichiometric matrix in order to establish under which conditions the reaction network is self-maintaining.

In previous work, we have developed a more complex example of a sustainable farm to illustrate such analysis [30]. The model includes resources such as water, cows, grain, grass, milk, chickens, eggs, and dung, with only water as an external input (from rain), and milk, eggs, and grain as external output leaving the farm. It includes reactions such as $water + grass + cows \rightarrow cows + dung + milk$. It shows under which conditions this network of reactions is self-maintaining and thus sustainable. It also shows which subsets of this set of resources can form self-maintaining organizations. For example, it demonstrates that the farm could still be sustainable without chickens and eggs.

Complementary to the notion of sustainability is the one of *resilience*. Sustainability denotes the ability of the system to maintain on its own without outside interference. Resilience [30,38–40] broadens this notion to the ability to maintain the essential organization even in the face of serious outside disturbances. A resilient system is one that will survive and recover from shocks induced by the environment. In contrast, a vulnerable or fragile system is one that is likely to disintegrate when it encounters an intense disturbance, such as an earthquake or a traumatic event.

In the sustainable farm example [30], we have also made an analysis of how different types of disturbances can affect the sustainability of the farm. Some of the disturbances affect the amount of available resources—e.g., some of the cows may die. Others affect the rate of certain reactions, such as a reduction in the amount of rain falling. Yet, others introduce new resources with the corresponding reactions they trigger, such as an introduction of mice in the farm that eat some of the grains.

In the qualitative version of COT, a disturbance can be represented as the removal of a resource that the organization relies upon (e.g., cows), or as the introduction of a new resource (e.g., mice) that reacts with some of the existing resources (e.g., grain), thus interfering with the network of reactions that defines the organization. Both types of disturbances may reduce the availability of certain resources that are part of the organization, either by removing them at the input stage or by inhibiting them via internal reactions. To survive such a disturbance, a resilient organization will need to either suppress the disturbing resources before they interfere with the organization's critical 'metabolism', or to replace the lost resources before their absence makes further self-maintenance impossible [11]. In other words, the organization will need to counteract or compensate the disturbance and/or its effects on the network of reactions so as to minimize the deviation from the viable configuration. This defines the cybernetic process of *regulation* or *control* [11].

The simplest method of control is *buffering*: maintaining a large enough reserve of resources so that temporary reductions in availability have little effect. This can be achieved by organizations that increase their resource base through overproduction of the most crucial resources.

The next method is *negative feedback*: organizing the network of reactions in such a way that deviations from the desired concentration of resources are automatically counteracted after each cycle of consumption and production. For example, a reduced supply of a particular resource may automatically trigger an increased net production of that resource. This kind of dynamic is common in metabolic pathways and in ecosystem interactions. For example, if foxes eat more rabbits, fewer rabbits will be left, and therefore some of the foxes will starve. A reduction in the number of predators will then let the rabbit population recover. Such a dynamic follows naturally from our earlier observation that reaction rates normally increase together with the concentration of their reactants. This creates an implicit negative feedback because the reactions consuming a resource necessarily slow down when that resource become scarcer (e.g., predation slows down when the prey population decreases), thus allowing the reactions producing that resource (e.g., reproduction of the prey population) to catch up.

The third basic control method is *feedforward*: neutralizing the disturbance *before* it has had the chance to perturb the functioning of the system. This can be achieved by reactions that consume the disturbing resource before it could have interfered with other, vital resources. The tricky part here is that these neutralizing reactions will only be enabled when a disturbance is present for them to react with. This means that for most of the time, these reactions will remain 'dormant': the organization has the potential to react, but will only do so when the right condition is present [11]. One way to implement such capability is by maintaining a collection of resources that can react with a particular disturbance, either getting consumed in the process, or, preferably, functioning as a catalyst that remains in the system after the reaction. The larger the variety of such potential 'neutralizers' contained in the organization, the larger the variety of disturbances it can survive. This implements Ashby's law of requisite variety [11,41].

An example of such a collection of neutralizers are the genes of an organism that are activated via a particular molecular pathway whenever the cell encounters a particular disturbance. Once activated, these genes produce enzymes catalyzing reactions that neutralize the disturbance. But as long as a specific disturbance does not occur, the genes remain non-active snippets of DNA. Other examples of 'dormant neutralizers' are antibodies, which are produced by the immune system in large quantities only in case of infection, and the armed forces of a country, which are mobilized only if the country is attacked.

6. The Evolution of Resilience

We have argued that arbitrary networks of reactions will self-organize to produce sustainable organizations, for the simple reason that organizations are attractors of their dynamics. It is less obvious that these organizations would also be resilient. However,

evolutionary reasoning shows that robust or resilient outcomes are more likely in the long run than fragile ones.

First, any dynamical process starts from some point in the state space of the system, while eventually settling down in some attractor region within that space. Attractors are surrounded by basins of attraction, i.e., subsets of the state space from which all states lead into the attractor [42]. The larger the basin, the larger the probability that the starting point would be in that basin. Therefore, the system is a priori more likely to end up in an attractor with a large basin than in one with a small basin. The larger the basin, the smaller the probability that a disturbance pushing the system out of its attractor would also push it out of the basin, and therefore the more resilient the organization corresponding to the attractor. The size of the basin corresponds to what in [40] has been called the *latitude* aspect of resilience. Large basins normally represent stable systems characterized by negative feedback, because a deviation from the attractor that remains within the basin is automatically counteracted by the descent back from basin into attractor.

The higher a priori probability of starting from a large basin does not exclude the possibility of ending up in an unstable attractor, characterized by a small (or empty) basin. However, these unstable attractors will normally not survive long, as nearly any perturbation will push the system out of that attractor's basin into the basin of a different attractor. After a number of such attractor-to-attractor shifts the probability increases that the eventual attractor will have a large basin, and therefore be stable. This very general, abstract reasoning makes it plausible that systems that are regularly perturbed will eventually settle down in a stable, resilient organization. This is an application of the *order from noise* principle [43], according to which increased variation ('noise') accelerates the self-organization of a stable configuration ('order').

We have tested out this scenario in a computer simulation [30], where networks of randomly generated reactions were first allowed to settle into one of their self-sustaining organizations, and then subjected to various random perturbations. What we found was a little more subtle than the simplest form of the scenario. Under continuing perturbations, the system did not settle into a single large attractor, but rather tended to repeatedly shift between a cluster or family of related attractors [44]. These attractors corresponded to largely overlapping organizations (meaning that they shared most of their resources).

The shifting from one attractor to a similar, neighboring one can be seen as a higher-order process of evolution, in which the system adapts to changing conditions by changing its organization (i.e., its set of resources), but in such a way as to maintain a continuity of identity by keeping most of its resources the same. Note that a 'sideward shift' to an overlapping organization normally happens as a combination of two 'vertical' shifts, one 'upward' that adds resources and one 'downward' that removes resources [45]. The ability of the system to undergo such minimal shifts of organization in response to great disturbances exemplifies a higher level of resilience that may be called *evolvability* [46], because it allows the organization to evolve into a new organization while keeping most its components and structures intact.

What needs to be investigated further is how such organizations are precisely organized: what kinds of arrangements of reactions make up a resilient whole? A theoretical decomposition of organizations [37] shows that complex organizations tend to be *modular*, i.e., they consist of subnetworks whose self-maintenance is independent of the self-maintenance of other subnetworks. Overproduced molecules and catalysts function as 'boundaries' that connect the subnetworks, however, without making them dependent on each other. Such decomposition makes it possible to delimit the effects of a perturbation. For example, a perturbation happening in a small subnetwork will leave the bulk of the organization intact.

Another source of inspiration for understanding resilience is the metabolic networks used by real organisms. These appear to be surprisingly robust in the face of random mutations removing or adding gene-regulated reactions [47]. A likely reason is the redundancy—or more precisely *degeneracy* [48]—of pathways for producing critical resources: there is a

variety of independent mechanisms that perform partly different, partly the same functions. Thus, the loss of a pathway through mutation is simply compensated by more activity in other pathways that perform the same function [11]. Such degeneracy is one of the factors that explain the remarkable resilience and evolvability of living systems [46]: they can afford to undergo a lot of variation without losing their essential ability to self-maintain. This allows them to explore an immense space of largely overlapping organizations, and thus to discover ever more resilient and adaptive ones.

