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Abstract: The origin and potential role of chiral asymmetry remain one of the most exciting issues in biology. In this paper we review the chirality of biological macromolecules, starting at the level of single molecules and continuing to the level of supramolecular assemblies. We discuss the physical and chemical consequences of the presence of chirality and their role in the self-organization and formation of structural hierarchies in cells. Homochirality may serve as an essential factor that invokes mechanisms required to control the formation of discrete structural hierarchies in macromolecules and macromolecular assemblies. Symmetry is of fundamental importance not only for all molecular biology as a systemic factor of its organization but also for pharmacology, as well as a systemic factor of drug stereospecificity.

Keywords: chirality; proteins; nucleic acids; hierarchy of structures; chiral drugs

1. Introduction

Over the past decades and especially in recent years, with the advent of the latest physical and molecular biological research methods, as well as computer processing and analysis methods, many review papers concerning intra- and supramolecular protein structures have been published. Most often the subject of discussion was the general structural analysis or the features of individual types of structures, the folding problem, the structural features of enzyme active site, etc. [1–14]. Nevertheless, the physical foundations of the unity of the structure and functions of proteins remain one of the crucial problems of molecular biophysics.

The phenomenon of asymmetric chirality in living systems has recently attracted attention as one of the most urgent fundamental problems in the scientific world [15–34]. Historically, the interest of physicists in the problem of chirality is focused on a separate search for mechanisms of symmetry breaking in the main classes of biomolecules at the initial stages of biopoiesis. Experimental data, approaches, and opinions on the issue of the Earth's or cosmic origin of the phenomenon are multiplying. The possible role of glycine—the only achiral proteinogenic amino acid, and racemic beta-sheets in the origin of homochirality of peptides is discussed [35–38]. However, the question of the biological significance of the phenomenon, this evolutionarily selected and entrenched general biological sign of a living matter, is rarely discussed. It is known that the homochirality of the L-amino acids included in proteins ensures the stereospecificity of complementary interactions and minimizes the amount of information required for unambiguous coding of amino acid sequences by nucleic acids [39]. It is also known that deoxyribose and ribose, which are part of unique DNA and RNA, are D-isomers.

The chirality of monomers that make up the basis of informationally determined proteins and nucleic acids is usually perceived as an irrational episode in a reasonable evolutionary process, as a "payment" for the unique ability of carbon to form a huge number of inorganic and organic compounds that harmoniously bind the structures and functions of living systems. And the homochirality of primary structures is perceived as a trivial way out of the dualistic situation.



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Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). In this review, we propose to consider the structural details and hierarchies of protein structures based on a single physicochemical symmetry principle—their chirality. Such a description, based on the concept of a sequential change in the sign of chirality in different-scale protein structures, allows formalizing the "vertical" discreteness of protein structures as molecular machines by one order parameter. At the moment, we are not able to directly relate the features of protein structures with their functions as molecular machines that convert energy, matter, or information. However, in the future, the approach to the consideration of molecular biological machines as chiral devices through the representation of their constituent hierarchies of chiral structures seems promising. For this, we consider the hierarchical structures of proteins as chiral details of their constructions.

2. Chirality of Macromolecules

The dualistic concept of chirality takes a special place in the category of symmetriesasymmetries in biological structures. In our consideration of molecular biological systems, we use the classical definition of chirality: chirality is the property of a molecules or objects to be incompatible with their mirror images in any combination of movements and rotations in three-dimensional space. An enantiomer (enantiomorph) exhibits neither between-side nor axial symmetry.

Chiral asymmetry is much more widespread in molecular biological systems than is traditionally discussed in the literature. For example, in addition to L-amino acids in proteins, as well as D-ribose and deoxyribose in nucleic acids, various lipids also constitute homochiral classes of compounds in organisms of different taxonomic ranks [40]. Chiral molecules serve as the basis for the formation of larger chiral molecular and supramolecular structures with selected degrees of freedom necessary for the creation and functioning of molecular machines: from individual enzyme machines to the whole cell-integrating machine system—the cytoskeleton.

