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Organoids, Biocybersecurity, and Cyberbiosecurity—A Light Exploration

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Abstract: Organoids present immense promise for studying organ systems and their functionality. Recently, they have become the subject of exploration outside of purely biomedical uses in multiple directions. We will explore the rapidly evolving landscape of organoid research over the 21st century, discussing significant advancements in organoid research and highlighting breakthroughs, methodologies, and their transformative impact on our understanding of physiology and modeling. In addition, we will explore their potential use for biocomputing and harnessing organoid intelligence, investigate how these miniaturized organ-like structures promise to create novel computational models and processing platforms allowing for innovative approaches in drug discovery, personalized medicine, and disease prediction. Lastly, we will address the ethical dilemmas surrounding organoid research by dissecting the intricate ethical considerations related to the creation, use, and potential implications of these in vitro models. Through this work, the goal of this paper is to provide introductory perspectives and bridges that will connect organoids to cybersecurity applications and the imperative ethical discourse accompanying its advancements with commentary on future uses.

Keywords: organoids; cyberbiosecurity; biocybersecurity; computing; models; organoid intelligence; biocomputing; Red Team

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1. Introduction

The Fourth Industrial Revolution is at hand, and it is diverse as well as dynamic in terms of the domains, speed of iterations, scale of production, and degree of possible automation. This revolution is enabled by computational biology, Artificial Intelligence, and IoT devices. These advances were introduced in the mid to late 20th century and started to bear fruit at the beginning of the 21st century. This work discusses the potential intertwining of organoid technology advancements with artificial intelligence, computational biology, and security, with the goal of opening further discussion. This work is meant to serve as an introductory discussion with the expectation for further dialogue, and some repetition is employed for newer audiences. The following sub-sections will lead with brief discussions of the core concepts used.

1.1. Enter Organoids

Developing cell complexes is an important step toward the development of organ intermediates, followed by replacement organs and organ systems; one must understand how to control tissue growth and function after getting cells to grow before building more biological complex structures, and this has been a long-running endeavor [1–11]. Organoids are an intermediate step toward the promise of replacement tissues; they can be formed within three-dimensional cell cultures and can replicate organ structure and or function. The concept of organoids dates back to the early 20th century, and significant understandings

in cell biology and equipment to facilitate growth have led to sophisticated techniques to effectively grow stem cells and those from established cell lines in three-dimensional matrices [1–11]. The early development of organoid technology involved pioneering efforts that helped lay the foundation for future investigations and advancements in more complex cell biological study, particularly in translational science to advance personalized medicine, disease modeling, and drug testing through better means of incubating and monitoring the development of cells, uncovering and deploying extracellular matrix components, developing sophisticated nutrient delivery systems, deepening understanding of gene regulation, and differing modeling modalities (in vitro, in silico, and animal models) over time [1–11]. Ultimately, insights from organoids can lead to more effective treatments, replacement tissues, food development, and product testing resulting in fewer adverse reactions for consumers. However, much work remains ahead to accelerate and consolidate research gains, optimize outcomes, and perfect treatments. It is reasonable to expect that greater technological developments and interfacing will be needed.

1.2. On Biocomputing and Organoids

Biocomputing, such as bioinformatics or biological computing, gained immense value due to the need to manage and interpret the vast and varied data generated by biological research in projects such as the Human Genome Project. It has grown in scope as the complexity of bodily states processed from gene clusters and their relationships to macro-states, have expanded in importance to observe [12–15]. This interdisciplinary field involves using computational tools to analyze and model biological systems, transforming raw data into actionable insights [16]. In the approach of biological computing, cells' natural processes and components can be harnessed for computational tasks, leveraging their ability to respond to environmental stimuli as models of organs [17,18]. Engineers can program living cells and components to aid in computation wherein they use genetic networks as circuits for parallel processing. This technology could advance biosensing platforms that detect and process environmental changes [19,20]. In medical diagnostics, such systems could process physiological data for real-time monitoring [21–24]. Biocomputing has been utilized in various capacities for many years to better identify clues to disease states in the body and also supports synthetic biology, especially in designing and modeling new biological systems [16,25–29]. Its applications extend to drug discovery, aiding in simulating molecular interactions and personalizing the approach of biological computing, cells' natural processes, and components. Organoids can offer a complex system where researchers can potentially program cellular interactions for data processing, leading to the development of medicine by analyzing genetic information to tailor treatments [16,22–30]. With the advent of AI, the process of integrating organoids with AI and machine learning can be better accomplished through real-time data collection and continuous feedback loops, allowing for immediate adjustments and more precise control of biological processes. This is different from relying solely on post-experimental analysis, which limits the ability to make dynamic adjustments and may not capture transient biological responses. This synergy between AI and organoids, highlights a possible future of biocomputing, integrating advanced biological models with cutting-edge computational technologies. Biologically-based computation faces challenges in standardization, control, and interfacing with digital systems, yet it holds promise for areas where traditional computing falls short [17,18,26,31–34]. Despite its nascent stage, there exists much opportunity to explore this emerging domain.

1.3. On Cybersecurity Interfacing with Organoids

Cybersecurity may benefit from researchers examining how communication within organoids, between organoids, and in processing organoids potentially offers new data protection approaches. Particularly, the examination of unique biosignatures and communication means within-organoid systems may yield unique and meaningful patterns around which to develop security algorithms. Most immediately, benefits may be derived from

the discussion of the preparation of data systems to interact with the organoids. A reliable means of achieving the above is speculative but is still worth considering given the pace of biocomputing, the growth of the fourth industrial revolution or 4IR intersections, and how biosignatures from the organoids may deliver meaningful algorithms to pattern security. It is also worth considering how biocomputing complexes that include organoids might deliver superior encryption and efficient data storage solutions. The role of organoids in biocomputing continues to expand. In the future, integrating organoid intelligence in biocomputing might lead to personalized healthcare security options, depending on patient consent and pairing. This is in part due to the customizability and personalization of organoids to patients and the fact that the researchers can tease meaningful data from the performance of organoids that are exposed to a bevy of tests and or otherwise interrogated by equipment with bio-interfaces [35–43]. Same-platform computations (in the biological domain) should theoretically support information transfers with minimized entropic loss. Further, DNA signatures give hope for product tracking processes being created, which would ensure that each organoid is used correctly and traced effectively, enhancing safety and personalization in treatments [44]. This signals the potential to efficiently interface organoids with cybersecurity architectures.

1.4. Into Biocybersecurity and Cyberbiosecurity

Key terms that have emerged in the course of this work include "organoids", "biocomputing", and "cyberbiosecurity" (CBS)/"biocybersecurity" (BCS). BCS and CBS refer to different mission orientations and attack origins [45,46]. BCS focuses on attacks originating from biological systems or using them as an interlock. CBS refers to attacks originating in hardware and computer systems with a focus on biological or biology-centric systems, though a useful primer is presented in past literature [45,46]. BCS is an emerging interdisciplinary field combining cybersecurity, bioinformatics, and biological research elements. The term reflects the growing need to secure biological data and systems because, most importantly, biological matter and signatures can be used as an interlock in an increasingly digital world [47]. The digitization of biological data requires a nuanced understanding of biological systems and digital security, creating a unique interdisciplinary field. The primary focus is safeguarding sensitive biological data, which has become increasingly vulnerable in the digital age [45–48]. This vulnerability is not just limited to hacking and unauthorized access but also affects data manipulation, poisoning, integrity, and more. As biological research continues to become more data-intensive, the importance of CBS becomes ever more critical [49,50]. Overall, the field aims to establish protective protocols by drawing attention to issues such as data breaches in biomedicine, the misuse of biological data, and the vulnerabilities of biotechnological devices to hacking, where biology is a core interlock as opposed to just any matter where cybersecurity and biosecurity converge [46,47]. For the purpose of this article, the relevance of CBS and BCS exists due to their ability to be used as an interlock in future computing systems and for the awareness for programs to be in place to protect these biological systems, data, and technologies.

1.5. On Integration of These Areas

Discussions about security, particularly in biocomputing and BCS, benefit from integrating organoids into the discussion due to their potential to mirror aspects of physiology and deliver intelligible outputs. This promotes the possibility of using neural organoids to serve as computing platforms with the potential to tackle problems in artificial intelligence and beyond [18]. Several security-facing possibilities may exist, although in speculation. We may see organoids providing a closer environment for testing biocybersecurity protocols via biocomputing applications compared to in silico models, for applications such as developing biological sensors or detectors based on an organ-like context [1,17,26,45–56]. STEM may eventually see organoids offer a more nuanced platform for studying how biological systems interact with cyber systems, enhancing our understanding of potential vulnerabilities and solutions in biosecurity. However, these are the domain of future pa-

pers that others may write. In general, incorporating organoids into security discussions can be achieved through interdisciplinary collaboration, where experts in cybersecurity, biotechnology, and organoid research work together to explore and address the unique challenges at this intersection.