7. Agents and Topological Structures

A priori, the world of reaction networks does not have any spatial structures or boundaries: all resources and reactions are supposed to be mixed within the same 'reaction vessel' where everything can react with everything else. Most real-world models assume some kind of subdivision of the elements of the model into objects, systems, or spatial regions. Typical simulations of complex adaptive systems (CAS) start with agents located in the cells or vertices of some discrete topological structure, such as a lattice or network. Coordinated groups of agents may form systems that function as 'superagents' at a higher hierarchical level. Without going into the necessary mathematical details of the construction, we will here argue that such spatial and hierarchical differentiation can be introduced into COT models without essential changes in the formalism.

First, as we already noted, the concept of agent is easily reinterpreted in COT as a catalyst [7]—i.e., a resource a that is necessary to enable a reaction, but that is not itself affected by the reaction it triggers: $a + b + c \rightarrow a + d$. This can be read as 'agent a processes $b + c$ into d'. Since an agent can catalyze several independent reactions (e.g., $a + f \rightarrow a + g + h$), it will be characterized by a list of 'condition-action rules' of the form a: $b + c \rightarrow d, f \rightarrow g + h$, etc. The input of the reaction without the catalyst here functions as the condition to which the agent will react, while the output of the reaction without the catalyst functions as the action that the agent performs whenever it encounters that condition. Thus, an agent a 'acts' by transforming some initial condition ($b + c$) it encounters into some subsequent condition (d). This characterization of agents as bundles of condition–action rules is the basis for common multi-agent simulations of CAS. The larger the set of reactions an agent catalyzes, the richer its 'skill set' or 'toolbox' of condition–action rules, and therefore the greater its power in manipulating its environment [7,11].

To define superagents, we may note that complex organizations often contain suborganizations: subsets of their resource set that are able to autonomously self-sustain while exchanging some of these resources with other processes or suborganizations within the larger organization. These exchanged resources can be categorized as either input, $In(S)$, or output, $Out(S)$, of the suborganization S. This allows us to summarize the activity of S by the following 'higher-order' reaction:

$$S + In(S) \rightarrow S + Out(S)$$

Suppose that $In(S) = \{a, b\}$ and $Out(S) = \{c, d, e\}$, then we can write this as a more conventional condition-action rule:

$$S\text{: } a + b \rightarrow c + d + e$$

The fact that S is itself constituted of a network of resources and reactions does not really make any difference when seem from the outside. S behaves like a 'black box' which processes a given input ($a + b$) into a specific output ($c + d + e$). If S is sufficiently resilient, it can maintain itself even when the input changes, producing a correspondingly changed output of 'waste products'. This means that S behaves like a higher-order agent, capable of executing a range of condition–action rules, while itself remaining invariant. The larger organization of which S is a subset may itself be embedded in a network of reactions, thus defining an agent of an even higher order. While we still need to investigate this construction mathematically, this appears to open the door to the modeling of the

dynamical hierarchies [49] and *metasystem transitions* [50] that characterize the multilevel self-organization that we see in the evolution of life and society.

To introduce a topology, we need to create the equivalent of 'cells' separated by membranes or boundaries. One way to achieve this in COT is to label resources with indices that indicate the specific cell in which the resource is located [10], while adding the constraint that resources can only react with resources that reside in the same cell (i.e., that have the same label). Topological structure can then be introduced as a network of 'neighboring' relations between cells, meaning that a resource can diffuse from a cell to a neighboring one via a reaction that merely changes the label but otherwise maintains the resource type: $x_{cell1} \rightarrow x_{cell2}$. By diffusing from neighbor to neighbor, resources or agents can in principle propagate throughout the whole topology.

A shortcoming of this construction is that the labeling must be introduced by the modeler. A perhaps more elegant approach is to view non-overlapping suborganizations as spatially separated, i.e., as residing in different cells, and their exchange of resources as processes of diffusion between neighbors. To make this realistic, we would need a large number of essentially equivalent suborganizations (or some less strictly defined distinguishable modules within a reaction network), playing a role similar to the cells of a multicellular organism. The resources of each cell, while a priori distinct, would play essentially the same role, and in that respect behave similarly to the resources in the previous construction that are merely distinguished by their labels. While apparently more complex, the advantage of such a construction is that the 'cells' would self-organize out of the network of reactions, instead of being imposed by the modeler.

To make this approach more concrete, we need further research into the possible structures and topologies of reaction networks and organizations. We here merely suggest that it is possible to introduce more complex entities, such as agents, hierarchies, cells, and topologies, into the COT formalism, while maintaining the conceptual and mathematical simplicity of resources and reactions.

8. Concrete Applications

After explaining some of the most important capabilities of COT on an abstract level, we wish to provide a brief survey of existing and future application domains.

Most obviously, COT has been used to simulate networks of chemical reactions, with a focus on the emergence of stable systems. The first examples were models of virus dynamics [51] and the chemistry of a planetary atmosphere [52]. The initial inspiration for the development of COT was to model how such chemical networks could develop the degree of autonomy that we associate with simple living systems [53]. Previously, this problem of the origin of life had been approached by looking for *autocatalytic cycles* of chemical reactions [26,54]. These are a more specialized type of organizations, which are both more difficult to build by evolution and less flexible and resilient than more general chemical organizations [27].

A related application domain is the study of metabolic networks in existing organisms, such as the bacterium *E. coli* [55]. This domain has recently attracted a lot of attention under the label of *systems biology*, but still lacks an integrated theoretic framework [56]—which COT may be able to provide [57]. A classic problem within this domain is the modeling of gene regulatory networks, in which genes activate or deactivate each other via the proteins they produce. These networks can settle into a variety of attractors characterized by specific patterns of expressed and dormant genes. Different attractors are assumed to correspond to different cell types (such as liver cells, bone cells, or neurons), or cell fates (such as apoptosis, quiescence, or proliferation) [46]. The reaching of such attractors is commonly modeled by means of Random Boolean Networks, a highly abstract formalism whose main advantage is that its dynamics is easy to simulate. But COT suggests a model that seems

both simpler and more realistic, in which the attractors are the organizations that emerge from a network of reactions with the following form:

active gene 1 → active gene 1 + protein 1 (*protein expression of an active gene*)

active gene 2 + protein 1 → non-active gene 2 (*expressed protein deactivates gene*)

non-active gene 3 + protein 1 → active gene 3 (*expressed protein activates gene*)

Because the reactions defining COT are intrinsically abstract, computable processes, they can be used as a foundation for a new method of computation, based on 'artificial chemistries' [58]. Here, the input of a chemical program is a list of resource concentrations. Because the dynamics of a reaction network settles in organizations, it is possible to build reaction networks where reactions play the role of complex logical gates, and organizations represent the final state of the computation. Such 'chemical computation' can, for instance, be used to check models [59] or to program distributed artefacts [60], helping them to coordinate their actions.

Modeling complex systems with many variables of course cannot be done manually. Yet, COT lends itself readily to the development of simple, modular computer programs that can examine a wide range of possible situations, and that are easy to extend or update. An important issue here is how the algorithmic complexity of COT models grows as the number of resources and reactions increases. A basic result is that verifying whether a set of resources is an organization is a Linear Programming problem, whose computational complexity is polynomial, albeit of a degree higher than 2. This motivated a first algorithmic study that builds the set of organizations of a given reaction network from a bottom-top approach that adds resources until an organization is found, and an intricate method that combines flux vectors of previously known organizations [61]. These algorithms were later extended to their parallelized counterparts [62]. The computational complexity of these methods is at first sight exponential because every subset of resources could in principle be an organization. However, it is possible to decompose organizations into subnetworks that are independently self-maintaining [37]. This technique could permit the classification of types of reaction networks in terms of how complex it is to compute their set of organizations. Note, also, that reaction networks are structurally equivalent to a formalism studied in distributed processing, namely Petri Nets [63], about which there is extensive algorithmic research.

Once we make abstraction of the molecules that originally inspired COT, the application domain immediately extends to the social sciences, where the resources to be processed by reactions can, e.g., be economic goods [64] or political decisions [9]. In the latter case, the self-sustaining network of decisions producing further decisions provides a simple formal model of the notoriously difficult theory of autopoietic social systems developed by Niklas Luhmann [65,66]. Another application of Luhmann's social theory is a framework to study the evolution of cooperation [67]. This problem is usually studied from an agent-based perspective. The reaction network models agents' decisions as resources that interact to produce new decisions together with the payoffs generated by the agents' interaction. This model manages to reconstruct the known conditions for the evolution of cooperation [68]—yet without including individual agents! More generally, COT can help us to develop an integrative view of social organizations as autopoietic, self-organizing, and complex adaptive systems [69].