2.1. Proteins

2.1.1. Primary and Secondary Structure

Proteins are known to be linear polymers composed of L-amino acid residues [39]. D-amino acid residues found in peptides are not encoded during matrix protein synthesis, but they are included in some cases in the polymer chain by special enzymes (or in the process of spontaneous racemization). When folded, the polypeptide chain forms a regular and irregular secondary structure. The main regular secondary structures are α -helices and β -sheets. Other regular helical structures are possible (such as helix 3_10, etc.), but they are much less common. The α -helix generally is the right enantiomer, and the right α -helix is more stable than the left one [41]. Several β -strands connected laterally by hydrogen bonds form a β -sheet. Due to the twisting of the individual β -strands, the β -sheets are always somewhat twisted as a whole, and the direction of the hydrogen bonds changes along the course of the strand [42]. A separate β -string has a left-handed twist. Thus, the torsion of the β -sheet is left-handed when viewed from the edge of this sheet (and right-handed when viewed from the rotation of the hydrogen bond line along the β -strands). It is customary to look along the course of the β -strands, and it, therefore, considered that the β -sheet has a right-hand propeller twist.

Another type of regular secondary protein structure is the polyproline helix, which is stabilized by van der Waals interactions. There are two types of polyproline helix: right-handed poly(Pro)I helix and left-handed poly(Pro)II helix (the difference in the direction of twisting is due to cis and trans isomerism, respectively). Since the cis isomers of the peptide bond are energetically less favorable [43], right-handed poly(Pro)I helices are much less common than left-handed poly(Pro)II with peptide bonds in the trans conformation. Two left-handed polyproline helices form a tertiary structure—a right-handed superhelix. A similar structure is realized in collagen: the collagen right-handed superhelix is formed from three left-handed poly(Pro)II helices connected with interchain hydrogen bonds [39].

In polypeptide chains, in addition to regular secondary structures, there are also non-regular ones—not forming long periodic elements. These include various types of loops and turns (or bends) that change the polypeptide chain direction. An important observation related to globular proteins should also be noted. The bridges in α/β , $\alpha + \beta$, and β proteins between parallel β -strands in the same β -sheet are right-handed [44]. In this case, the bridge may contain both an α -helix (in α/β and $\alpha + \beta$ proteins) and even a separate β -sheet (in β and sometimes in $\alpha + \beta$ proteins), and very rarely it may not there are neither α - nor β -structures, but the bridge is still right-handed. It is believed that the right-handed twisting of the bridge is energetically more favorable [44].

2.1.2. Superhelices

The formation of nontrivial structures by several α -helices attracted the interest of researchers shortly after Pauling proposed his α -helix model. Pauling and Crick's research carried out independently in the early 1950s became fundamental [45–47]. Crick noticed that two α -helices twisted at an angle of about 20° relative to each other interact, and this interaction has a period of 7 amino acid residues. He called such a bundle of α -helices "coiled-coil", or superhelix, and the type of side chain packaging characteristic of this superhelix as "knobs into holes" (KIH). The amino acid residue of one helix ("knob") fits into the space between four residues of the other helix ("hole"). It is known that up to 10% of the proteome contains coiled coils [48,49].

The original Pauling's α -helix model was left-handed, and the Crick's superhelix consisting of left-handed model helices was right-handed. Crick also suggested the existence of right-handed α -helices bundles and bundles of combinations of right-handed and left-handed α -helices. However, in general, he considered the question of twisting to be completely unresolved at that time.

Later, Crick's assumptions were developed: the canonical sequence of the supercoil consists of heptad repeats [50]. The positions of the residues in the heptad are usually designated as a—b—c—d—e—f—g. As a rule, hydrophobic residues reside at positions a and d (most frequently, Leu, Ile, and Val), and polar amino-acid residues (most frequently, Lys and Glu), at positions e and g. [51]. The interaction of residues a and d gives a hydrophobic core, while ionic interactions take place between residues e and g. From a physical standpoint, it is necessary to add the interaction with the surrounding aqueous solution to the consideration of intramolecular and supramolecular structure formation. An adequate thermodynamic evaluation of the complete system should take potential formation of aqueous chiral structures induced by chiral structures of macromolecules into account [52].

In addition to the heptad repeat, other periodicities are also possible. They are limited only by the periodicity of the unperturbed α -helix. This limitation is responsible for the supercoiling of the bundle. For the packing of helices and the preservation of hydrophobic contacts, the amino acid residues must occupy equivalent positions. The alternation of hydrophobic residues with three and four residues gives a periodicity close to that of a regular α -helix. Since the ideal straight α -helix has a periodicity of about 3.65 residues per turn, the superhelix with the heptad repeat has a left-handed twist to reduce the periodicity to 3.5 residues per turn relative to the bundle axis [50]. The periodicity of the hendecad coiled coils is slightly greater than the periodicity of the ideal α -helix: 3.67 residues per turn. Therefore, such superhelices are slightly twisted to the right. Moreover, coiled coils with periodicities equal to 15/4, 18/5, 25/7, and 9/3 can be found [53].