This rapid evolution brings ethical and regulatory challenges to the forefront. Issues surrounding the use of human-derived materials, patient consent, and the potential for organoid consciousness raise profound ethical questions. The field must navigate these challenges while ensuring responsible research practices. The immediate aims of the regulatory and policy landscape can help us tackle task complexity, neural systems, hormone systems, or otherwise, in organ replacement, pharmaceutical manufacturing, and improved security. The potential for organoids to significantly contribute to AI, particularly in processing and learning capabilities, is an exciting prospect but will be beyond the scope of this discussion; Bai et al. (2024) delivers a thorough exploration of AI and organoid interfacing [51]. In a different section of this work, we will discuss significant advancements and ethical concerns before providing concluding remarks on the state of the intersection. This work aims to open discussion rather than provide a full review. The authors believe this area is too new and undeveloped for a full review. This paper should be a starting point for conversations to delve into the complexity of organoid research and its implications while simultaneously encouraging policymakers and other stakeholders to develop policies that ensure an ethical and just future.

2. Methods

This paper was aided using Google Scholar to identify papers at the intersections of the terms “Cyberbiosecurity”, “Biocybersecurity”, “Organoids”, “Organoid Intelligence”, “Biocomputing”, and “Security”. We conducted brief searches to gauge the current number of searchable papers. These searches create a snapshot of the research into these domains that took place before the expected mass article generation that will be made available via Large Learning Models and will allow for the proliferation of mostly AI-generated articles [46]. The authors expect that this search is essential given that the automation of literature generation and associated work may significantly warp value, perhaps less than two years after the publication of this article. The core assumptions are that human-compiled and handled literature is temporarily superior, that automated compilation and handling of literature is the longer-term future of publication, and that the quality of compiled human vs. AI-compiled literature may soon be incomparable. Thus, a snapshot here is for a future data point of unknown potential use or, at the very least, a partial calibration of mostly human-managed thought at the precipice of mass LLM processing of biotech information, specifically organoid information. As of 24 November 2023, Google Scholar’s search function lists article counts when entering various quote terms. The starting year range was 2018, allowing for a five-year window between 2018 and 2023. Article counts are listed in Table 1 but are only exhaustive for some combinations. The authors have deemed the combinations of search terms to be sufficient. We await articles that provide an in-depth review of the relationships between organoids and cybersecurity, and such articles are welcome.

To further analyze the trends in research, the authors selected the five group terms from Table 1 to create Figure 1. These terms were chosen because they consistently yielded non-zero results from 2017 to 2023. The graph in Figure 1 illustrates the evolving trends of research activity surrounding these five group terms throughout the specified timeframe. In addition, it provides valuable insights into the trajectory of inquiry and sheds light on the dynamics influencing interdisciplinary exploration.

Extrapolation from the results yields a perspective of limited understanding. At the very least, academic discussion of the integration of organoids and cybersecurity implications is relatively low. An understanding of organoid roles in biocomputing exists, but the operational extension in security discussion does not appear optimal at the time of this writing. We expect this state of affairs because biological-to-digital conversions

outside of a medical or agricultural basis are still relatively new. Technologies that enable bio-digital storage and bio-digital hacking are relatively new (in the last 20 years) [52,53]. Active and cheaply accessible means of using biological means to execute attacks, the type of activity to help kick off and accelerate the field of CBS, is six years old. Academia is remarkably slow in keeping pace with cybersecurity's in-field advances [54]. CBS is the preferred accepted term for the intersection of cybersecurity, biosecurity, and cyber-physical security. The discussion of a split using the alternative term "BCS" is relatively recent, so the slight split in mention between search pairings between the two terms and "organoid" is expected—the further expectation is that the number of mentions of "cyberbiosafety" is expected to be minimal [46,55,56]. This circumstance leaves the authors open to discussing an exploration of the fields of BCS/CBS with organoids early in the intersecting field's development. Note that some articles after November 2023 were included to supplement this work prior to and after the review.

Table 1. Article count search results in Google Scholar.

Terms Entered	Filter	Article Count
"Organoid" "cyberbiosecurity"	2018–2023	2
"Organoid" "biocybersecurity"	2018–2023	0
"Organoid" "biocomputing"	2018–2023	136
"Organoid" "cybersecurity"	2018–2023	40
"Organoid" "biocomputing" "cybersecurity"	2018–2023	4
"Organoid" "biocomputing" "cyberbiosecurity"	2018–2023	1
"Organoid" "biocomputing" "biocybersecurity"	2018–2023	0
"Organoid" "biocomputing" "cyberbiosafety"	2018–2023	0

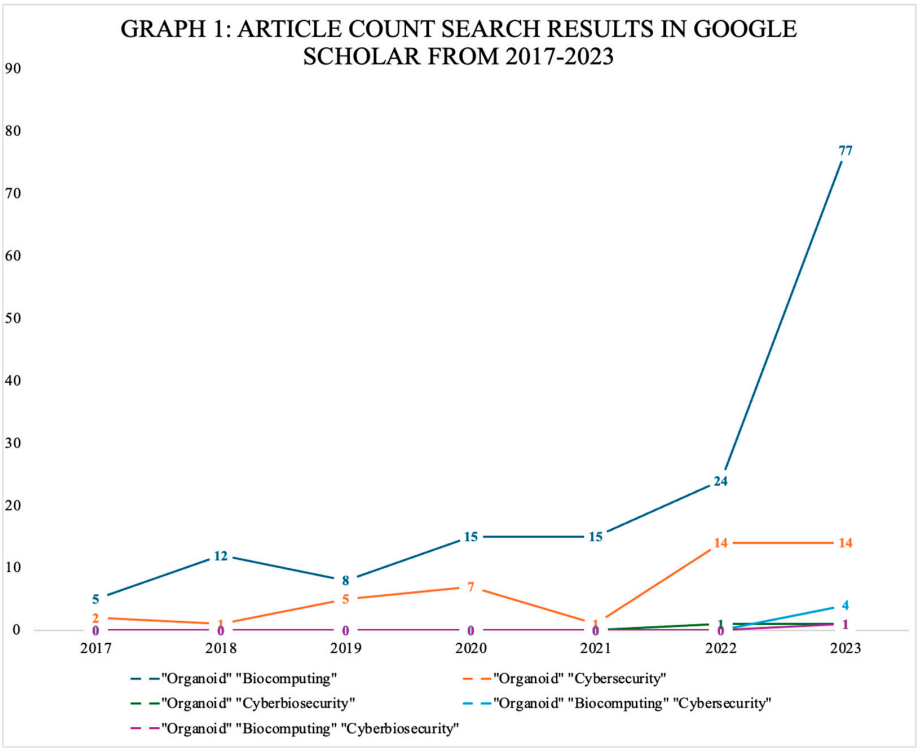

Figure 1. From 2017 to 2023, this graph illustrates the trends in interdisciplinary research, examining Google Scholar's article count results for papers intersecting terms that include "Organoid", "Biocomputing", "Cyberbiosecurity", and "Cybersecurity".

3. Some Organoid Advances

3.1. Diversification of Organoid Types

An important aspect of organoid research is the diversification of research and development into various organoid types and examining different organs and tissue aspects. Organoids offer a powerful platform for engineering and testing artificial biological systems, allowing researchers to mimic and manipulate organ-specific cellular environments [57,58]. Scientists have successfully developed brain, intestinal, liver, and other organ-specific organoids, including those with cells from various cell lines [59–61]. These complex organoids offered new models to study organ development, function, and disease pathologies in a controlled environment. Integrating organoids in synthetic biology opens possibilities for creating more complex, organ-like structures with specific and novel biological functions, paving the way for innovative medical treatments and a deeper understanding of human biology [62]. Sophisticated bioprinting has allowed for a shift from simple tissue cultures to sophisticated structures capable of replicating some organ functions and interactions [3–5,40,51].

3.2. More Applications in Research and Medicine

Organoids have significantly impacted research and medicine, particularly in disease modeling and drug discovery. Researchers began exploring organoids' potential in personalized medicine, disease modeling, and regenerative therapies, harnessing their ability to reflect patient-specific pathologies and responses. For example, liver organoids have been crucial in studying drug metabolism and liver diseases, providing valuable data for biocomputing models [2,63,64]. Intestinal organoids have offered insights into gut health and the microbiome, impacting research in gastrointestinal disorders [65–68]. Heart organoids have been instrumental in cardiac research, particularly in understanding heart diseases and testing cardiotoxicity in drugs [69–72]. Kidney organoids have emerged as valuable tools in nephrology, aiding in studying renal diseases and drug-induced nephrotoxicity [73–78]. Lung organoids were especially relevant during the COVID-19 pandemic and have been used to model respiratory diseases and study virus-host interactions, as well as regeneration [6,79–84]. The development of skin organoids has opened new avenues in dermatology, offering models for skin disorders and wound healing [85–88]. Brain organoids have applications applied in studying neurodevelopmental disorders, neurodegenerative disorders, infectious diseases of the central nervous system, and mental illness, as shown in Figure 2 [89].