We have alluded several times to the potential for applying COT to problems in ecology [21], sustainable development [30], and the resilience of social and ecological systems. A related issue is the understanding of business ecosystems [70–72], an approach that sees companies producing and consuming different goods and services as forming a symbiotic, co-evolving network, where the ones provide the resources for the others. Existing formalisms in ecosystem modeling, such as food webs or systems dynamics, tend to be limited to networks of one-to-one interactions, in which one variable (e.g., a predator

population) positively or negatively affects another variable (e.g., a prey population). In COT, we can examine how several resources in combination produce a combination of other resources. While this at first sight makes modeling more complicated, the mathematics of COT shows that it actually becomes easier to model the emergence of stable organizations.

A general advantage of COT is that you can freely mix resources of very different types, such as organisms, chemicals, economic goods, and even human decisions [12]. This makes it eminently suitable for modeling the truly complex social–technological–economical–ecological–physical systems that surround us, such as cities, businesses, regions, or our planetary society. This is the objective of the new approach of global systems science [73,74].

To further illustrate the power and generality of COT, we wish to briefly suggest some more speculative applications. The section on resilience noted that a highly evolved organization is likely to exhibit a variety of regulatory mechanisms characteristic of a cybernetic or autopoietic system. Such a system acts like a goal-directed agent [42] that aims to sustain its essential organization while suppressing any disturbances that may push it away from this goal. That means that it exhibits not just the most basic features of life, but of cognition [11,22], intelligence, and intentionality. Like all living systems, the implicit goal or intention of an organization is to maintain and grow. To achieve this, it needs to produce the right actions for the right conditions (e.g., produce the right resource to neutralize a particular disturbance, or to exploit a particular input). This means that it implicitly follows a system of 'condition–action rules' that play the role of the organization's 'knowledge' on how to act in its environment. The capability of 'computing' the right combination of action(s) to solve a given problem constitutes the organization's 'intelligence'. To do this, it needs to 'perceive' what is going on in its environment. For example, a unicellular organism will sense the presence of certain resources (such as food) or disturbances (such as toxins) when the corresponding molecules diffuse into the cell, and respond by activating the right combination of genes to produce the enzymes that will catalyze the reactions for effectively dealing with this condition. In this way, an organization can be seen as a rudimentary 'intelligence' or 'mind' [11].

Because this abstract conceptualization is independent of any specific substrate—such as a brain—it is applicable to systems that exhibit intelligent behavior, but that are otherwise very different from the human individuals that we tend to see as the sole possessors of minds. Examples are the intelligence exhibited by insect societies, plants [75], bacterial colonies [76], human organizations, the self-regulating planetary ecosystem—i.e., 'Gaia' [32,77]— and the Internet in its function as a 'Global Brain' [78]. In all these cases, intelligence is *distributed*: it is not localized in some central decision-making component, but it emerges from the coordinated interactions between many agents and resources working in parallel. Providing simple models of such self-organizing, distributed organization is precisely the strength of COT.

Even the human brain is a complex, distributed network, where all the important features such as intelligence, intentionality, and consciousness are emergent rather than localized in some specific neuron or assembly of neurons. Recently, great progress has been made in understanding consciousness as a coherent pattern of activity taking control of the 'global neuronal workspace' in the brain [79,80]. For conscious processing of thoughts, we need to maintain a pattern of activity long enough in our working memory so that it can be examined and processed by different brain modules. This is intrinsically difficult, because neural activation cannot stay in the same place: a neuron that is excited by an electrical signal ('action potential') cannot retain that electrical charge, but must pass it on to one or more neighboring neurons via its outgoing axon ending in synapses. If a sufficient number of incoming synapses pass on a signal, the newly reached neurons will become activated as well, passing on this activation via their outgoing synapses to further neurons. This transmission of activation can be described as a reaction of the form: $a + b + \ldots \rightarrow e + f + \ldots$, where a, b, etc., are the initially activated neurons whose combined activation is necessary to activate the subsequent neurons e, f, etc. We may say that the activation of a and b is 'consumed' by the reaction in order to 'produce' the activation of e and f.

What the neuronal workspace theory proposes is that conscious patterns of activation—in contrast to subconscious or subliminal processes—are to some degree self-sustaining: activation that leaves a neuron comes back to it at a later stage after having propagated through some complex, closed network. This creates coherent assemblies of neurons that are firing in a synchronized, cyclic manner, so as to keep the idea 'alive' long enough for it to be monitored and processed in a controlled, focused manner—the hallmark of consciousness. Mathematical models of this process have been built [79], but they are rather complicated, making many ad hoc assumptions about specific neurophysiological properties and structures, while being able to simulate only the most basic dynamics of a neuronal assembly reaching 'ignition' (self-sustaining activation). By interpreting coherent neuronal activation patterns as organizations, we may reach a simpler, broader, and more qualitative understanding of the different conscious patterns that the brain can produce. Moreover, we may be able to model how such patterns can evolve into different but overlapping patterns as new stimuli make them deviate from their initial organization, thus producing a 'train of thought' or 'stream of consciousness' [81].

9. Conclusions

Chemical Organization Theory (COT) proposes a very powerful formalism for the modeling of complex, self-organizing systems. Its power results from several advantageous properties:

- The components of the formalism—resources and the reactions that map combinations of resources onto new combinations—are extremely simple and intuitive. This makes it easy even for people without mathematical background to start expressing their understanding of a system in the form of a COT model.
- Reaction networks are intrinsically modular: it is easy to add (or remove) resources and reactions, and thus to develop an increasingly realistic model of a complex system.
- These components are so general that they can be used to represent a wide variety of real-world objects and variables, including particles, molecules, biological species, economic goods, technological infrastructures, human or animal agents, ideas, and decisions. This makes it possible to apply COT to modeling systems in the most diverse scientific and social disciplines [12], and in particular to multidisciplinary issues, such as interactions between ecological, economic, social, and technological systems.
- COT models are easy to analyze computationally: entering a set of reactions into an appropriate computer program will allow you to quickly discover the different possible outcomes together with the conditions under which they can arise.
- The COT formalism is intrinsically dynamic, starting from reactions rather than from static objects or properties. This makes it particularly suitable for describing systems characterized by an on-going creation, process, or flow of resources. Such systems, which include organisms, ecosystems, societies, and brains, are intrinsically difficult to fit in a traditional, Newtonian framework [7].
- COT shows how such dynamic networks of production and consumption tend to spontaneously settle into invariant 'organizations', thus providing a simple model of the hitherto difficult-to-understand phenomena of self-organization and autopoiesis that produce self-sustaining systems [11].
- These organizations can be easily analyzed for further properties, and in particular for the characteristics that make them more or less resilient [30] in the face of perturbations: overproduction of resources, latitude of the basin of attraction, precariousness, feedback, degeneracy of pathways, evolvability, etc.
- As such, COT is a promising approach to a range of notoriously difficult problems, including the origin of life, the modeling of metabolic and genetic regulatory networks in systems biology, the resilience of ecosystems, the formalization of sustainability, the self-organization of socio-economic systems, and even the dynamics of consciousness.

One of the reasons why COT manages to achieve so much with so few assumptions is that the formalism consists of two levels: the very simple qualitative level listing the

resources and reactions active in a particular network or organization, and the more advanced quantitative level (which we have largely ignored in this introductory survey) examining the rates of the reactions and the changing concentrations of the resources. Precise modeling at the quantitative level is of course more difficult, both analytically and numerically, but that does not prevent us from deriving clear, unambiguous results by just examining the qualitative level. While the qualitative model can be seen as a mere 'abstraction' of the full quantitative dynamics [34], its algebraic properties are so strong that many non-trivial properties can be established at this level without need to determine quantitative dependencies or concentrations. These properties can be used to simplify the model to such a degree that it not only becomes intuitively easier to grasp, but easier to turn into a computable quantitative model without need for unrealistic simplifications. Moreover, in many cases, we do not need to know the full quantitative dynamics, but just need to establish which combinations of reactions and resources (such as species in an ecosystem, or active genes in a genetic regulatory network) form a self-sustaining and resilient whole.