The simplest coiled coil construction is a dimer, and the orientation of the α -helices can be either parallel or antiparallel. Coiled coils are consisting even of 7 or more α -helices [54]. In the case of 2 α -helices, the coiled coil pitch is about 150 Å, and in the case of 3–4 α -helices, it is about 200 Å [55].

There is a systematic classification of coiled coils, the authors of which compiled a "periodic table" of these structures [54]. Proteins were divided into two groups: classical

(with one coiled coil and consequently one hydrophobic core) and complex, containing two or more classical coiled coils connected in some way.

Among the variety of coiled coil structures of the "periodic table", right-handed twist was observed only in a few cases: in the tetrabrachion of *Staphylothermus marinus* thermophiles (PDB ID: 1FE6 [56]) and in the designed tetramer (PDB ID: 1RH4 [57]). The tetrabrachion of *Staphylothermus marinus* thermophiles is of particular interest for consideration. It consists of an α -helical stalk, and from the proximal end of it, there are four arms formed mainly by β -strands [58]. The stalk is divided into two parts by a single proline residue, which changes the frequency of the hydrophobic residues from heptads to hendecad. Thus, in the α -helical stalk, there is a switch from the left-handed coiled coil to the right one through the proline residue.

The authors of [58] noted two more special structures going beyond the coiled coils periodic table. The right-handed coiled coil was found in glycophorin A and LEA ("late embryogenesis abundant") proteins of plants [59,60]. However, it is not known whether LEA proteins are fibrillar or even α -proteins. As for glycophorin A, it differs from the classical coiled coil since the packaging observed there does not belong to the "knobs into holes" type.

The proteins with large superhelical domains can perform intricate functions associated with manipulations involving other proteins or interaction with membranes. One example deserves special attention since the superhelix in this case is formed by α -helices of different proteins. These are the SNARE superfamily proteins (SNAP or NSF receptors, sensitive to N-ethylmaleimide), which are involved in membrane fusion, for example, during the release of neurotransmitters or exocytosis. These proteins linked to the plasma membrane contain a SNARE motif enriched for heptads, with a length of 60–70 residues, and form a superhelix of four α -helices. However, these four α -helices belong to different proteins: one to syntaxin 1, one to synaptobrevin, and two to SNAP-25. Syntaxin and SNAP-25 are integrated with the cell membrane and synaptobrevin, with the vesicle membrane. Twisting of these four α -helices into a lefthanded superhelix allows the vesicle and cell membranes to fuse [61].

2.1.3. Cytoskeleton

Changes in the chirality sign at higher levels of intracellular structures, namely, in supramolecular protein structures cytoskeletal elements, are of particular interest. These include microfilaments, intermediate filaments, and microtubules.

Microfilaments underlay the cell membrane, making it mechanically hard. Due to the ability to form various spatial configurations, microfilaments are involved in lamellipodia and filopodia formation. It is necessary for cell motility in space. Microfilament bundles anchor membrane proteins and form focal contacts. A microfilament is composed of G-actin (globular actin) monomers. G-actin molecules form into a single-stranded left-handed helix with a turn of -166° around the helix axis [62]. The molecules are arranged on the same helix with a repeat in every 13 molecules for almost six left turns. The increment per molecule is 2.76 nm, and the twist per molecule is $-166.6 \pm 0.6^{\circ}$ [63,64]. It is a quaternary microfilament structure. Finally, two left-handed G-actin chains twisted into a right-handed helix form a supramolecular microfilament structure (also called F-actin). Right-handed double helices of microfilaments are likely oriented upon interacting with the "left" phospholipids of the eukaryotic cell membrane.

Intermediate filaments have a scaffolding function. They permeate the entire cell from one desmosome to the other, imparting mechanical strength to the cell. A separate type of intermediate filaments is a nuclear lamina which is a network that underlies the nuclear membrane and affects chromatin compaction. The intermediate filament has a rope-type structure. That is a superhelix formed from 32 extended right-handed α -helices in the filament cross-section [65]. Note that the relative position of these 32 α -helices within the intermediate filament has not been established experimentally. Various models of its assembly are being developed [66]. However, two α -helices form a left-handed

dimer according to the "head-to-head, tail-to-tail" principle [65,67]. Two dimers combining the "head-to-tail" principle form a protofilament—a tetramer. Moreover, these dimers are twisted rightward relative to each other to maximize the contact area [68]. The right-handed tetramer represents the quaternary level of the intermediate filament structure. Finally, eight tetramers are assembled into a left-handed intermediate filament corresponding to the supramolecular structural level [39,69].