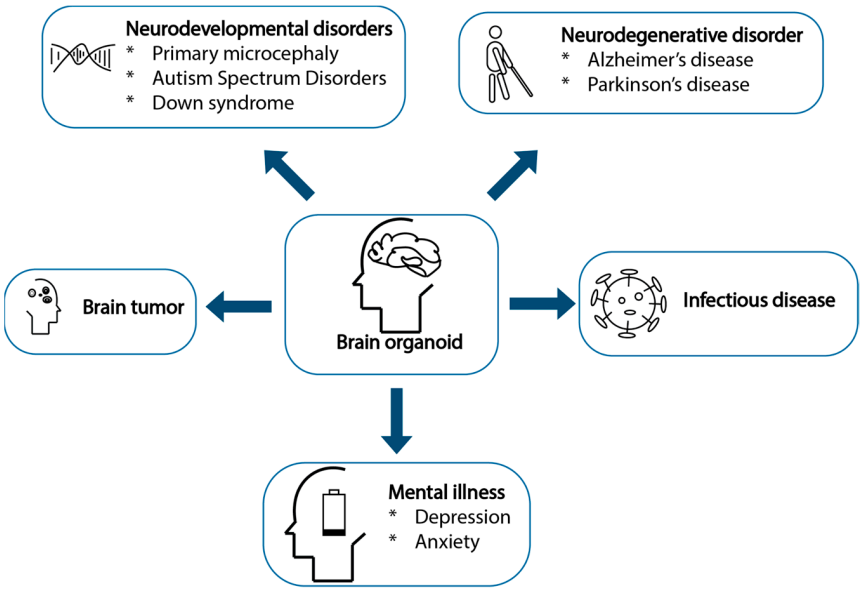

Figure 2. Applications of brain organoids as models for investigating neurological diseases.

In neurodevelopmental disorders, brain organoids have been used to simulate the brain development process during in vitro learning, and they have been applied as models to study the progression of disorders such as primary microcephaly [89]. In neurodegenerative disorders, 3D cell culture systems and neural organoids have been used to investigate important components of the disease, namely, amyloid beta and the pathology of tau [89]. Furthermore, cerebral organoids have successfully been used to model primary human glioblastoma (GBM), the most malignant form of brain tumors, in vitro [89,90]. The cultured organoids were able to form tumors closely related to those of patients, showing that the model sufficiently reflects the malignant properties of GBM [89,90]. This type of brain organoid can be used in screening antitumor drugs [91]. Each of the above examples is by no means exhaustive; in general, each organoid type and sub-type has broadened the scope and depth of research in their respective organ study sub-fields, contributing significantly to our understanding of complex organ systems and diseases, especially when researchers integrate organoid outputs with biocomputing.

The important ability of organoids to closely mimic human organ physiology has led to more accurate and ethical alternatives to animal testing in drug development. For example, organoids are effective platforms for high-throughput drug screening, allowing for rapid drug efficacy and toxicity assessment. Organoids also facilitate the study of rare diseases, offering insights into pathogenesis and treatment options that cannot be examined traditionally due to small sample sizes. Furthermore, they provide valuable models for studying infectious diseases, especially in understanding host-pathogen interactions [83]. In personalized medicine, researchers use patient-derived organoids to model individual responses to treatments, aiding in developing tailored therapeutic strategies and more precise modeling of individual disease processes and treatment responses [92,93]. The widespread adoption of organoids in biomedical research underscores their versatility and utility in advancing our understanding of human health and disease. By the early 2020s, organoid intelligence had become a key player in personalized medicine [18]. It marks a significant step toward functional and implantable organ-like forms, wherein treatments can be specifically designed and tested to suit an individual's unique genetic makeup [5–10,13–23,35,62,94–98].

3.3. Breakthroughs, Important Methods Integrated, and Design

Numerous breakthroughs were necessary to make much of organoid development and the possibility of integrating them into hybrid systems possible. The core of this can be broken down into sourcing the cells that make up the organoid, sourcing components for and building the material of the matrix in which these organoids develop, and the equipment that allows for their maintenance, observation, and efficient data extraction [1–11,15–30,36–43,57–100]. Examples include advances in 3D culture techniques, directing of stem cell differentiation, development of bioengineering tools and assays, bioprinting, deployment of microfluidic devices, and artificial matrices to emulate tumor environments effectively in the development of tumoroids [1–11,15–30,36–43,57–100]. Gene editing techniques, especially modern ones using tools such as CRISPR/Cas9, have been integrated into organoid research, enabling precise manipulation of genetic material and expansion of potential situations to assay in some projects [101]. These methodologies and the above have facilitated the creation of organoids that more closely resemble aspects of human organs in both structure and function. Another breakthrough that could be compounded with all the organoid advances is the creation of artificial cells wherein they are capable of producing proteins and simulating biological processes [102]. Looking ahead, combining this innovation with the principles of the minimal cell could lead to the development of optimized organoids built from the ground up [103]. These organoids would be constructed from the foundation, featuring precisely tuned functionalities for enhanced performance in medical and research applications, embodying a fusion of synthetic materials and biological processes to address complex challenges in healthcare and biotechnology. Combining all these breakthroughs with automated and autonomous workflows promises

to impact the efficiency and scalability of developing precision treatments, potentially lowering costs and accelerating access. It is important to note that, while automation could streamline research and foster innovation, it must be deployed with the goal of ensuring equitable distribution of healthcare advances for all groups of people.

4. Organoids and Biocomputing

4.1. Brain Organoids: Uses from Now and Potentially into the Future

Brain organoids can enable the exploration of brain-computer interfaces and similar devices, enhancing our understanding of neural signal processing. The advancements in organoid technology also have use in facilitating testing and developing neural network models. As mentioned previously, the development of cerebral organoids alone marked a significant breakthrough, providing models to study human brain development and diseases; however, with expanded models that looked at relationships with other tissues, researchers could seek to model more complex system interactions [90,101,104]. For example, researchers have modeled intestinal organoids with neural organoids to study gut–neuro interactions [105]. So far, this is rather par for the course for biomedical research, and some researchers have reflected and built on other uses, particularly that of computing. In the world of biocomputing, there is already a rich, albeit new, tradition of using simple reactions from biochemical cascades to logic circuits with cells for simple and intermediate computations [26]. The idea that this can extend to cell complexes in the form of organoids is not science fiction; however, work remains on how the computation can be done efficiently and in a worthwhile manner. The hope of the integration of organoids in biocomputing exists, especially in the discussion of developing brain organoids, in addition to a reasonably concentrated and focused community forming around them [2,104,106,107]. Towards the year 2030 and the years following, the world may see applications of neural computing that are more than a demonstration.,. As the products result in something useful at the institutional and consumer level, society can possibly expect to use novel interfaces to assess the information and products created from them. In the meantime, we can reasonably expect more intimate medical usage. In reflection, the 2010s and 2020s saw intestinal, liver, and neural organoids used for insights into the systems that they normally comprise, later built on by studies looking at metabolism extrapolations and applications of genetic engineering via CRISPR/Cas9 [108–115]. These are useful to mention for their analogy of abstract systems of relations and rewiring in computer systems. When reflecting on where society might find applications of biocomputing, one could look at potential applications of diagnostics in diets or closer investigations into senses of intuition that we have called “the gut feeling”. Personalizing medicines and simulations of appetite are close steps, but using them as a separate platform for computations in ways that institutions and consumers require calls for greater and more diverse work.

4.2. On Some Approaches Integrating Organoids in Biocomputing

The methodologies developed for integrating organoids with biocomputing have been a blend of biological science, computational modeling, and engineering. Advanced culturing techniques have been instrumental in growing organoids that can interface effectively with computing systems. Researchers have focused on creating microenvironments that accurately replicate the conditions of human organs or patient pathologies [36,116–119]. Some have used microfluidic devices to construct complex organ structures or network processes [37,105,120]. Computational models have been vital in predicting how organoids grow and react to stimuli. These models help in understanding the intricate cellular mechanisms at play within organoids. Researchers have refined techniques for monitoring and measuring the responses of organoids to various inputs. Researchers have endeavored to scale up these methodologies to enhance the accessibility and practicality of organoid-based biocomputing for broader applications. Improvements in iPSCs technology greatly enabled foundations for the generation of patient-specific organoids, which can influence and enhance the creation of personalized biocomputing models [121,122]. Numerous improve-

ments in imaging techniques have also accompanied computing developments allowing for ex vivo and real-time 3D imaging of organoids, aiding the ability for enhanced visual and computational analysis [123–127]. Researchers in and around 2020 developed numerous microfluidic platforms and guides for brain organoid development and maintenance, enabling more accessible paths to the precise delivery of nutrients and pharmaceuticals to organoid complexes—a boon for future biocomputing studies [128–131]. Further, this time also saw researchers investigate alternative means of information storage and novel material development capable of supporting neural computing platforms using traditional methods as well as DNA programming [132–134].