The COT formalism is hardly two decades old and has as yet only been investigated by a relatively small number of researchers. Thus, there is of course still a lot of work that needs to be done, both in further clarifying its mathematical and conceptual foundations and in applying it to concrete problems. Yet, the results we have reviewed here illustrate the power and flexibility of this formal framework. We hope that after reading this paper, others may become as enthusiastic as we are in applying COT to various domains, and thus potentially revolutionizing our conception of complex, self-organizing systems.

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Review

Dynamical Systems Research (DSR) in Psychotherapy: A Comprehensive Review of Empirical Results and Their Clinical Implications

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Abstract: In psychotherapy research, the first applications of dynamical systems research (DSR) date back to the 1990s. Over time, DSR has developed three main lines of research: the study of oscillations in synchronization; the study of oscillations between stability and flexibility of process variables (S–F oscillations); the mathematical modeling to analyze the evolution of psychotherapy process. However, the connections among the empirical results and their implications for psychotherapy practice are unclear. For this reason, for the first time in the literature, this work carries out a comprehensive review of all three lines of research, including the main scientific contributions from the 1990s to the present day. For each line of research, the work critically analyzes the results, proposes future developments, and underlines the connections between empirical results and implications for psychotherapy practice. Furthermore, the work highlights the model of change that emerges from the empirical results, and its clinical correlates. In the conclusions, the author summarizes the results and the evolution of psychotherapy process in accordance with the DSR.

Keywords: psychotherapy research; dynamic systems; change process; process–outcome research; dynamics of change

1. Introduction

Scientific contributions based on a systemic approach within psychotherapy research have increased over time. A special section focused on dynamical systems research (DSR) has developed within the International Society for Psychotherapy Research. The scientific contributions within this framework have undoubtedly brought an important methodological advancement in the field. However, such contributions have often struggled to obtain full recognition within the broader landscape of psychotherapy research due to the difficulty in connecting the empirical results to their clinical implications. In short: DSR has often been perceived as a set of sophisticated mathematical methods devoid of any clinical relevance. The purpose of this work is to overcome this difficulty. In fact, this contribution constitutes the first comprehensive review on the topic, made with the aim of clarifying the connections between the empirical literature of DSR in psychotherapy and clinical practice.

DSR is not an exclusive line of research of psychotherapy but, rather, represents a general scientific advancement. In fields such as biology or medicine, for example, there are extensive discussions on the problem of the recent lack of new scientific discoveries. The problem of scientific reductionism has turned out to be the issue underlying the lack of new results in various branches of science [1]. In fact, until recently, the predominant idea was that the collective behavior of a complex system, regardless of its scientific domain, could be understood and predicted by studying the dynamics of all its subunits, considering each one in isolation. However, this approach of analysis proved to be insufficient when studying emerging behaviors, i.e., all the properties of the system arising from the interaction among its different internal components. Emergent properties highlight the need to focus scientific research on the most suitable level of abstraction, in such a way as to maximize the

variability of the scientific phenomena explained. Recent evidence of the importance of this topic is the contribution by Sadri [2], in which the author performed a manual systematic review of 32,000 articles from the last 150 years of scientific research in the field of drug discovery. The results clearly show the inadequacy of the current paradigm, which is based on a "target-based" approach that aims to search for molecules that directly modify the gene responsible for a pathology, in favor of a "phenotypic-based" approach, which prioritizes, in selecting and optimizing molecules, higher-level phenotypic observations that are closer to the sought-after therapeutic effects using tools based on a systems approach to science. In fact, phenotypic variability is not directly linked to single genes taken in isolation, but is determined by the emerging properties of complex genetic networks. Along this line, the most recent review of data on evolutionary processes highlighted the role of epigenetic factors and genetic networks, active during embryogenesis, in orchestrating variation-inducing phenomena underlying evolution, much more than the genome only [3]. With the transition from analyzing elements in isolation to complex networks, all the scientific literature based on the dynamic-systems approach develops.

In psychotherapy research, this fundamental transition, from studying a complex system by dividing it into simple components to the use of macro-parameters aimed at explaining the behavior of the entire system at hand, began in the 1990s. The first contributions belonging to DSR studied the applicability of self-organization principles to the psychotherapy process (e.g., [4,5]). Self-organization processes are a prerequisite for DSR, and they are particularly important for the introduction of the concept of circular causality on which the Palo Alto school of psychology also worked extensively [6]. In fact, the notion of self-organization emphasizes the process through which complex interactions between different elements of a system spontaneously generate a new property in the system itself. In clinical terms, with our patients we can sometimes talk about "family climate" to refer to that set of affective dynamics that have served as fertile ground for the formation of the patient's defensive strategies. In fact, often there is not a single event that produces psychopathology, but a set of conditions that resonate with a specific family member. Another synonym for self-organization is emergence. This term also underlines the lack of a single external agent responsible for the spontaneous generation of a new property of the system. In summary, spontaneity and the lack of a single external cause are the main characteristics of self-organization processes.

The applicability of DSR to psychotherapy has two main advantages. First, as in other sciences, it avoids scientific reductionism, which is particularly evident in the field of psychotherapy due to the multitude of different theoretical approaches. The concepts underlying DSR constitute a common fertile ground on which the clinical aspects, specific to each approach, can be developed. This ensures that research in psychotherapy can acquire a trans-theoretical and trans-disciplinary strength: that is, it can be enriched through scientific contributions coming from research based on different theoretical approaches and different scientific fields. Secondly, DSR promotes an empirical, methodological, and theoretical framework for the study of change within the psychotherapeutic process: Empirical, because the study of change within complex systems has produced a vast body of literature; methodological, because the methods used within the DSR are very innovative within psychotherapy research; theoretical, because the results of the literature have produced models of change that are studied within the psychotherapeutic process [7].

The importance of DSR for the study of change in the psychotherapy process is reflected in the lines of research that have developed over time: namely, the study of oscillations in synchronization; the study of oscillations between stability and flexibility of process variables (S–F oscillations); and the study of mathematical models to analyze the macro-parameters characterizing the psychotherapy process. These three lines of research represent the three main vertices of the study of change processes in psychotherapy and, importantly, they also represent the three chapters of this work. Three literature reviews were performed, one for each chapter. All contributions on DSR in psychotherapy were taken into consideration, therefore, from the 1990s to 2023. Within each section, the

work particularly focuses on the connections between empirical results and their clinical relevance. In detail, in the first part of each chapter, the status quo of the scientific literature is presented, while in the second part, the literature is critically analyzed, underlining significant future developments. Finally, in the conclusions, a general picture of the state of the art of DSR in psychotherapy is drawn, highlighting the research areas that have had the greatest development and those on which we need to focus our efforts the most.

2. Preliminary Requirements for Dynamical Systems Research (DSR)

There are two main requirements to set up a research work based on dynamical systems. The first refers to the length and frequency of the data time series. To monitor change processes within a time series, a homogeneous sampling frequency of data is needed. If possible, one measurement per day, or one every two days, should be taken. One measurement per session is also sufficient as long as the length of the time series is adequate: a minimum of about 40 time points. The second requirement refers to the choice of variables to analyze. To make DSR, the variables must be able to monitor change processes within psychotherapy. However, in this field, the problem of different therapeutic approaches arises, with their different language and corresponding different operationalizations of the variables probably being the most significant in supporting therapeutic change. For example, in a systematic review which ONLY considered the patients' characteristics that proved to be predictors of the outcome of cognitive-behavioural therapy (ONLY) for eating disorders (ONLY), the authors found 6 mediators, 13 moderators, and 20 predictors of outcome [8]. The review excluded any relational and therapist-related variables, as well as, obviously, any other therapeutic approaches and diagnoses.

In addition, nonindependent variables are increasingly included in moderation or mediation studies, violating the assumptions of statistical models based on analysis of variance [9]. The problem of nonindependence of process variables is particularly serious due to the nature of our clinical work. For example, both in empirical and clinical terms, it is absurd to consider variables of the therapeutic relationship as independent with respect to variables referring to the psychotherapeutic technique. Yet, it is enough to insert "mediation" as a keyword in one of the most accredited journals in the field of psychotherapy research to be able to observe how, for example, the "psychodynamic techniques", the "therapeutic alliance", and the "interpersonal and intrapersonal distress" can be considered constructs independent of each other, probably because the researchers measured those variables by using three different questionnaires. It is difficult to study the complex phenomenon of psychotherapy by reducing it into small independent components based on our need for simplification. This scientific reductionism, derived, on the one hand, from the theoretical–clinical fragmentation of psychotherapy and, on the other, from empirical oversimplification, produces a fragmented and sterile scientific corpus. How, then, do we choose the variables to analyze and avoid problems of scientific reductionism? It is of help to include second-order variables, abstracted from the original variables, in the study. We will see in the chapter on "stability–flexibility oscillations" (S–F oscillations) most of the parameters that can be measured starting from process variables, provided that the latter respect the frequency and length requirements mentioned above. These parameters, as the title of that chapter underlines, refer to two main dimensions: the stability and flexibility of the psychotherapeutic system. They lie at a higher level of abstraction than the original process variables. For example, seven subscales of a questionnaire can be correlated with each other, and the absolute values of the Pearson coefficients summed up. In this way, a score of stability or rigidity of the network made up of the seven subscales is obtained. This "stability score" is at a higher level of abstraction than the original process variables. Obtaining these parameters facilitates the comparison between results of different studies, avoids problems of scientific reductionism, and produces truly independent variables suitable for all types of models based on analysis of variance.