In humans, approximately seventy different types of intermediate filaments have been found [39,65]. They differ in their cell location and functions but are very similar in structure, except for the tail domains. So, there are cytoplasmic intermediate filaments and nuclear ones. Cytoplasmic intermediate filaments include the vimentin-like, epithelial, and axonal intermediate filaments. Nuclear intermediate filaments, lamins, underlay the membrane of the cell nucleus. Left-handed lamins are oriented upon interacting with chromosomal DNA (the right-handed double helix in the unwoven form) [70,71].

Finally, microtubules at the supramolecular level of their structure represent a triple left-handed helix [72,73]. They are directed from the nucleus to the periphery and are necessary for a relatively rapid directed intracellular transport, which is critical in mitosis when chromosomes are pulled to the poles of daughter cells. Left-handed microtubules are evolutionarily "targeted" at interaction (albeit indirectly) with chromosomal DNA during mitosis [39].

The chirality sign alternation was noted earlier at the supramolecular structural levels of the complexes of actin, tropomyosin, and myosin in our previous manuscript [74]. The fibrillar protein tropomyosin is a coiled-coil structure that is characterized by the formation of a left-handed superhelix from two right-handed α -helices [75]. Tropomyosin interacts only with F-actin, not with G-actin. The left-handed tropomyosin coiled coil is wound on F-actin in a rightward way [63]. The interaction of these proteins (F-actin and tropomyosin) is a vivid example of the interaction of the supramolecular structures. Myosin II tails at the quaternary level of their structure form a right-handed fibril, while a left-handed overlap of α -helices is observed at the tertiary level. During muscle contraction, the right-handed myosin fibril interacts with the left-handed actin fibril.

The bacteria locomotor apparatus represents another type of supramolecular structure. To move in space, bacteria use a flagellum consisting of a helical filament, a hook, and a basal structure. The flagellum is made up of the flagellin protein. The number of flagella in different bacteria is different. There is no direct complementary interaction, but there is a clear dependence of the nature of the bacteria movement on the flagella helicity and their rotation direction. When the flagella rotate counterclockwise, their protofilaments are twisted into one elastic thread, the rotation of which ensures the rectilinear movement of the bacteria. When switching the direction of rotation of the flagella, the thread unravels, and the bacterium movement becomes chaotic: it runs and tumbles [76].

Summing up, it should be noted that when considering the structural levels of protein organization, the following pattern can be traced. The primary structure of proteins is formed by a sequence of "left" amino acid residues. The polypeptide chain can be folded into the right-handed α -helix or the right-hand propeller twisted β -sheet. Structures with the canonical heptad sequence represent a left-handed coiled coil. The chirality sign alternation was also noted at higher levels of organization of cellular structures than intramolecular. Since the cytoskeleton is a system that permeates the cell, we can assume that the chirality of its elements serves as a guiding motive for intracellular interactions between structures that include molecules of different types of chirality. The interaction between different types of molecules with different chirality signs was found. Thus, right-handed microfilaments are oriented towards interaction with the 'left' phospholipids of the cell membrane. Left-handed lamina and microtubules are aimed at interacting with right-handed DNA double helices.

Since 1951, when Pauling and Corey proposed a model of the secondary structure of proteins (α -helix), and a year later Linderström-Lang introduced the definition of structural levels, dividing them into primary, secondary, etc., the classification of structures was

based on the description of their types, chemical composition, and chemical bonds. A complete thermodynamic description of the structural hierarchy implies not only a direct account of intramolecular physical interactions (reflected mainly in the enthalpy term) but also various factors associated with the entropy component. The search for the possibility of describing the hierarchy of structures of protein molecules in terms of "symmetry violations" associated with the entropy of the system with a single physical parameter is of particular interest. In other words, we try to describe the stratified structure of a protein macromolecule by a "series of symmetries". It is fundamentally significant that all these structural levels, regardless of the type of symmetry, have a common symmetry property—chirality. We note an important limitation of the developed approach: the fundamental physical and mathematical problem is the lack of a universal method for quantifying the "chirality measure" of individual structures in the total array of chiral formations. Without this, it is impossible to carry out a general thermodynamic assessment of the "chiral polarization" of the entire system and its subsystems.

There is a sufficient number of various methods for developing a criterion for symmetry breaking [77–81]. However, even the most successful of these methods only allow one to determine the degree of similarity of the initial set of points with its mirror image and, therefore, do not allow tracing the "switching" of the chirality sign for opposite stereoisomers. For example, according to Ramachandran's maps [82], only the predominant conformation of amino acids in a protein can be established. The method does not allow determining the sign of chirality and is not universal for all major classes of chiral macromolecules since it does not apply to nucleic acids.