Machine learning algorithms for data analysis from organoid studies may soon become prominent, offering sophisticated tools to interpret complex biological data. A question worth asking is the distance from now to when synthetic multi-level regular circuits may help drive multi-organoid signal processing for advanced computation [135]. We might one day see an application of organoids stacked like shields applied to an Arduino or Raspberry Pi in some way. The sci-fi world of Warhammer 40K might find itself an inspiration, borrowing the idea of customized, upgraded, but ultimately implantable and transferrable organs from the "Gene Seed" concept wherein super soldiers could obtain enhanced abilities [135].

4.3. Transformative Impacts of Organoids in Biocomputing

Biocomputing, in practical terms, has largely been useful for aiding computational models through feedback, and that is still quite helpful across many biomedical subfields. These models have provided new platforms for testing the efficacy and safety of drugs, revolutionizing the pharmaceutical industry. The application of organoids in pre-personalized medicine is potentially impactful, allowing for the development of potential treatments tailored to individual patients. In bioengineering, the availability of data on organoid behavior has allowed for foundational material for the creation of more accurate and sophisticated biological models for computational analysis and has led to advancements in machine learning algorithms that can more accurately predict physical responses, while AI is also helping to develop better organoids [51,119,136–138]. Organoids have also been crucial in developing bioinformatics, which help to manage and analyze complex biological data. The convergence of organoid technology with computing has spurred research in the development of hybrid systems, assays, and processes that combine biological and digital elements; these advancements, if fulfilled, have significance for future research and have potential applications in clinical settings, offering new avenues for diagnostics and therapy [139–150]. This is not without considerable ethical and regulatory implications, highlighting the need for guidelines in this rapidly evolving field.

Researchers used brain organoids to model Zika virus infection, demonstrating organoids' potential to understand pathogen interactions [144–147]. The role of organoids in cancer research, particularly in modeling tumor environments, has been popular and seen as a means to address complexities previously unknown or otherwise hard to test against [148–151]. A 2019 study utilized organoids to mimic Parkinson's disease, opening new avenues in neurodegenerative disease research using biocomputing [152]. The COVID-19 pandemic in 2020 saw the use of lung organoids to study SARS-CoV-2 interactions, showcasing organoids' role in infectious disease modeling [144,145,153–156]. On a much more rudimentary level, just within 2023, there were reports of a researcher enabling the PC Game "Doom" to display by activating fluorescent proteins in E. Coli [151]. This finding is very early, and results are pending review, but it is a clue of where we may find new interfaces of biology and computation in the next 20 years. This work follows earlier work by a team of researchers who discovered how to play pong with neurons, which is less graphically intensive. Advancements in integrating organoids with biosensors around 2021 enhanced real-time monitoring of biological responses, an essential step in biocomputing for diagnostic applications [21,22].

4.4. Biocomputing and Organoid Intelligence

4.4.1. Towards Developments in Biocomputing and Organoid Intelligence

Researchers focused on understanding how organoids could perform computational tasks via experiments to determine how they could be used for data storage and processing, leveraging their inherent biological processes [18,91,105–107,122,157]. During this phase, researchers examined the electrical activity of organoids to decode patterns that translated into computational data. Scientists explored ways to stimulate organoids and extract feedback from them and observed changes in activity for potential use in data processing. These developments set the stage for complex integrations of organoids in biocomputing, promising innovative solutions for various technological and medical applications.

4.4.2. Case Studies on Biocomputing and Organoid Intelligence Applications

As highlighted in the preceding sections, organoid intelligence is a relatively new sub-field that has roots in the broader field of tissue engineering, organoids, AI, and computational biology. Cai et al. describe the development of living AI hardware called Brainoware [157]. This was built by mounting a functional brain organoid onto a multi-electrode array (MEA). This setup allows the brain organoid to receive inputs and send outputs, forming a basis for AI computing. The architecture seeks to answer the questions of how we can develop AI hardware that fully mimics brain function and processes and learns from spatiotemporal information, as well as solves non-linear dynamic systems with chaotic behavior. The organoid can harness the computational power of 3D biological neural networks in an attempt to fully mimic the brain's function and processes to provide new insights into organoid intelligence with low energy consumption and fast learning capabilities [157].

Additional significant advances in this field include the integration of nanotechnology for more precise control and interaction with organoids. Nanomaterials can be used to enhance the structural integrity and stability of organoids, allowing for long-term culture and maintenance of their 3D architecture [158]. Le Floch et al. (2022) developed a tissue-like stretchable mesh nanoelectronics system that is integrated with brain organoids. This nanoelectronic system matches the mechanical properties of the brain organoids, allowing them to fold with the organoids as they develop without impeding their growth or altering their morphology. The electrode arrays embedded in the organoids provide stable, non-invasive, and continuous electrical interfacing with neurons, facilitating long-term recordings of neural activity within the brain organoids [158,159]. Furthermore, Park et al. (2020) performed research focused on using human colon organoids to evaluate the toxicity induced by SiO_2 and TiO_2 nanoparticles and to monitor changes in the expression of the apoptosis marker Bax/Bcl-2. This study highlighted the distinct responses between traditional 2D models and 3D organoid cultures, emphasizing the relevance and enhanced sensitivity of organoids for drug toxicity studies [160]. The scope of organoid intelligence extends to studying human development, disease mechanisms, and personalized medicine. It also allows for the faithful mimicry of the complexity and organization of human tissues or organs, making organoids invaluable tools in biomedical research [104]. The ongoing advancements in this field represent a promising frontier in the convergence of biology and technology, offering new solutions to some of the most challenging questions in science and medicine.

4.4.3. A Hypothetical Case: Organoids through the Lens of Both Biocybersecurity and Cyberbiosecurity

Reflecting on earlier sections of this work, we are reminded that biocybersecurity and cyberbiosecurity together entail thwarting threats to biological systems made accessible by computing resources and weakened security. We may one day see unique attacks that ultimately use both perspectives. With reflection on the security of hardware used to create organoids, largely 3D bioprinters, hardware security is starting to be taken more seriously, as can be seen by initial work by Isichei et al. (2023), which draws attention to

the security needed in these systems [161]. Parupelli and Desai (2023) note the potential for 3D-printed wearables and biosensors to affect healthcare and industries, which can benefit from complex wearables [162]. A combined cyberbiosecurity/biocybersecurity threat may first be seen within an industrial context. It is not far-fetched to anticipate an advanced persistent threat (APT) targeting a biotech or bioengineering company that is engaged in 3D bioprinting, aiming at the hardware used to produce bioprinted organoid sensors. Initially, this could be a complex operation requiring staff to be engaged in and collaborating on using techniques and perspectives found in and between bioengineering, cybersecurity, and artificial intelligence. The latter, artificial intelligence, would be most helpful in wading through immense amounts of biological data, such as the genome and proteome, in which computing threats may become embedded. This is all speculative, but it is prudent for researchers and security professionals to remain imaginative, creative, collaborative, and vigilant, for if such a day and machinations of similar threats emerge.

4.4.4. Organoid Intelligence and Machine Learning Applications

Organoid intelligence combined with machine learning can provide novel and diverse applications. Figure 3 describes how machine learning can be used to analyze complex data extracted by organoid intelligence systems and enable researchers to find hidden insights and patterns, leading to a deeper understanding of organoid function as well as neurotoxicity prediction [18,19]. Machine learning can also lead to the development of optimized algorithms for interactions between organoids and computational models provided that meaningful patterns from each system can be applied back and forth. This will contribute to the development of more sophisticated biocomputing systems [19]. Furthermore, organoid response to different stimuli can be predicted from historical data through machine learning. This predictive modeling can allow researchers to optimize the outcomes of experimental designs [19]. By integrating machine learning with organoid intelligence, researchers can significantly accelerate the identification of potential therapeutic targets for neurological disorders and other diseases [19,163]. Lastly, brain organoids interfaced with functional neural probes in brain-computer interfaces can enable real-time recording, feature extraction, and decision-making processes. This setup has the potential to advance deep brain stimulation techniques and facilitate pilot clinical trials for neurological disorders [163].

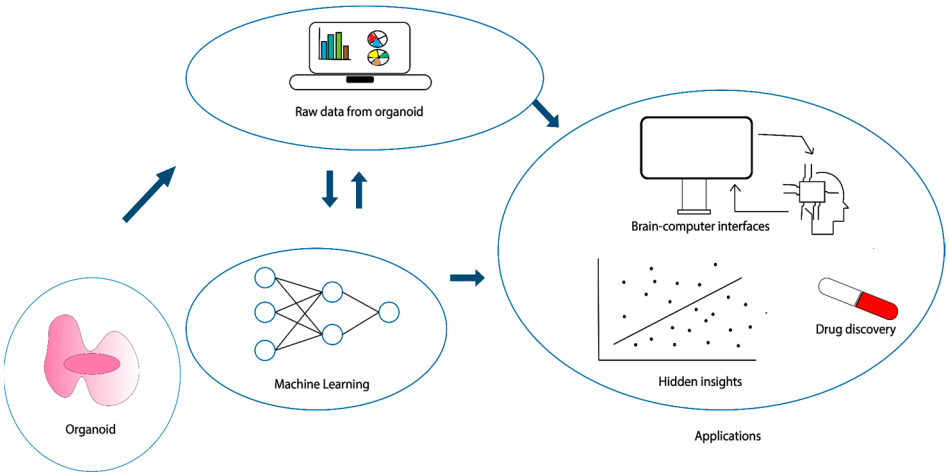

Figure 3. Applications of the interfacing of machine learning and brain organoids.