Years ago, we called this type of approach based on the abstraction of second-order parameters "A Statistical-Mechanics-Inspired Approach to Psychotherapy" to underline the

origins of this line of research [10,11]. In fact, statistical mechanics is the branch of physics that investigates the possibility of extracting a small number of relevant "macroscopic" parameters for the study of the mechanical and thermodynamic behavior of systems composed of a large number of particles.

3. Preliminary Concepts

As mentioned in the introduction, the study of the dynamics of change within the psychotherapy process constitutes the main focus of DSR. The key model of change on which the literature is based is the *order-to-order transition* (e.g., Schiepek et al., 1997, one of the first contributions on the topic) [12]. It is called order-to-order because it describes the transition from a stable dysfunctional state to a new stable state that is more functional than the previous one. The clinical work of psychotherapists is entirely focused on trying to promote, in the patient, a more functional psychic organization than that present at the time of the request for help. These transitions occur through moments of destabilization of the previous psychic organization. These moments of destabilization are often called *critical fluctuations*, and represent unstable states in which new patterns of feeling, thinking, and behaving (i.e., new information) are introduced into the patient–therapist relationship. This new information is then reintrojected in the patient as soon as he[1] obtains access to the new stable state. Therefore, the sequence characterizing order-to-order transitions is the following: (a) presence of a stable state or dysfunctional psychic organization; (b) entry into an unstable state of transition characterized by the inclusion of new patterns of feeling, thinking, and behaving in the therapeutic relationship; (c) emergence of a new and more functional stable state in which the new information is reintegrated into the patient. A given dysfunctional psychic organization is characterized by a level of anxiety directly proportional to the severity of psychopathology. The more severe the psychopathology, the higher the anxiety, and the greater the degree of distortion that the psychopathology produces to the reality perceived by the patient. Sometimes the literature uses the term "*attractor*" to identify the presence of a *stable state*. Although the two terms are very similar, there is a difference, in that the attractor can be made up of one or more stable states. For example, the oscillations between depressive-manic states generate the psychopathological attractor called bipolar disorder.

In accordance with the literature, the unstable state at point (B) is characterized by an increase in the correlation and variability of the system at hand (Figure 1) (see Gorban et al., 2021 for a review) [13].

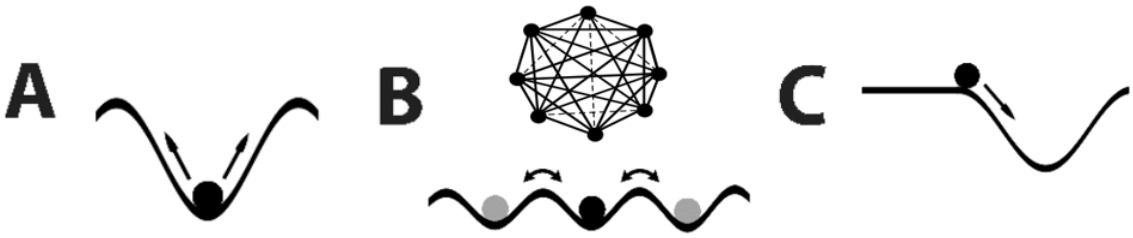

Figure 1. Dynamics of change according to DSR. (**A**) Patient in current stable dysfunctional state. (**B**) Patient-system opening up. Increase in correlation and variability. (**C**) New information reintegrated and patient-system in a more functional stable state. Decrease in variability and presence of new correlations, different from those characterizing the initial state. Parts of the figure are taken from Olthof and colleagues [14].

At point (A), the patient-system resides in the current stable dysfunctional state. At point (B), it opens up to new patterns of feeling, thinking, and behaving. At point (C), the new information is reintegrated and it resides in a more functional stable state than the initial one.

As can be seen in the figure, point (B) is characterized by two different aspects. Increase in correlation, upper panel: the patient's narratives acquire coherence, the core problematic

theme emerges with ever greater clarity, the same dysfunctional relational modality permeates the different domains of the patient's life (professional, emotional, familial). The patient's current psychic organization becomes more integrated and correlated with other aspects of his functioning. This greater understanding of the patient's functioning allows him to lighten the burden of anxiety associated with the current stable dysfunctional state. This allows the patient greater openness towards new patterns of feeling, thinking, and behaving. Increase in variability: in the bottom panel, the possible valleys that could host the ball multiply, that is, the variability of the patient's narratives increases, laying the foundations for a change that will occur in (C).

The stable states at point (C) can be of two types. They may be structurally the same as the previously dysfunctional state, but present less distress, or they may be structurally different from the previous stable dysfunctional state. In the first case, we are faced with a *first-order change*; in the second case, we are faced with a *second-order change* [15]. An example of the former is the patient who resolves his phobic symptom and manages to board the plane, or enter the elevator, or participate in gatherings with many people. An example of the latter is the patient who manages to restructure the phobic organization of his personality. First-order changes are more frequent and involve the patient's body of *knowledge*, whereas second-order changes are rarer, as they imply a general restructuring of the current psychic organization (i.e., the way of *being* of the patient).

The process of psychotherapy is a catalyst for first- and second-order changes with the final aim of promoting, within the patient, the ability to come into contact and experience a highly diversified range of relational modalities. In fact, the patient who begins psychotherapy presents a rigid and repetitive way of experiencing the relationships that surround him. As the therapeutic relationship progresses, the patient gradually obtains access to an increasingly wider range of relational modalities (e.g., [16,17]). The patient is healthy when he is courageous enough to feel happiness, sadness, desperation, physical and mental pain, tenderness, light-heartedness, and the other emotional colors that make life worth living. Order-to-order transitions, stable states and attractors, unstable states and critical fluctuations, first-order changes, and second-order changes are the basic notions allowing a full understanding of the empirical and clinical depth of the research presented below.

4. High–Low Synchronization

Studies on synchronization in psychotherapy mainly include three areas: the study of physiological synchronization between patient and therapist, measured mainly through skin conductance, ECG, EEG, fMRI (see Kleinbub et al., 2020 for a review) [18]; the study of nonverbal synchronization, measured mainly through postural and gaze movements of patient and therapist (see Koole and Tschacher, 2016 for a review) [19]; and the study of verbal synchronization, measured mainly through the prosodic elements of language (e.g., see Orsucci et al., 2016; Scheidt et al., 2021 for a review) [20,21]. Initially, findings in the literature from these three areas supported a simple equation: the higher the synchronization among patient and therapist, the better the psychotherapy outcome. This simple model also seemed to be supported by the results of studies that established a linear positive correlation between therapeutic alliance and synchronization (see the work by Koole and Tschacher for a review). Therefore, from this perspective, high synchronization between patient and therapist was associated with a good therapeutic alliance, which in turn was responsible for the successful outcome of psychotherapy. It is not known what the therapist should do in this model once a good therapeutic alliance has been established. However, as research on this topic progressed, much conflicting evidence emerged. For example, higher synchronization has been observed in poor-outcome dyads, and interpreted as the therapist's struggle to promote the good development of therapy (e.g., [22]). Current studies show how high synchronization is not always associated with the good development of a therapeutic relationship. In fact, a more accurate hypothesis is grounded on the idea that

two tendencies exist simultaneously, one to synchronize with others and the other to move out of synchrony and act independently (see Mayo and Gordon, 2020 for a review) [23].