Together with colleagues, we develop a method for evaluating the chirality of structures based on cross products [83]. In contrast to the mentioned methods, the developed approach for estimating chiral structures is more general and allows us to more fully determine the secondary structure (its type and sign of chirality with information about the spatial structure). Currently, this method is already being tested on protein superhelices.

2.2. DNA

In the case of DNA and RNA, alternation of the chirality sign is observed in A- and B-forms of DNA and the A-form of RNA during the transition to higher-order structures. D-deoxyribose molecules linked by phosphodiester bonds constitute the primary polymer chains of DNA. The nucleobases within a single chain are connected in the left-handed gauche conformation, and that makes folding into the well-known right-handed DNA double helix (in A- and B-forms) possible. B-form is the most common form of DNA in nature. The A-form of DNA is also a right-handed helix, similar in structure to the B-form, but it is more compact. It is most often formed under conditions of cell dehydration. The A-form originally discovered for DNA turned out to be the form that the RNA double helix always has. Although double-stranded RNAs are rare in living cells (although they do occur), even if there is a single-stranded RNA, it forms a very complex structure in space. In particular, it develops hairpins, and distant sections form short double helices. All these RNA structures are in the A-form. Finally, in addition to the canonical A- and B-forms, there is an unusual Z-form—a left-handed double helix. This form is not favorable for the organism, and only a tiny amount of DNA is in this state.

With further folding in bacteria, the circular right-handed DNA double helix is twisted in a left-handed fashion into a right-handed supercoil [84]. Negative supercoiling facilitates the melting of the double helix, which is required for transcription and replication.

In eukaryotes, there is a chirality sign alternation at the nucleosome level of the structural and functional organization of DNA. The protein octamer is divided into four "histone-fold" dimers defined by H2A-H2B and H3-H4 histone pairs. The eight histone molecules form the so-called left-handed protein superhelix [85,86]. The left-handed superhelical protein "spool" is formed by the ordered spiraling assembly of one H2A-H2B dimer to one side of one (H3-H4)2 tetramer and a second to the other side of the tetramer [87]. The surface of the octamer is traversed by several grooves and ridges, which

appear to follow the left-handed path. The 146 base pairs of right-handed DNA double helix wrap around the histone octamer in 1.65 turns of a flat, left-handed superhelix [88]. It can be assumed that such a configuration creates an opportunity for easier opening of the helical structure of a lower scale (unwinding is associated with functioning). Symmetry features of the packing of chiral structures at subsequent hierarchy levels are not yet entirely clear, but they are a field for further research within the framework of our concept.

Starting from the level of an asymmetric carbon atom in the amino acids of the primary structure of a protein and in DNA deoxyribose, we have earlier noted that there is a tendency to switch the chirality sign at the subsequent structural levels, resulting in a sequence of the type "left-handed"-"right-handed"-"left-handed"-"right-handed" in proteins (Figure 1) and "right-handed"-"left-handed"-"right-handed" in DNA [89–91]. The chirality sign alternates during the transition to higher-order structures of DNA structural and functional organization in A- and B-forms.



Figure 1. Chirality sign alternation during the transition to the next level of protein hierarchy. The movement along the abscissa axis is accompanied by a decrease in free energy.

The ranking of structures based on sign-alternating chirality does not always coincide precisely with the traditional classification of the structural levels, revealing the "fine structure" of the levels. In proteins, "right-left" alternation of the chirality sign in structural hierarchies is not absolute, since deviations may have physical justification and serve certain biological purposefulness.

3. Chiral Hierarchy Establishment

The question of whether there are also hierarchical structures with a chirality sign alternation in initially homochiral systems of non-biological origin is of particular interest. Segmental phenomena of spontaneous self-organization in inanimate nature at the initial stages of evolution could become a systemic principle in biological objects. The study of systems demonstrating a change in helicity sense is actively developing at present [92–96]. We mentioned earlier that the chirality of molecules or macroscopic objects is not a feature, but one of the general and fundamental structure-forming factors in both living and non-living nature [89–91]. On the other hand, it has been observed that artificially created homochiral systems may undergo the same process of spontaneous formation of hierarchies of molecular and supramolecular structures with an alternating chirality sign.

The influence a dumbbell-shaped guest derived from tartaric acid on the chirality of the structure formed by aromatic oligoamide sequence has been demonstrated [97]. The helix handedness of the host was induced by the guest ("left-handed"). This complex was found to be a long-lived kinetic supramolecular byproduct. It slowly transformed into a 2:2 host–guest complex with two guest molecules bound at the extremities of a double helix formed by the host. The handedness of the double helical host switched to the opposite ("right-handed").