5. Ethical Considerations and Future Prospects

Moving toward 2024 and the future, biocomputing and organoid intelligence prospects continue to expand. The potential for organoids to revolutionize healthcare, particularly in diagnostics and treatment strategies, has become a focal point of research. Ethical considerations, especially regarding the use and treatment of organoids, have gained prominence in recent science and policy discourse. The possibility of organoids possessing

neural activities akin to consciousness raises profound ethical and philosophical questions [51,104,143–165]. Researchers have begun to explore regulations and guidelines to govern the use of organoids in biocomputing. The potential for organoids to contribute to artificial intelligence, particularly in learning and processing capabilities, is an active research area. The use of organoids in artificial intelligence should become a topic of discussion for stakeholders in the defense and national security sectors. The field looks toward developing sustainable and ethical practices for using organoids in computational models. Discussions around patient consent and using human-derived cells in organoid research become increasingly important. The intersection of biocomputing and organoid intelligence opens new avenues for innovation in biology and technology, promising transformative changes in various fields. The ongoing advancements in this area challenge our understanding of the boundaries between biological and computational systems, paving the way for future discoveries and applications. Considering possible futures that corporate technology behemoths will influence through IoT and synthetic biotechnology stacks, much work is required on the policy side to ensure the adequate protection of users [166,167].

5.1. On Ethical Concerns

It has been stated previously in this paper that there is limitless potential in applying organoid research. Organoid research is at the cutting edge and is progressing faster than many academic ethicists could potentially pace. There is a case for valuing the ethical side of research, There is a delicate balance between innovation and ethics that requires scientists to strive for scientific knowledge while maintaining ethical principles. Organoids, such as brain organoids, have played very important roles in new medical research as well as the clinical environment. However, these improvements come with moral and ethical challenges [91]. Although brain organoids are currently not fully developed and resemble the embryonic brain, with the development of sophisticated organoid technology, brain organoids may become conscious and will be able to evoke emotion or develop memories [91]. Another noteworthy concern is the possibility that brain organoids could experience pain and suffering. This introduces a conversation on the moral status of the organoid [168] and subsequently leads to the argument that some of the applications of brain organoids discussed in the previous section may no longer be moral or ethical to perform, such as causing the growth of malignant tumors. It is imaginable that more dilemmas will emerge on the bio-informational front as scientists and those adjacent have to consider negotiations of the technology and interface with complications across international legal lines, which will be especially compounded by threats by adversarial AI [50,169]. Policymakers and legal minds are pioneers in the development of new policies and regulations around CBS but are expected to lag, reflecting the backlog of cybersecurity legal developments [50,170–174]. COVID-19 taught the world that applying biosecurity management and ethics on an international scale with pandemics is not so simple—why should we expect it with the management of increasingly complex organoids, especially as they are used to interface with computing apparatuses for a variety of applications [50,175–178]? These lessons taught by the pandemic should and need to be applied when creating and discussing policy surrounding organoid research. Due to the growing implications of this budding field, it must be at the forefront of policymakers and other stakeholders including, the companies leading the research, minds, to prioritize the creation of much-needed guidelines and policy. Creation of these policies requires a multi-prong approach ensuring that all relevant stakeholders are a part of these important conversations.

5.2. Consent Models for Organoid Research

Let us begin our discussion of consent with a famous story of a young African American woman who sought care at Johns Hopkins Hospital in the 20th century [172,174]. Dr. Howard Jones, a distinguished gynecologist, identified a cervical tumor [172]. Mrs. Lacks, as per her medical records, initiated cancer treatments after

the discovery [172]. A biopsy sample of her cervical cancer cells, sent to Dr. George Gey's nearby tissue lab, proved unique as they were the sole cells in his collection that did not perish, leading to widespread experimentation in various health areas [172].

In the realm of biomedical research, the narrative surrounding Henrietta Lacks underscores the foundational importance of informed consent, particularly in the context of utilizing patient-derived samples. Informed consent serves as a cornerstone for ethical scientific research, emphasizing the necessity for individuals to be fully and holistically informed about their participation in research and to consent to the use of their biological materials [179]. Just as informed consent plays a crucial role in research ethics, it also holds relevance in the domain of biocybersecurity, which aims to safeguard individuals' biological data from unauthorized access, manipulation, or exploitation. The connection between informed consent and biocybersecurity is clear when acknowledging individuals' fundamental rights to control their biological data and to be aware of how it is used.

When conducting organoid research involving human donors, researchers can seek a spectrum of consent types to ensure the upholding of ethical standards. The issue of using organoids, especially those of brain organoids, poses numerous problems for those in ethics, and the importance of consent deepens [164,180]. de Jongh (2022) lists multiple types of consent. Specific consent requires specificity for each use of a patient's tissues and follow-up uses [176]. Tiered consent offers specificity in project lists where patient tissues can be applied [176]. In biocybersecurity, tiered consent can be established to categorize different levels of data access or usage permissions based on the sensitivity of the information involved. This model allows individuals to provide varying levels of consent for different research projects or data sharing, which enhances data protection and privacy. Broad consent involves patient consent in the presence of a relatively high number of unknowns and considerable patient trust [176]. While broad consent may seem less limiting, it still serves an important role in biocybersecurity by allowing individuals to provide consent for a range of potential future research uses of their data. However, it needs strong security measures and transparency to make sure that individuals remain informed and trust how their data is being handled. Blanket consent removes restrictions, and ethics are taken care of, of course, but without consideration of the project to which patient tissues are applied [176]. While this model may simplify the consent process, it also raises concerns in biocybersecurity regarding transparency and responsibility. Without clear limitations on data usage, there is a risk of data misuse or unauthorized access, emphasizing the necessity for strong cybersecurity measures to protect against potential threats. Opt-in consent requires explicit donor consent for entry, while opt-out consent requires explicit donor refusal [176]. Both opt-in and opt-out consent give individuals the power to control their data by actively choosing whether to participate in research or data-sharing activities. In biocybersecurity, these models promote transparency and respect for individuals' autonomy by providing clear methods for individuals to express their preferences regarding the use of their biological data. Governance consent grants donors access to privacy and welfare considerations based on governance obligations, but donors will not be explicitly informed about the work involving their tissue [176]. Both donors and researchers actively and digitally facilitate dynamic consent [176]. Each type of consent promises to ensure that researchers act ethically. However, obtaining consent from human donors differs starkly. Governance consent and dynamic consent view obtaining consent from individuals as an ongoing process rather than a one-time check with the donor.

The various types of consent models discussed, such as specific consent, tiered consent, and dynamic consent, reflect the changing landscapes of ethical considerations in biomedical research. Similarly, within biocybersecurity, ongoing communication and transparency between researchers and individuals are essential for ensuring the responsible and secure handling of biological data. In addition, the evolving nature of consent models reflects the adaptive strategies necessary in biocybersecurity to address emerging threats and technological advancements. Just as consent mechanisms must evolve to accommodate

changing research practices, cybersecurity protocols must continuously adapt to protect against evolving risks in the digital realm.

5.3. Monetization of Organoid Research

The second topic to consider is the monetization of organoid research applications. With organoid platforms being considered the premier frontier in the development of precision treatments, commercial interests are increasing in variety, viability, and a number of possible applications [178]. This technology derived from the research can become patentable, which gives way to commercialization. The commercialization of the technology gives way to a set of ethical questions how the benefits of the research are distributed what are the ways in which researchers protect the donor's right to privacy. The story of Henrietta Lacks and her immortalized cell lines is pertinent because it demonstrates the lack of protection for her rights and the lack of compensation until recent times, despite the value that her cell lines yielded for society [172,174]. Her cell lines were part of research that brought us many biomedical advances, including but not fully exhaustive: the first modern vaccines, valuable insights on pathologies, and human cell behaviors in both standard and microgravity [181,182]. This story is an essential example of the big question of who reaps research benefits, and implications are many when reflecting on whose cell lines comprise various organoids that are mass-produced and used for processing operations, biologically or as part of an interlock in digital operations. The digital aspect is fundamental in reflections on BCS [48,183]. Researchers asked patients about their compensation viewpoints in 2018 [181]. Researchers surveyed 126 patients undergoing surgical tissue removal to gather their perspectives [181]. Ninety-five participants responded "no" to being paid for their donation [181]. Out of the 95 participants, 55 attributed their "no" to a belief that donating biological materials should be driven by altruism rather than monetary gain [181]. A total of 11 participants expressed interest in receiving compensation, while 14 participants felt they deserved compensation based on specific circumstances [181]. This study reveals varying opinions on whether patients should receive compensation for donations. However, amidst the prospect of commercialization, we cannot overlook an imperative aspect—the potential impact on the cost of treatment and its accessibility to diverse socioeconomic groups [176]. Advanced therapies are expensive [176]. The significant expense of treatment indicates that not all patients in need will be able to afford costly personalized care [176]. Promoting equity in life-saving medicine ensures that treatment does not rely on exploiting any particular socioeconomic group [176]. An individual's ability to receive life-saving treatment should not be dependent on one's socioeconomic status.