From a clinical perspective, the model based on the linear association between high synchronization and good outcome of therapy due to good therapeutic alliance is unsound. The psychotherapy process develops if new information and points of view are introduced, often unexpectedly for the patients, producing moments of rupture and repair of the therapeutic alliance (e.g., [24]), and, more likely, moments of rupture and repair of synchronization. It is for this reason that the literature on synchronization acquires clinical depth if applied to the understanding of the dynamics of change within the psychotherapy process, i.e., to investigate how new information is processed within the therapeutic dyad. There are two particularly brilliant examples in the literature on this topic. The first, in chronological order, is by Villmann and colleagues [25], and focuses on the relationship between the physiological entropy of patient and therapist and the language used by the patient within a 37-session psychodynamic psychotherapy. Specifically, the authors highlight how, in the period in which the patient processes new information ("connecting phase", high abstract language, and high emotional language), the physiological entropy of patient and therapist is high. Subsequently, the patient reintegrates the new information, moving to the "reflecting phase", characterized by high abstract language, low emotional language, and low physiological entropy. Since entropy is a measure of variability, the results suggest an "opening" of the therapeutic dyad towards new information coming from the "connecting phase", followed by a reintegration of these novelties within a new point of view (i.e., new stable state). The entire oscillation can be summarized as follows: (a) Flexibility phase, in which entropy is high, emotional language is high, a new perspective is entering within the psychotherapeutic relation; (b) Stability phase, in which entropy is low, emotional language is low, abstract language is high, the new perspective is worked through until it is fully integrated. In this study, the analysis of synchronization of physiological variability plays a vital role in the understanding of the characteristics of this change dynamic. A further example comes from the work by Stukenbrock and colleagues [26], which focuses on gaze synchronization in moments when therapists deliver interpretations to patients. Fifty sessions of two different therapeutic dyads were analyzed. The results clearly show how therapists look away from their patients during the interpretation, recovering eye contact only when the most audacious content of the interpretation is made explicit. Hence, the initial distance (gaze avoidance) is used by the therapist to "grasp" the new information to introduce it into the therapeutic process, finding the most suitable words and modality of delivery. The following proximity (recovery of eye contact) is used to observe the patient's reaction to the new content previously expressed. The study of low–high synchronization oscillations, in relation to the dynamics of processing the new contents conveyed by the interpretation, produces extremely relevant clinical results. It would be interesting to delve deeper into this line of research by analyzing the dynamics of successful and unsuccessful interpretations separately; in other words, interpretations whose emotional content is subsequently reintegrated or rejected by the patient.

Finally, another rather forgotten application of physiological measurements within psychotherapeutic sessions is associated with the patient's anxiety. The patient's physiological arousal, being an expression of the activity of the sympathetic branch of the autonomic nervous system, constitutes an efficient thermometer of the patient's internal anxiety. This application of physiological measures in psychotherapy is potentially very clinically relevant, and should certainly be developed more. For example, it could be studied in relation to the interpretations reintegrated or rejected by the patient. In this case, the hypothesis could be that an emotional content causing too much internal anxiety is rejected by the patient. On the other hand, with a more macro-analytical design, it could be studied in relation to first- and second-order change processes to identify when the level of internal anxiety prevents such changes, i.e., when it prevents the reintegration of new information.

5. Stability–Flexibility Oscillations

5.1. Macro-Parameters

The definition of macro-parameters is not the most common in the literature on this topic. In fact, most contributions use the term "early warning signals". In practice, there is no difference; both terms identify a set of parameters measured on a time series with the aim of studying their changes over time. However, there is a substantial conceptual difference at the root of the two terms. The majority of contributions in the literature on early warning signals applied to psychology study their applicability in predicting or anticipating a transition of the patient's symptoms (see Schiepek et al., 2020 for a review of methods in psychotherapy research; Helmich et al., 2021; Dablander et al., 2023 for a general review in psychology) [27–29]. In fact, the term "early warning signals" precisely indicates this purpose; to have parameters whose increase identifies a transition in the time series of symptoms. This scientific perspective, although important, is not the one with the greatest clinical implications for the study of change within psychotherapy. On the other hand, the use of the term "macro-parameters" does not convey any exclusive application of these indices in relation to the possible transition of symptoms; rather, it promotes a broader application: to the study of oscillations between stability and flexibility within psychotherapy and to their relationship with first- and second-order change (e.g., [30,31]). The clinical importance of this last topic overshadows the question of the association between the increase in these parameters and the possible transition of symptoms. Clinically, it is more important to understand the ingredients that promote and prevent a symptomatic change regardless of whether or not the latter can be included in the category of "phase transitions", or even in a specific subset of phase transitions (e.g., "zero-eigenvalue bifurcations"; see, for example, the work by Dablander and colleagues).

Therefore, what are these parameters? The literature highlights two large groups of indices: the first quantifies the degree of stability or rigidity, while the second the degree of flexibility or dispersion. To date there are few studies comparing the majority of indices within psychotherapy process (see, for example, the work by de Felice and colleagues, 2019b, 2022) [10,31]. However, two renowned research groups focus on specific indices. The research group of Prof. Schiepek has been studying the application of "dynamic complexity", an index of dispersion of a time series, for many years (e.g., [32,33]). The research group of Prof. Lichtwarck-Aschoff and Dr. Olthof have more recently focused their efforts on the application of autocorrelation at lag-1, an index of time series memory to which we will return shortly (e.g., [34]). Schematically:

- *Indices that quantify stability or rigidity*. The most used are the sum of Pearson coefficients in absolute value, calculated on each pair of process variables; the percentage of variance explained by the first principal component (see Gorban and colleagues for a review). If applied within a network, they are called connectivity indices as they measure the strength of connections within the network. Clinically, we can associate the increase in these indices with an increase in coherence of the patient's narratives. In fact, as psychotherapy progresses, we can observe how the patient's dysfunctional relational pattern becomes similar in the different domains of his life: professional, emotional, and familial. Achieving such a high coherence of the patient's narratives allows the therapist to intervene to promote the emergence of a new and more functional psychic organization.
- *Indices that quantify flexibility or dispersion*. The most used are dynamic complexity, obtained by multiplying the fluctuation and distribution of the scores of process variables; the standard deviation, a classic measure of dispersion of the scores of a time series; the Shannon entropy, often applied on eigenvalues (see de Felice and colleagues, and Gorban and colleagues for a review). Clinically, we can associate these indices with the variability of the patient's narratives. Often, in the moment before a change, the patient does completely new things such as looking at old photographs from his childhood, asking his family members things he had never talked about before, organizing his life differently, with new hobbies and new relationships whose diversity

he previously would not have been able to manage. The oscillation between periods of high and low stability and flexibility (i.e., S–F oscillations) in the psychotherapy process promotes the good outcome of treatment (see Section 5.2).

It is necessary to address a separate discussion for the *lagged autocorrelation*. This is a time series memory index. In other words, it measures how similar the relationships between the nodes of a network at time t are to the relationships between the nodes of the same network at a previous time point (e.g., [35]). In the case the comparison is among time t and time t-1, it is defined autocorrelation at lag-1; in the case the comparison is among time t and time t-2, it is defined autocorrelation at lag-2, and so on. The clinical meaning of this index is similar to that of the stability indices, with the addition of the temporal dimension. As psychotherapy progresses, the patient's narratives acquire internal coherence, allowing the main problematic theme to emerge. The latter becomes increasingly present in sessions and often repeats itself between one session and the next. Therefore, the correlation between the patient's narratives at the session at time t and the session at time t-1 (i.e., the previous session) increases. This redundancy of the main problematic theme often increases until, together with the therapist, a way is found to include a new perspective within the therapeutic relationship. The introduction of new information (i.e., new patterns of feeling, thinking, and behaving) generates space in the patient's mind, giving greater variability to the therapeutic relationship.

In the empirical literature, the increase in autocorrelation at lag-1 has often been interpreted as an index of loss of resilience (see, for example, Dablander and colleagues). This interpretation, completely detached from psychotherapeutic practice, is misleading. To understand the rationale of the empirical perspective, it is useful to replace point (B) of Figure 1 with Figure 2.

Figure 2. Illustration of the role of autocorrelation within order-to-order transitions in accordance with the empirical perspective. The reader should replace point (B) of Figure 1 with point (B1). In the initial state, the system is healthy and resilient. At point (B1), the system lies in a shallower valley, losing resilience. The system ends up lying in a dysfunctional state, causing the onset of psychopathology.