The authors showed that synthetic C3 symmetric tris [3(3'-carbamoylamino)-2,2'bipyridyl]-benzene-1,3,5-tricarbonamide derivatives containing three chiral bis[(R) or (S)-2methylbutylthio]-tetrathiafulvalenyl units at the periphery can assemble into twisted fibers with a right-handed helix assembled from left enantiomers, and a left-handed helix from right enantiomers [98].

Several dimeric ("gemini") cationic amphiphiles are not chiral, but in the presence of polar chiral tartrate counterions, they assemble into twisted or helical ribbons consisting of stacks of bilayer membranes [99]. Right-handed helices are formed in the presence of L-tartrate, and left-handed helices are formed with D-tartrate.

Self-assembly of gemini-shaped chiral amphiphilic hexa-peri-hexabenzocoronene having two chiral oxyalkylene side chains has been demonstrated [100]. The nanotubes with right- and left-handed helical senses were obtained from the (S)- and (R)-enantiomers of the amphiphile, respectively.

The authors showed the successful fabrication of flower-like structures using an achiral porphyrin and chiral amphiphilic histidine [101]. Curved nanosheets were arranged in a clockwise manner or counterclockwise manner depending on the absolute configuration of histidine—the L- or D-enantiomer, respectively.

The cited examples illustrate the rule for changing the chirality sign during the transition to the next hierarchical level (Figure 2). This phenomenon, exemplified by examples of systems of various origins, has come into living nature in the form of the principle of hierarchical formation of discrete structures making up the backbone of biological macromolecules. The above properties of abiotic systems are conjectured to create a prerequisite for the systematic character of the saltatory development of the biosphere during prebiological and biological evolution.



Figure 2. Changing the chirality sign during the transition to the next hierarchical level in initially homochiral systems of non-biological origin.

In matters of biological chirality, the question of the physical mechanism of the occurrence of chiral asymmetries remains a generally recognized and discussed problem. We raise an equally important question about the physical aspects and the systemic role of (homo)chirality in the processes of structure formation, interaction, and transformation of biomacromolecules and supramolecular structures.

The formation of sign-alternating chiral hierarchies in macromolecular structures is associated with the assumption of the existence of a funnel in the configuration space on a potential energy surface with a complex landscape, which directs the folding process into the native conformation. It is assumed that this funnel, characterized by a minimum of free energy, sets the direction of the folding trajectory in the configuration space of the macromolecule, passing through a chain of local energy minima. We stated earlier that this process is due to a clear physical reason—the necessity for a system to lower the initial level of free energy formed during the energy-dependent selection of homochiral monomers of the macromolecule primary structures from their racemic mixtures [90,91]. Indeed, in living cells, the anti-entropic selection of L-amino acids by t-RNA molecules occurs. ATP molecules serve as energy sources for this process [39]. In this way, an L-homochiral polypeptide chain (protein primary structure) becomes an active one-dimensional medium with a distributed resource of free energy (three-dimensional in the case of globule formation).

Dissipation occurs not due to local racemization of individual monomers, but due to a switch in the chirality sign during the formation of a larger-scale structure with a different symmetry type. In this case, a wave of structural rearrangements in the polypeptide chain forms stable regular secondary and tertiary structures only in those parts where hydrogen bonds and van der Waals interactions can fix the effect of "crystallization". The formation of helices during folding is aperiodic—here Schrödinger's idea of the "aperiodic crystal" phenomenon is realized [102].

4. Chirality of Drugs

Enantiomers may have the same physical and chemical properties (boiling and melting points, density, etc.), but differ in their optical activity, characterized by the direction that they rotate the plane-polarized light. However, enantiomers, including pharmaceuticals, may exhibit utterly different chemical specificity in processes involving chiral compounds, as well as different biological activity. It is crucial to take into account the peculiarities of interaction of enantiomers with asymmetric compounds of the organism when creating drugs, since it may turn out that just one form of the drug has a therapeutic effect. At the same time, the other is not metabolized, is less active, or even causes severe side effects, being toxic. This phenomenon has attracted the attention of the scientific community for many years [103–107].

More than half of the drugs currently in use are chiral, and most of the last ones are marketed as racemates [106]. More than half of the drugs being developed in recent years consist of chiral molecules. Chiral drugs are used in the treatment of a wide range of diseases, including cardiovascular and gastrointestinal. Obtaining optically pure forms of the substance is a complicated and expensive task, but their use in many cases could reduce the dosage and the number of side effects of the drug.