In addition to acknowledging the stark differences in responses about the compensation of participants in scientific research, we must consider the underlying conflicts that exist when monetization of organoid research is considered. An insightful concept to illustrate the cost and benefit analysis of these conflicts is the prisoner's dilemma. This famous concept has been applied to multiple academic areas, such as economics and political science. To begin our discussion, let us start with this word prompt. Two individuals have been arrested without sufficient evidence to support a conviction of a crime [184]. The suspects are unable to communicate with each other [184]. To obtain a conviction, the police present a deal to each individual: the suspect could betray his partner or keep silent [185]. If the suspect chooses to betray his partner by saying his partner committed the crime, then he will be set free, and the partner will receive the maximum punishment [184]. If both suspects choose to stay silent, then they will serve the minimum sentence [184]. These two options illustrate of multidisciplinary concept called game theory. Game theory helps scientists understand how and why decision-makers make decisions. [186] The game can be as mundane as every day decision of deciding where to eat and as complex as deciding whether or not to sign a peace treaty. [186] Game theory provides individuals in this scenario with two choices of betrayal and cooperation, which can be applied to the monetization of organoid research [184]. In the context of monetization of organoid research, there are two different ways this concept arises. The first is the potential revenue

of organoid research versus sharing of the information to benefit the entirety of society. This paper has emphasized that organoid research has the potential to revolutionize the way companies and medical professionals treat patients. Companies that create this revolutionary technology to develop medications and new medical procedures must decide between potential profit versus overall benefit to society. The companies could choose to "betray" society by choosing to prioritize the profit over the societal benefit [184]. This decision would leave the "other partner" (society) worse off than before [184]. Alternatively, the companies could decide to "cooperate", which would be sharing the information with society, and would leave society better off.

Intellectual property rights versus sharing knowledge for the betterment of society is worthy of consideration. Intellectual property is defined as "the creations of the mind, such as inventions; literary and artistic works; designs; and symbols, names and images used in commerce" [187]. Researchers and scientists have the ethical choice to either assert their intellectual property rights to avoid sharing their hard work with others or freely disseminate it. If these scientists and researchers choose to "betray" society by holding onto their work and not sharing it, doing so would hinder the development of new treatments and medicine from their findings [185]. Or these scientists and researchers could choose to "cooperate" by freely sharing their hard work to better society by allowing their access to information that could lead to medical advances. In conclusion, ethics are the guiding light in the world of science. In science's equitable and just advancement, scientists must uphold ethical principles through each step of the research process.

5.4. Possible Connections between AI-Driven Cyberattacks and Organoids in Timelines

Cyberattacks, AI-driven or not, with organoids are not a documented phenomenon to our knowledge. AI is included for discussion as the technology is crucial for accounting for the numerous varied datasets that comprise understanding organoid development. It is a potential topic that is nonetheless valuable to explore toward potential defenses. Specifically, it is valuable to consider attack surfaces that may emerge, as well as new types of attacks that may be amplified or given an alternate end state. At least four possible cases denote the possibility of organoid development or process manipulation, theft of sensitive or otherwise personal data, the disruption of organoid function, and the combinatory case.

5.4.1. Organoid Development or Process Manipulation (Research and Development)

Disruption of organoid development and the manipulation of the involved processes carries importance in laboratory spaces. Targets come in the form of datasets that are generated, software that is designed or used in processing organoids, and hardware that is used in processing organoids. The end goal of these attacks results in the corruption of protocols, theoretical or practical, that result in under- or maldeveloped organoids. Sophisticated equipment and education are currently required to perform organoid research. The research produced appears rare, and the dependencies are potentially many. Mistakes in developmental organoid research are likely to be both difficult and expensive to either find or correct. Obvious mistakes and possible espionage could motivate resource expenditure and prompt an examination of security procedures. However, errors that appear clerical and or otherwise non-threatening would not necessarily be rectified quickly or thoroughly. Here, a malicious actor could gain in attacks that mimic honest mistakes caused by fatigue, manual processes, or hardware and software errors to embed attacks via the path of obscurity. In a more devious case, manipulation that leads to improper development of organoid development functions in a way that seems directed by the researchers could be attempted. The importance of monitoring the AI use by researchers, their mentees, PIs, and graduate students becomes important as they may lean too heavily on instruction from generative AI for their next research idea. The result in all of these cases is the poisoning of organoid development research, which could hold back important advances in the development of helpful applications that involve organoid intelligence and computing.

A huge question of why this is important lies within the speculation that organoid intelligence-powered computation could exceed current AI-derived outputs. Negatively influencing the public perception of what are possible benefits current extant entities, such as maliciously acting companies and or nation-state actors looking to pause or misdirect research by competitors. Such actors may perceive this path as useful in combination with other actions to either maintain or gain their lead in this area of research. These potential attacks are concerning as mistakes in research and development can have wide-ranging effects on other work, especially where derived data sets are shared. Consider two scenarios illustrated in Figure 4. In the first scenario, an AI could be designed to gain access or trigger upon gaining access to a critical lab infrastructure (a la Stuxnet). Malicious agents using AI could potentially infiltrate and disrupt organoid development within laboratory settings, exploiting software vulnerabilities, compromising connected devices, or deceiving personnel. Once inside, the AI can navigate laterally across the network, seeking out systems linked to organoid cultures. This maneuvering may exploit weaknesses in network segmentation or compromise other devices with access to organoid systems. Subsequently, the AI targets specific vulnerabilities within the software or hardware controlling the organoid cultures, potentially manipulating environmental parameters, or injecting malicious code into growth mediums. The consequences of such actions can be severe, disrupting organoid development and function by altering nutrient supply, temperature, or even neural activity, with outcomes ranging from impaired brain development to unintended releases of harmful agents if the organoid is utilized for disease modeling.

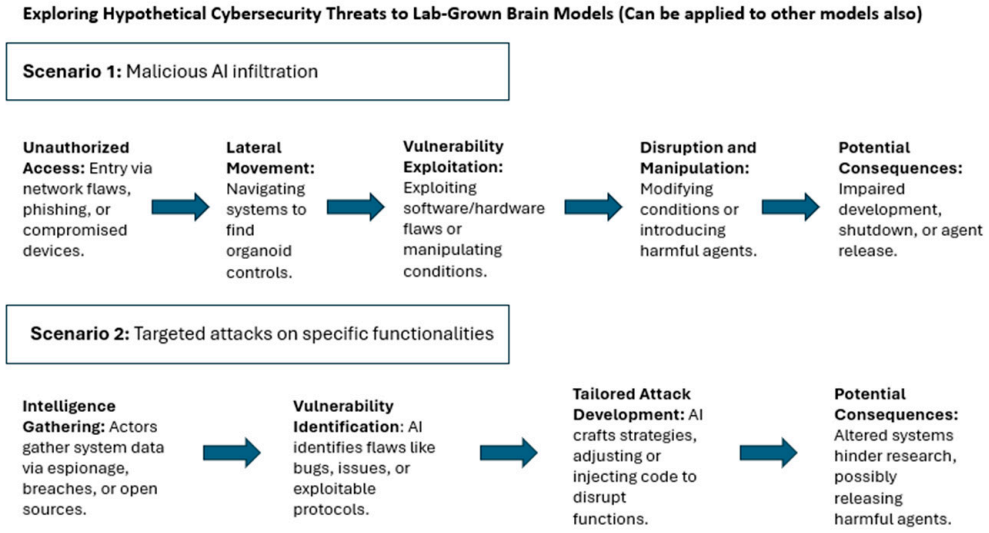

Figure 4. Hypothetical cybersecurity threats to lab-grown brain models.

The second scenario could involve the use of AI, but it is not necessary. Targeted attacks on specific functionalities can unfold through intelligence gathering. In an attack's initial phase, malicious actors gather intelligence to meticulously collect information about targeted organoid systems and their operational characteristics. This data acquisition spans various methodologies, including espionage, data breaches, or the scrutiny of publicly available information. After this data collection, sophisticated AI algorithms are employed to meticulously scrutinize the acquired information, pinpointing potential vulnerabilities in the system's architecture. These vulnerabilities range from discernible software vulnerabilities to vulnerabilities within environmental controls or exploitable communication protocols. Following the identification of vulnerabilities, AI is then leveraged to craft a meticulously tailored attack strategy, precisely engineered to exploit the identified weaknesses to achieve the desired outcomes. Such attacks may encompass the manipulation of specific environmental parameters, the introduction of precisely targeted toxins or pathogens, or the injection of malicious code aimed at disrupting specific organoid func-

tions. The culminating phase of the attack involves its execution, which could be performed through remote access or physical infiltration. Upon execution, the maliciously manipulated organoid systems yield altered results, significantly impeding research progress. Such attacks could unleash harmful agents, mainly if the organoid is employed for critical functions such as disease modeling or the production of sensitive biological materials.