In Figure 2, we see that the ball (i.e., the system studied) lies in a shallower valley than at point (A) of Figure 1. This change of depth is interpreted as a loss of resilience. In fact, from this perspective, the system is healthy and resilient at point (A) as it is more resistant to external stressors (i.e., a greater force must be applied to move the ball out of the deeper valley). Conversely, at point (B1), the external stressors must apply a smaller force as the valley is shallower. This loss of resilience is identified with the increase in the autocorrelation at lag-1, as the system at point (B1) takes longer to dissipate the external stressor and return to its stable state at the center of the valley. The process ends at point (C), which the empirical literature interprets as the onset of the pathology of the observed system. This type of change process, deriving from other scientific fields (see the work by Scheffer and colleagues), does not agree with the specific reality of the clinical progress of psychotherapy. The patient who begins psychotherapy tends to be unwell and wants to achieve better health. Furthermore, resilience in clinical terms is related with the concept of stability, as underlined by the empirical perspective, but it is also associated with the patient's flexibility (see, for example, the work by Lingiardi and McWilliams). The acquisition of psychic flexibility helps the patient to be able to manage new relational experiences without perceiving them as stressors. In other words, the resilient patient possesses, on the one hand, a stable self-coherence and, on the other hand, has the ability to

experience a wide range of different relational modalities. If the concept of flexibility were not included in the definition of resilience, we would observe the paradox of the patient who never ends up in a psychopathological condition as he has such a rigid relational modality that he avoids any external stimulus that does not match his expectations. It is clear that in this case stability becomes rigidity, and the patient's mind is not at all resilient but, rather, impoverished. Therefore, in accordance with clinical practice, researchers studying resilience in psychotherapy should relate the concept to both dimensions of stability and flexibility of the patient. We see once again how central the study of S–F oscillations in DSR is.

We presented indices that quantify the stability or rigidity, flexibility or dispersion, and memory or redundancy of the psychotherapeutic system. The reader has perhaps already noticed the main lack exposed in the literature: the measures of quality of change. All the macro-parameters presented are excellent quantitative resources, but when we want to investigate the quality of change within psychotherapeutic process, it seems we have no major alternatives to the analysis of clinical transcripts. The analysis of clinical transcripts should not be taken lightly. Certainly, the literature abounds with possible codings based on the variables that a given research group considers to be the most relevant to analyze the clinical transcript (see Mergenthaler, 2008 on Therapeutic Cycle Model; Caro Gabalda and Stiles, 2021 on Assimilation of Problematic Experiences Scale for two well-established methods) [36,37]. For example, the coding of the Therapeutic Cycle Model is based on the segmentation of clinical transcript into subsequent word-blocks of 150-word length, coded in terms of "abstract language", "positive emotional language", and "negative emotional language". However, we are still far from developing a scientific consensus on an agile and efficient method of automatic coding of clinical transcripts able to abstract the most relevant clinical dimensions. Mainly, this is because the clinical dimensions derive from the transcript but are latent, that is, they represent a subtext that is generated by the specific encounter between the patient and therapist's subjectivities. However, the efforts of some research groups are commendable: the research group of Prof. Salvatore and Prof. Gelo developed the Automated Co-occurrence Analysis for Semantic Mapping (ACASM) [38], a method that is able to transform a clinical transcript into a network of recurrent clusters of words; Christensen and colleagues developed an automatic tool for semantic network analysis [39]; the research groups of Prof. Mergenthaler and Prof. Bucci developed two different automatic tools to analyze clinical transcripts with a focus on the evolution of abstract and emotional language within psychotherapy (e.g., Mergenthaler, 2008 on Therapeutic Cycle Model; Christian et al., 2021, on Referential Activity) [36,40].

While the analysis of clinical transcripts is certainly very important to compare with the performance of quantitative indices, the literature offers a further alternative to monitor the quality of change, which is yet unknown in psychotherapy research. The time series of process variables considered in a given research design can be investigated with a sliding window principal component analysis. This approach allows the researcher to observe the evolution of the loadings within the first (PC1) and second (PC2) principal components over time (see Zimatore et al., 2021 for an example in biophysics) [41]. In fact, a change in PC1 loadings reflects a change in the quality of the current stable state. On the other hand, it is possible to consider PC2 as an "entropic reservoir", that is, as a reservoir of new information that the good-outcome patient, over the course of treatment, is able to integrate into the current stable state (PC1), causing its modification. This is why the study of S–F oscillations is so important. The concept of flexibility (PC2) is linked with the ability to reintegrate new and more functional information within the current stable state (PC1). Having both a stable and flexible component seems to be an evolutionary characteristic selected in order to obtain a good dynamic stability (e.g., [42,43]). In summary, the researcher can monitor the quality of change through a comparison of macro-parameters with clinical transcripts, as well as by looking at the evolution of the loadings of a sliding window principal component analysis applied over process variables.

5.2. S–F Oscillations

The oscillations between stability and flexibility of process variables constitute the main focus of DSR. During periods of flexibility the psychotherapeutic system is able to come into contact with new patterns of feeling, thinking, and behaving, which can then be reintegrated into the patient, causing the modification of the previous dysfunctional stable state. The cycle terminates with achieving a new and more functional stability. We list the corpus of literature on this topic below.

One of the first studies on this subject investigates the patterns of interactions among therapist and patient of a single case of psychodynamic psychotherapy lasting 32 weeks. The results highlight stable and unstable nodes within the network of therapist–patient interaction [44]. The study of episodes of pronounced destabilization leading to a loosening of old patterns has proven to be a characteristic of good-outcome psychotherapies (see Hayes et al., 2007 for a review, including personality disorders and mood disorders) [45]. The investigation of clinical transcripts relating to a single case of emotion-focused therapy using discourse flow analysis highlighted a two-step process of change: a decrease in semantic variability in the first part of treatment, then an increase in semantic variability in the second part of treatment [46]. The alternation of periods of high and low destabilization of patient–therapist relationship characterized the process of psychodynamic psychotherapy in a sample of 15 inpatient treatments for mood and personality disorder. Additionally, a high correlation among patient and therapist destabilization processes has been observed in good-outcome cases only [47]. In seven patients suffering from obsessive-compulsive disorder with predominantly checking symptoms, the process variables "beliefs", "anxiety", and "compulsions" were characterized by periods of high and low correlation in cognitive-behavioral therapy [48].

By using the Innovative Moments Coding System (IMCS) to describe the process of change in narrative therapy (NT), emotion-focused therapy (EFT), and client-centered therapy (CCT), Prof. Gonçalves and colleagues revealed that the overall number of innovative moments (i.e., variability) is significantly associated with symptom improvement. In addition, they proposed a heuristic model of change based on the alternation of a period of innovation (i.e., increase in variability) followed by the reintegration of novelties (i.e., increase in stability) [49]. In detail, the period of innovation is characterized by an alternation among narratives pertaining to the dysfunctional stable state and narratives pertaining to the new and more functional organization [50].

In 27 patients diagnosed with avoidant or obsessive-compulsive personality disorder, destabilization, and emotional processing during the central phase of cognitive therapy were both significant predictors of the good outcome of treatment [51].

The research group led by Prof. Schiepek has been applying a daily monitoring procedure to inpatient treatments in Austria and Germany for several years. Every day, patients must complete the Therapeutic Process Questionnaire (TPQ), a questionnaire monitoring seven process variables: "well-being and positive emotions", "relationship with fellow patients", "therapeutic alliance and clinical setting", "emotional and problem intensity", "insight/confidence/therapeutic progress", "motivation for change", and "mindfulness/self-care". In addition, outcome questionnaires are administered to evaluate symptomatic change. Over the years, a remarkable database has been collected. Some ongoing studies include hundreds of psychotherapies. The published articles revealed the presence of periods of destabilization characterized by high variability followed by its reduction, particularly in good-outcome cases (see Schiepek et al., 2003 with a sample of 91 inpatient treatments; Schiepek et al., 2014 with a sample of 23 patients with obsessive-compulsive disorder; Heinzel et al., 2014 with a sample of 18 patients with obsessive-compulsive disorder) [52–54].

The macro-parameters of order and flexibility proved to be efficient indicators in describing the evolution of 28 psychotherapies, 14 good-outcome, and 14 poor-outcome cases. In detail, cycles of high order and high flexibility characterized the successful cases (see de Felice et al., 2019b; de Felice et al., 2022) [10,31]. Furthermore, the

alternation between stable and unstable states was also highlighted in four child psychotherapies [55,56].