The therapeutic activity of enantiomers, their pharmacokinetics and pharmacodynamics are currently being intensively studied [108–111]. In addition to differences in metabolism, distribution and excretion rates, there is also a process of chiral inversion of optical isomers (one enantiomer of a drug is converted into its antipode in the internal environment of an organism) in living systems. However, it should be emphasized that the physical nature of the differences in the therapeutic effects of enantiomers has not yet totally been established. We believe that the key to understanding the chiral drug—chiral target interaction may be the systemic molecular-biological regularity that we have identified: there is a tendency to alternate the chirality sign of structural and functional levels for DNA, proteins, and the cell cytoskeleton [89–91].

Chiral drugs can be divided into three groups according to the chirality sign of the bioactive enantiomer: with a bioactive "left-handed" S-enantiomer, with a bioactive "right-handed" R-enantiomer, and with two bioactive enantiomers.

4.1. Drugs with a Bioactive "Left-Handed" S-Enantiomer

"Right-handed" R-enantiomer of drugs with a bioactive "left-handed" S-enantiomer can be responsible for side effects, have a lower therapeutic effect or whose therapeutic effect is not observed. Ethambutol is an example of a drug with a "right-handed" R-enantiomer responsible for side effects. Ethambutol is used in the treatment of tuberculosis, and its S,S-enantiomer has higher activity. Initially, the drug was used as a racemate, but later it was found that R,R-ethambutol leads to optic neuropathy [111].

One more example of this subgroup is penicillamine. The enantiomers of penicillamine have different biological activities. S-penicillamine is used in the treatment of Wilson disease as well as in the treatment of rheumatoid arthritis [112]. Besides, this isomer is used as an antidote for some heavy metal poisoning. In turn, R-penicillamine causes side effects such as neuritis and osteomyelitis.

Bunolol refers to drugs with a bioactive S-enantiomer, the R-enantiomer of which is less active. Levobunolol is the pharmacologically active S-isomer of bunolol. It is a potent non-selective β -adrenergic receptor antagonist [113]. It is known that S-bunolol has 60 times greater β -blocking activity than R-bunolol [114]. Levobunolol is used clinically in the treatment of arterial hypertension, angina pectoris, and glaucoma.

4.2. Drugs with A Bioactive "Right-Handed" R-Enantiomer

Two subgroups can be distinguished: whose "left-handed" S-enantiomer is responsible for side effects and whose "left-handed" S-enantiomer has a lower therapeutic effect or whose therapeutic effect is not observed.

The most well-known example of a bioactive "right-handed" drug whose "lefthanded" enantiomer is responsible for side effects, is thalidomide. Thalidomide was marketed as a racemate, and the fact that only the R-isomer of thalidomide has a therapeutic effect, while the S-isomer has a teratogenic effect, was not initially known [115,116]. In the next few years after the start of sales, about 10,000 children were worldwide born with phocomelia, congenital defects in the limbs and internal organs. Only half of those babies survived [117]. According to the recent studies, the S-enantiomer of thalidomide displayed a 10-fold stronger binding to cereblon (CRBN, a thalidomide-binding protein) and inhibition of self-ubiquitylation compared to the R-isomer [118]. Thus, the teratogenic effects are induced by the S-enantiomer of thalidomide.

An example of the second subgroup is methadone. This drug is used as an analgesic, as well as in the treatment of drug addiction. Methadone is a racemate, but R-methadone is known to be large, if not entirely, responsible for the opioid effect [119].

4.3. Drugs with Two Bioactive Enantiomers

Methorphan enantiomers exhibit various pharmacological and toxicological effects [120]. Dextromethorphan is widely used as a non-narcotic antitussive agent; it has no analgesic effect at a therapeutic dose. The levorotatory enantiomer, levomethorphan, is a potent analgesic and its use as a narcotic drug is strictly controlled worldwide.

Both enantiomers of econazole have significant biological activity. The R-enantiomer of econazole showed higher inhibition values for *Candida krusei*, while for the S-enantiomer of econazole, higher inhibition values were observed against *Cryptococcus neoformans*, *Penicillium chrysogenum*, and *Aspergillus niger* [121].

The division of chiral drugs into groups according to the chirality sign of the bioactive enantiomer is schematically shown in Figure 3.



Figure 3. Three groups of chiral drugs according to the chirality sign of the bioactive enantiomer: with a bioactive "left-handed" S-enantiomer, with a bioactive "right-handed" R-enantiomer, and with two bioactive enantiomers.

Enantiomers' specific interactions with chiral biological macromolecules determine differences in their pharmacodynamic and pharmacokinetic properties. Thus, in the development of the previously developed concept of sign-alternating chiral structure formation in initially homochiral biological macromolecular systems, a hypothesis about the role of certain chiral correspondences between chiral drugs and target molecules is suggested.