For cyberbiosecurity, it is essential to recognize that while these scenarios are hypothetical, they underscore the deeply interdisciplinary dynamic and evolving nature of threats that may occur in organoid research, especially where the value of the research and projects is large. As technology progresses, the methods and technologies employed by malicious AI agents may also evolve and become more complex, resulting in the production of unique and greater attack surfaces. Therefore, maintaining vigilance and staying abreast of advancements in AI and cybersecurity while keeping an open mind is paramount.

5.4.2. Theft of Sensitive and or Otherwise Personal Data

Considering ethics and earlier monetization, both academic and industry-based groups need to consider theft that may occur as AI is factored into organoid-focused cyberattacks that specifically target theft. Section 5.4.1 gave a general idea of laboratory espionage. Two additional potential scenarios, drawing on examples previously discussed in literature based on concerns with brain-computer interfaces (BCIs) being a source of non-consensual data extraction, are offered for consideration: extraction of sensitive data from organoids based on brain activity insights and industrial espionage toward industries centered around neuro-centric data [188,189].

In terms of extracting information from brain activity, neural organoids represent a treasure trove of insights into brain processes and cognitive functions. Malicious actors, leveraging AI-driven cyberattacks, may target these organoid research facilities to illicitly obtain valuable data. Special neuron lines that comprise neural organoids from particular patients can yield sensitive data about patients and may potentially yield personally identifiable information (PII) whose ramifications are difficult to escape. The implications are profound; the acquired information could be weaponized to develop methods or technologies capable of manipulating individuals' thoughts or actions. Those most susceptible could be patients from whom samples have been extracted. Furthermore, the intricate understanding gained from brain activity data could facilitate the creation of personalized bioweapons; however, it is difficult to determine given the novelty and state of the currently publically available technology. This underscores the critical importance of robust cybersecurity measures within organoid research environments to safeguard against such malicious incursions and protect the integrity of sensitive neurological data.

Targets include the people from whom data might be extracted, but it is also essential to discuss the vulnerability of intellectual property that interfaces with these organoid systems. In the second scenario, industrial espionage similar to brain-computer interface (BCI) research is executed through targeted tactics to steal valuable insights. The accelerating pace of research in domains like brain-computer interfaces and neuroprosthetics underscores the heightened significance of organoid research. Attackers could gather intelligence on ongoing BCI projects by monitoring scientific publications, employing industrial espionage techniques, or bribing insiders. By exploiting vulnerabilities within research systems, they steal valuable data such as design documents or intercept data from BCI experiments. The ramifications of a successful breach are profound, as stolen information could be exploited for commercial gain, enabling competing entities to gain an edge in product development and market dominance. This intellectual property can then be utilized for competitive purposes or may be sold on the black market to interested parties.

5.4.3. Cases of AI Cyberattacks Focused on Organoids

To the authors' knowledge, as of the time of this article's submission, there is no record of AI-driven cyberattacks on organoids despite cases of AI-based malware targeting healthcare systems and medical devices. The proximity of occurrences serves as a warning

of the potential dangers that arise when AI is introduced to biological systems. Organoids are valuable resources that have immense potential for tissue regeneration and replacement. Therefore, it is prudent that the international scientific and industrial community take necessary measures to ensure that organoids remain relatively secure from any threats that may compromise their value.

5.4.4. Imagined Defenses

It is challenging to positively identify all potential types of sabotage. The means of protecting labs in this 21st-century modality are outlined in Figure 5. Much of effective security comes down to how we treat people and the environments involved with assets to protect. Ontological security is important for the world of organoids and subsequent research.

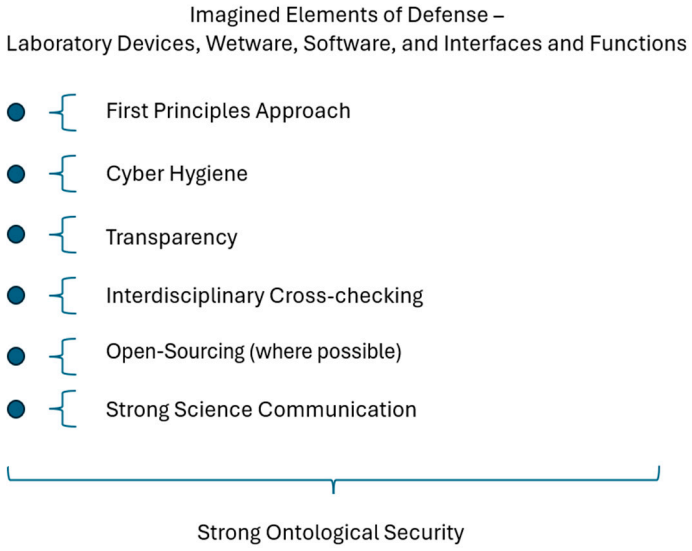

Figure 5. Imagined elements of defense.

Imagined Defenses for All of the Above: First Principles Approach and Cyber Hygiene

Firstly, a return to the first principles of research is key. Cutting out excess reporting and processing can reduce the number of spots in which malicious actors can poison processes, equipment, software, and datasets. Next, there needs to be greater cyber hygiene. Modern laboratories are employing greater amounts of hardware with bio-interfaces, and these create more attack surfaces that malicious actors can target [47,56]. A higher degree of cyber hygiene is needed to protect the integrity of these sophisticated lab tools, the software employed, and the datasets to be input and output from them. It is much easier for a malicious actor to convince an inexperienced lab member to click a spiked link, grant unauthorized access to lab spaces and resources, or be bribed than it is to infiltrate a sophisticated encryption protocol. Addressing issues with lab members regarding financial, social, and mental stress, along with insecurities, is paramount to increasing the likelihood that they operate at their highest level. Since there is a greater capacity for PIs and administrators to be used to impact research, the same concept applies to them.

Transparency, Open Sourcing Where Possible, and Interdisciplinary Cross-Checking

Secondly, maintaining transparency in work processes and the use and open sourcing of research wherever possible can allow others to more thoroughly critique others' work. Negative research needs to be highlighted so that research resources are not wasted, and then teams can be more accountable for their resource use. The future is interdisciplinary and open-source out of necessity. The ability for malicious actors to injure research through database poisoning and bottlenecking is greater than ever. We need researchers of different domains to be able to critique and cross-check each other to identify mistakes and improve

the processes being engaged with. Further, this openness and transparency need to expand to the community. For this reason, community education through expanded Science communication (sci-comm) is of great importance. Better informed community members allow for better Institutional Animal Care and Use Committees (IACUCs) and Institutional Review Boards (IRBs), especially given that one of the members on these boards is not permitted to have institutional connections. This makes for more efficient meetings, as less time and resources are spent educating these members on the steps of the research involved. Further, greater public education allows for enhanced public support, which can translate into better funding. This results in an improvement in the ability of research teams to get better funded. More funding allows for multiple outcomes that can result in greater robustness, security, and reliability of the world's available, publicly accessible organoid research. The benefits of greater funding are as follows, although this list is not exhaustive:

- More precise and secure equipment
    - Less reliance on less-maintained hardware and software prone to leak information
- More teams are able to investigate the same core phenomena related to the development, function, and or use of organoids
    - Greater redundancy gives greater portals to available variances in research outcomes and makes it harder for malicious actors to bottleneck and poison avenues of research
- More teams are willing to publish negative results, as they can view the endeavor as productive
- Create a workload that is more feasible and allows for flexibility; this alone has multiple benefits
    - More time on fewer tasks, allowing for more quality work
        - More replications and deeper insights
        - Fewer mistakes generated through exhaustion
        - A greater degree of cyber hygiene
    - A greater degree of collaboration across the globe and between institutions
        - Less fear of "scooping" taking research not originally created)
        - More shared resources
            - Along with greater eyes on resource misuse
        - More perspectives shared on pivotal areas of this research

However, this optimistic view and list of benefits typically requires an engaged public that is willing to encourage and support increased scientific funding. Science communication, or "sci-comm", is part of security and should be treated as such. The inability to maintain ontological security makes it easier to narrow the available means of defense, which makes it easier for malicious actors to target assets for corruption.