A questionnaire on the psychotherapeutic process was administered daily in 328 patients who received psychotherapy for mood disorders. A continuous measure of destabilization was defined as the relative strength of the highest peak in dynamic complexity. The presence of periods of destabilization and, therefore, the alternation between stable and unstable states was found to be related to a better treatment outcome (see Olthof et al., 2020) [34].

Finally, the study of clinical transcripts through the Therapeutic Cycle Model and Referential Activity revealed the presence of specific cycles in good-outcome cases. In detail, these cycles were constituted by an alternation of phases characterized by high emotional language in which the patient expressed the current dysfunctional pattern of feeling, thinking, and behaving, and phases characterized by a copresence of emotional language and abstract language in which the patient reflected on that dysfunctional organization (i.e., self-reflection) (see Mergenthaler, 2008 for a review on the Therapeutic Cycle Model; Cornell and Bucci, 2020 for a review on referential activity) [36,57].

These results, taken together, clearly show the robust body of literature on S–F oscillations. It would be very significant, through multilevel studies, to compare the temporal evolution of:

- High and low physiological or bodily synchronization;
- S–F oscillations of relational process variables;
- Cycles of emotional and abstract language and their semantic contents;

With the objective of highlighting the ingredients promoting and impeding first- and second-order changes in the psychotherapy process.

6. Mathematical Modeling

In this section, differential equation models based on empirical data from psychotherapy research are considered. Completely theoretical models without an empirical connection or based on data from other sources are excluded.

In a study with a sample of 180 psychotherapies (with an average of 29 sessions per psychotherapy), the "Working Alliance Inventory-Short Revised" questionnaire was filled out by the patient and the therapist at the end of each session [58]. The authors used a differential equation model based on the scores of the patient and therapist at session at time t and at session at time t + 1 and their rates of change. The parameters reflected the stability of the scores between session t and session t + 1 (i.e., internal consistency), and the levels to Ih one's perception influenced, and was influenced by the other's perception. Contrasting results do not allow a reliable interpretation.

Paz and colleagues analyzed the vocal arousal (i.e., speech sound frequencies) of 30 dyads, using as parameters the vocal arousal scores of the patient and therapist at state t and at state t + 1 and their rates of change [59]. The results showed the presence of an intrapersonal and an interpersonal homeostasis. In particular, (a) the patient's scores, in the first part of the treatment, tended to be "pulled" towards the therapist's baseline (interpersonal homeostasis), and (b) the patient's scores, in the second part of the treatment, tended to return to his baseline levels (intrapersonal homeostasis).

Taken together, the results highlight the importance of preverbal coregulatory processes. It would be important to replicate this type of model on relational variables or on the semantic content of language.

Tschacher and Haken proposed a mathematical model based on the Fokker–Planck equation in order to identify the deterministic (i.e., stability) and stochastic (i.e., flexibility) component of one or more time series within the psychotherapy process [60]. The method was tested in a case series where client's and therapist's heart rate, heart rate variability, and respiration were monitored in 20 psychotherapy sessions. The authors also developed an app (FPE app) for automatic calculation. This methodology requires high-resolution time series, such as those derived from physiological variables. The results confirm the

applicability of the Fokker–Planck equation in identifying stable and unstable states within the physiological time series recorded over the course of the psychotherapy process.

Schiepek and colleagues worked on a mathematical model based on the Therapeutic Process Questionnaire (TPQ) factors, the instrument used by this research group for the daily monitoring of inpatient treatments. In fact, the model variables are (E) emotions; (P) problem intensity, symptom severity; (M) motivation to change; (I) insights; (S) success, therapeutic progress, confidence in a successful therapy course. On the other hand, the four parameters that govern the relationships between the variables are (a) working alliance, capability to enter a trustful cooperation with the therapist; (c) cognitive competencies, capacities for mentalization and emotion regulation; (r) behavioral resources or skills which can be applied to problem-solving; (m) self-efficacy, positive expectations in one's development. Five coupled nonlinear equations, one for each variable, describe the behavior of the variables in relation to the selected parameters [61,62]. As can be seen from the brief description, this is the most sophisticated model in mathematical terms. Yet, there is no comparison with the complexity of clinical reality, which is greatly simplified through these equations. Five variables and four parameters certainly cannot represent the personality of a patient. But, precisely, the awareness of this simplification highlights the importance of the efforts of this research group. The simulations of the model give rise to temporal dynamics characterized by attractors, alternation between stable and unstable states, critical transitions, and order-to-order transitions, all of which are typical phenomena of the change model proposed by DSR. Therefore, if such a simplified model generates a typical evolution of a dynamic system, we must assume that DSR is the most appropriate perspective for the study of the psychotherapy process.

It would be interesting to use the models by Paz and colleagues and Schiepek and colleagues to study the evolution of the macro-parameters of therapy process. In this way, the temporal dynamics of stability and flexibility could be explored in relation to first- and second-order changes. The model proposed by Tschacher and Haken based on the Fokker–Planck equation is highly relevant because it generates stability and flexibility measures as output. However, its application is limited to high-resolution time series, pertaining to physiological variables only. It would be remarkable if a similar model could be developed for lower-resolution time series, such as those derived from daily questionnaires or from linguistic variables measured on consecutive text segments.

7. Conclusions and Future Directions

This work carries out a comprehensive review of DSR in psychotherapy, from the 1990s to the present day. In the first section, the results of research on oscillations of physiological and nonverbal synchronization between patient and therapist were presented. This area of research is relevant because it investigates the processes of preverbal affective coregulation. The patient–therapist relationship is not exclusively governed by shared cognitive objectives but is, above all, a relational experience between two bodily subjectivities. Often, in our patients, we observe a discrepancy between the bodily and cognitive processing of an experience, and we consider the realignment of these two aspects a necessary ingredient for the patient's health (e.g., Lingiardi and McWilliams, 2017; Cornell and Bucci, 2020) [17,57]. Therefore, investigating the processes of preverbal affective coregulation becomes clinically very relevant if placed in relation to the patient's first- and second-order changes. In the second section, the results of the research on S–F oscillations of process variables were presented. The study of the evolution of stability and flexibility within the psychotherapy process is clinically very significant. In moments of high flexibility, the patient comes into contact with new patterns of feeling, thinking, and behaving; in moments of high stability, these patterns are reintegrated in the patient. Hence, this area of research directly investigates change processes. In the third section, the results of mathematical modeling were presented. In this area, the most clinically meaningful aspect lies in the contrast between the clinical simplification presented by these models, and the complexity of the results obtained through simulations (see, for example, Schiepek et al., 2017) [61]. Given

that such clinical simplification shows a psychotherapy process characterized by all those elements typical of dynamic systems, it follows that DSR constitutes the most suitable research framework for its investigation.

According to such a perspective, psychotherapy is a relational field into which a new patient enters. The latter presents rigid and dysfunctional relational models. With the help of the therapist, the patient acquires stability and flexibility. Stability because he becomes aware of his own functioning. Flexibility, because he comes into contact with new relational models. The increase in stability and flexibility promotes the patient's first- and second-order change. At the end of a successful psychotherapy, the patient's functioning (i.e., his phase space) has a stable area, which represents his basic personality, and a flexible area, which represents his ability to live new experiences and exchange new information with the environment. We can imagine the good-outcome patient's network as made up of a group of central nodes with stable edges, and a group of peripheral nodes with flexible edges. The peripheral nodes allow the network to come into contact with new information generated by the patient–environment interaction. Some of these can modify the group of stable central nodes (basic personality); others dissipate at the periphery of the network. A good balance in these two areas of the patient's network constitutes his good dynamic stability. There is still certainly a lot of empirical evidence to be obtained to fully support this model of change promoted by the DSR. The intriguing aspect is that the network of the good-outcome patient hypothesized here resembles the structure of the complex macromolecules central to cellular function and central for life: proteins. In fact, together with a stable native structure, they exploit intrinsically disordered segments in order to exchange information and modify their functions (see Keul et al., 2018; Henzler-Wildman et al., 2007; Malaney et al., 2013) [42,63,64]. Therefore, it seems that, for adaptive purposes, nature selects the copresence of stability and flexibility within a given organism to promote its dynamic stability. Researchers dealing with DSR in psychotherapy will not remain unemployed in the coming decades: evaluating the model of change proposed here and its possible transdisciplinary connections will keep us at our desks for quite some time yet.

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Notes

[1] In this article, the author only uses the masculine pronoun to refer to the patient to make reading easier. It is intended that in each sentence the pronoun encompasses any gender.

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