The following considerations should be made regarding the relationship between the chirality signs of interacting intramolecular and supramolecular structures. Spontaneous intramolecular or intermolecular assembly is generally accompanied by a decrease in the free energy level in the system. At the same time, the uncertain combination of the enthalpy and entropy, or symmetric components of free energy change during interactions does not make it possible to characterize the binding affinity totally.

At present, with a sufficient degree of certainty, it can be assumed that chiral drugs, as well as biologically active substances, are included in the system of chiral spatial correlations with chiral biomolecular structures, creating a single chiral thermodynamic system. The data on the drugs systematized on the chirality sign make it possible to develop this direction of biophysical pharmacology for incomparably more successful drug design.

It is necessary to say a few words about symmetry breaking in neurodegenerative diseases that has attracted the attention of the research community [122–129]. An aggregationprone peptide Amyloid β 42 is believed to play a crucial role in Alzheimer's disease. Chirality can serve as a unique tool to study the process of cellular uptake of this peptide [122–126].

In 1951, Pauling and Corey proposed two pleated-sheet structures (parallel and antiparallel) that are suited to polypeptide chains constructed entirely of L- or D-amino acid residues [130]. In 1953, they predicted "rippled" β -sheets, in which the β -sheets would consist of alternating D- and L-peptides [131]. The formation of such heterochiral interfaces was demonstrated predominantly with amphipathic peptide sequences composed of alternating hydrophobic and hydrophilic amino acid residues [132]. Besides, it was shown that such structures could be formed from biologically relevant peptides [34,37,122].

Racemates often have lower solubility than their enantiopure counterparts [122]. The addition of mirror-image D-Amyloid β 42 reduces the concentration of toxic oligomers formed from natural L-Amyloid β 42, and the mixing of enantiomers accelerates the formation of non-toxic fibrils [122].

The age-related epimerization of the serine 26 residue of Amyloid β 42 can change its structure and function, leading to attenuated aggregation propensity and reduced toxicity of the peptide [124].

Chirality sign alternation can also be observed during the fibrillation of bovine serum albumin. Six distinct classes of coexisting amyloid fibrils of bovine serum albumin were identified [129]. They include flexible left-handed twisted ribbons, rigid right-handed helical ribbons, and nanotubes. Two flexible left-handed twisted ribbons form a right-handed twisted ribbon, and then a rigid right-handed helical ribbon polymorphic conformation. The flexible left-handed twisted ribbons, to finally evolve into nanotube-like structures.

Consideration of symmetry breaking can make a valuable contribution to the study of the pathogenesis of neurodegenerative disorders.

5. Discussion

One of the productive methods of theoretical biology is the geometrization of the approach to solving the problem. It seems natural to suppose that the genetic world of nucleic acids and the world of proteins should function in a space of the same rank of symmetries, but with a certain difference in material carriers. We are talking about the relations of symmetries in primary, secondary, etc. structural levels in nucleic acids and proteins. At the same time, both systems should be built hierarchically to have executive

and regulatory subsystems. A chiral dualism of elements at all levels of the structural organization becomes a natural tool in structural correlations in these subsystems. The purpose of biological hierarchies is the ability to combine processes of different scales in space and time.

We believe that the homochirality of amino acids, ribose, and deoxyribose is a free energy resource and an essential tool for folding and stratifying intramolecular and supramolecular structural levels. The symmetry factor associated with the formation of a cascade of chiral structures determines the optimal folding trajectory, which is a key problem in the molecular dynamics of the folding of the primary peptide chain into a unique protein globule or fibril forming a molecular machine.

The developed principle is relevant for biophysics and molecular biology since it reveals an analytical physical criterion not associated with a specific (bio)chemical "filling" of macromolecular structures, but determines the mechanisms of structural discreteness based on sign-alternating chiral motifs. The existing gradations of biomacromolecule structures are based on their qualitative description. In the known concepts of the structure of macromolecules, there is no single through criterion similar to sign-alternating chirality allowing to reflect the discreteness of the structural levels of biomacromolecules as a universal invariant.

The existing theories and models of folding are based on physical concepts related to isotropic systems. The symmetry factor can act as a component of the entropy contribution to the free energy change during the folding process. This approach is based on the phenomenon of chiral dualism as a stratification tool in the hierarchies of sign-alternating chiral structures of macromolecules and supramolecular formations.

Thus, the authors propose a systematic approach that allows forming a physical concept of a single periodic space of molecular biology within the framework of symmetry breaking and chiral dualism ideas.

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