6. Discussion

The collaboration between cybersecurity experts and biologists across governments, industries, and community labs across multiple levels is essential in developing and implementing effective CBS strategies; this has been spoken of at length by numerous authors [190–194]. They highlight the importance of such interdisciplinary collaborations, which bring together the expertise of cybersecurity professionals with the domain knowledge of biologists. This collaboration ensures that cybersecurity measures are robust and tailored to each community's needs, based on regional and pertinent cybersecurity expert-driven insights on security technologies and threat landscapes. At the same time, biologists can guide the application of these technologies in a way that supports and enhances research processes. These collaborations can foster innovation and develop new

security solutions for biomedical research challenges. Effective collaboration also facilitates a shared understanding of the importance of CBS, fostering a more secure and resilient research environment.

Expect future organoid research to become more complex as it involves increased interfacing with computing, spanning from the molecular to the organoid level [1,32,51]. This evolution will lead to more nuanced molecular disease mechanisms, facilitating the development of targeted therapies. However, managing this complex data, which is rich in detail and volume, necessitates advanced security measures. The sheer volume and specificity of the data make it an attractive target for cyberattacks; thus, safeguarding this data becomes a critical priority. The challenge is to develop data security protocols that match the sophistication of the research they protect. Beyond that, it is worth engaging in the ontology of new types of data that biological structures based on organoids will be processing. It is not unreasonable to imagine that they may use data compiling and transmissions that require newly imagined interfaces to decipher, utilize, and counter. The threat of attacks via various platforms will require imaginative players and collaborators from diverse backgrounds and perspectives [195]. Murch et al. (2018) emphasize the importance of anticipating future cyber threats and developing preemptive CBS strategies in the context of organoid research [45]. The field is rapidly evolving, and the nature of cyber threats is also changing. Preemptive strategies involve staying ahead of cyber threats and predicting and preparing for future vulnerabilities. This proactive approach is crucial to ensure that cyberattacks do not undermine the advancements in organoid research. It involves a continuous assessment of the CBS landscape, regular updates to security protocols, and the incorporation of the latest cybersecurity technologies and practices. The goal is to create a research environment where security measures evolve with technology, ensuring organoid research's safe and ethical progression.

With future reflection on data mining regarding AI and organoids, the potential for AI-driven cyberattacks may become a significant concern once both reliable organoid processing and new intuitive bio-interfaces become more commonly produced and integrated into consumer devices [51,196,197]. We must address the infrastructure used to maintain organoid systems. Water, a significant resource that modern infrastructure protects and manages, is a considerable target in CBS planning [188]. The current conversation is about using AI for organoid optimization, while the other way around is mainly in the prototypical demonstrative stages. That is not to say that greater amounts of state investment could not advance timelines for the weaponization or gamification of organoids for cybersecurity purposes. Such investment would vindicate calls for funding at the intersection of synthetic biology and BCS. That said, AI pipelines, while enhancing the capabilities of organoid research, also introduce new vulnerabilities. These AI-specific threats require specialized security measures, as traditional cybersecurity protocols may not adequately address the nuances of AI-driven attacks. The challenge lies in developing cybersecurity strategies to protect against AI-based vulnerabilities, excluding human-bias-introduced vulnerabilities, ensuring that the AI tools used in organoid research are secure and reliable.

Ensuring reliability requires a deep understanding of AI technology and cybersecurity, highlighting the need for expertise in both fields to safeguard organizational research against these emerging threats effectively. Future research should prioritize the development of advanced CBS research areas and explore new technologies for data protection, such as blockchain and community-enhanced AI-driven security systems. If organoids will be part of computing processes, there must be guidelines for standardizing them and security processes around their maintenance and processing. Further, the data they process are essential to guidelines similar to those held for traditional computing hardware, wherein the interface with traditional hardware. The ethical guidelines for data management need to be enforced, rather than just being created and treated as decoration. Developing these advanced protocols is essential in creating a robust defense against sophisticated cyber threats. Additionally, establishing and enforcing ethical guidelines ensures that the management of organized research data is conducted well and in a manner

that builds on an already wounded public trust. This focus on developing advanced CBS measures is nothing to ignore for safeguarding the future of organoid research, ensuring that it continues to advance in a manner that is secure, ethical, and aligned with the broader goals of biomedical science.

As Murch et al. (2018) point out, the collaboration between biologists and cybersecurity experts is critical in navigating the evolving cyber threats in organized research [46]. This interdisciplinary partnership combines biologists' domain-specific knowledge with cybersecurity professionals' technical expertise. Biologists contribute a deep understanding of the nature and requirements of organoid research, while cybersecurity experts map the latest and provide insights into the latest security technologies and threat landscapes. This synergy is vital for developing comprehensive CBS strategies tailored to the unique needs of organoid research. Collaborations foster an innovation environment where new solutions to CBS challenges can be developed and implemented. Such partnerships are fundamental in ensuring that organoid research continues to advance securely and effectively in the face of increasing cyber threats. As organoid technology continues its rapid advancement, the strategies for CBS must be prepared to develop in parallel. The dynamic nature of organoid technology, with its continual innovations and increasing complexity, demands an equally agile and forward-thinking CBS approach. Such an approach involves keeping pace with technological advancements and anticipating future developments and the potential cyber threats they may bring. The evolution of CBS strategies with organoid technology is essential for this field's safe and responsible progression. It ensures that as we push the boundaries of what is possible in biomedical research, we do so with a framework that protects and preserves the integrity of the work.

7. Conclusions

This work underscores the remarkable potential of organoids in propelling the frontiers of biomedical research and the necessity to provide security measures. With their unparalleled ability to model human biology in three dimensions, organoids are revolutionizing our approach to understanding and treating diseases. However, parallel to their scientific potential is the necessity of CBS. This facet of research safeguards the integrity of the data derived from organoids, ensuring that this field's groundbreaking progress remains secure and credible. The importance of CBS is understated and can be a linchpin for ensuring the reliability and applicability of organoid research findings. As we delve deeper into the complexities of human biology through organoids, the need to protect this venture from cyber threats becomes increasingly paramount, intertwining the destiny of organoid research with the efficacy of its cyber defenses.

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Glossary

Term	Definition
APT	**Advanced persistent threat [195].**
Amyloid beta	Amyloid beta is produced via the proteolytic cleavage of. a transmembrane protein, an amyloid precursor protein (APP), by enzymes called β- and γ-secretases. It is proposed to be an early detrimental occurrence in the development of Alzheimer's disease [196]
Biocomputing	Biocomputing is an innovative technological domain that operates where biology, engineering, and computer science intersect and aims to utilize cells or their molecular components (such as DNA or RNA) to perform tasks traditionally performed by an electronic computer [197].
Biocybersecurity (BCS)	Biocybersecurity is the intersection of biotechnology, biosecurity, and cybersecurity issues and is part of an initiative aimed at protecting the bioeconomy [198].
Bioinformatics	Bioinformatics is a scientific subdiscipline that involves using computer technology to collect, store, analyze, and distribute biological data and information [199].
CRISPR/Cas9	CRISPR/Cas9 is a gene editing technology that involves two components: a guide RNA to match a desired target gene and Cas9- an endonuclease that causes a double-stranded DNA break, allowing modifications to the genome [200].
Cyberbiosecurity (CBS)	Cyberbiosecurity refers to attacks originating in hardware and computer systems with a focus on biological or biology-centric systems. A useful primer is presented in past literature [45].
Human Genome Project	The Human Genome Project is an international research project whose main objective is to decode the chemical sequence of the entire human genetic material (genome), identify the 50,000 to 100,000 genes encompassed within it, and provide research tools for the analysis of genetic information [201].
Induced pluripotent stem cells (iPSCs)	Induced pluripotent stem cells are derived from adult somatic cells that have been reprogrammed back into an embryonic-like pluripotent state that enables the development of an unlimited source of any type of human cell needed for therapeutic purposes [8,9,92,100,110,202,203].
In silico	In silico is experimentation performed by computational models that explore pharmacological hypotheses through various methods, including databases, data analysis tools, data mining, homology models, machine learning, pharmacophores, quantitative structure-activity relationships, and network analysis tools [17,204].
Organoid	An organoid is a self-organized 3D tissue that is derived from stem cells (pluripotent, fetal, or adult), which imitate the functional, structural, and biological complexity of an organ [205].
Organoid intelligence (OI)	OI is an emerging interdisciplinary scientific field aiming to establish a new type of biological computing system using 3D cultures of human brain cells (brain organoids) and brain-machine interface technologies [18].

Pathology of tau	The Pathology of Tau are neurodegenerative disorder characterized by the accumulation of abnormal tau protein in the brain [185].
Pluripotent stem cells	Pluripotent stem cells are cells that have the capacity to self-renew by dividing indefinitely, producing unaltered cell daughters maintaining the same properties as the parent cell [206], and are capable of differentiation into any cell type found in the human body
Primary microcephaly	Primary microcephaly is a disorder of brain development that results in a head circumference more than three standard deviations below the mean for age and gender [207].
Raspberry Pi	Raspberry Pi is the name of a series of single-board computers made by the Raspberry Pi Foundation, a UK charity dedicated to enhancing computing education and accessibility [208,209].

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