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REVIEW

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The Chain of Chirality Transfer as Determinant of Brain Functional Laterality

Breaking the Chirality Silence: Search for New Generation of Biomarkers; Relevance to Neurodegenerative Diseases, Cognitive Psychology, and Nutrition Science

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Abstract

Biomolecules are the products of an evolutionary history. As a result, the phenomenon of molecular chirality is relevant to protein folding, neuronal proliferation, brain functional laterality, as well as the nature of cognition, consciousness, behavior, and psychiatry. Molecular chirality, discovered by Faraday (1846) and Pasteur (1848), helped to reveal that the biochemistry of the living beings has a prevalent chirality. At present, the essence of biochirality is widely recognized, appreciated, and exploited in neuroscience and psychology. In a more general sense, molecular chirality is recognized as the universal "Force of Nature." From the formal geometrical perspective, a chain of chiral bifurcations is the chain of the chirality transfer between the molecular micro-, meso-, and macro-scales. Consequently, the symmetry is considered as a critical issue in the brain information processing. The fundamental laws of information theory reflect the relationship between entropy, symmetry and information. At the cellular level, signal transduction mechanism involves the wave of chiral transformations in the process of protein-protein, protein-phospholipids, and protein-DNA interactions. The symmetry dynamics at the molecular and cellular levels are considered in connection to the laterality of cognitive functions. The abnormal symmetry dynamics viewed as a primary reason of an aggregation of mis-folded proteins in the neurodegenerative diseases and psychiatric disorders. The molecular basis of the "symmetry evolution" in the biological systems is a question of interest. In this short review, we briefly summarize advances in the broad field of biochirality connecting two poles of the phenomena: the atomic orbitals and the brain's cognitive function. Analysis of current results allows introducing the new generation of entangled biomarkers ranging from the molecular chirality to laterality of cognitive and executive functions.

Introduction

The essence of biochirality[I] is widely recognized, appreciated and exploited. Partially it is illustrated by chronologically sequencing citations from the publications in the diverse branches of the science. "Almost every biochemical process occurring in the cell of all living organisms is based on some specific, stereoselective interaction between reacting molecules" [1]. "From a chemical point of view, proteins are by far the most structurally complex and functionally sophisticated molecules known" [2]. "Stereospecificity is one of the hallmarks of enzyme catalysis" [3]. "One of the most dramatic aspects of biological systems involving proton transfer is their high stereoselectivity" [4]. "Chirality plays a fundamental role in the activity of biological molecules and broad classes of chemical reactions" [5]. "Controlled mirror symmetry breaking arising from chemical and physical origin is currently one of the hottest issues in the field of supramolecular chirality" [6]. "Chiral recognition is the fundamental property of many biological molecules" [7]. "Chiral compounds…pose the significant impact on the understanding of the origin of life and all processes that occur in living organisms" [7]. "Cell chirality may be a general property of eukaryotic cells" [8]. "Chirality is one of the ubiquitous phenomena in biological systems" [9]. "Consistent left-right (LR) asymmetry is a fundamental aspect of the bodyplan across phyla" [10]. "Among the most readily observed topological features in natural structures are chirality, hierarchy, and hierarchy of chirality" [11]. "Chirality is a fundamental property and vital to chemistry, biology, physics and materials science" [12]. In most general sense, molecular chirality is appreciated as the universal "force of nature" [13]. "How chirality at one length scale can be translated to asymmetry at a different scale is largely not well understood" [12].

In such situation, it is reasonable to view the enormous amount of facts of biochirality as the hierarchical system unifying by the common underlying mechanism.

Stereospecific Phenomena

Chirality

The chiral, spiral and helical structures and shapes are seen in the morphology of many physical [15] and biological [16] systems including the spiraling of plants [17] the shape of the mammalian cochlea [18], and the shape of human brain [8]. In any organism, the geometrical patterns are seen in a position of the heart and visceral organs [10], and in the spatial distribution of brain activity [19]. Left-right asymmetry recognized as a fundamental property of the brain, evident at all levels of an organization, including molecular, cellular, morphological, and functional [20-23]. At the same time, it is well known that the majority of biologically active molecules such as amino acids [22], proteins [23], carbohydrates,[II] and phospholipids [24] are chiral. The ability of proteins to fold into the chiral sec-

[I] We assume that the readers are familiar with the basic concept of the chirality in relation to the theory of symmetry groups, quantum electrodynamics, and stereochemistry [14].

[II] Carbohydrates contain multiple stereocenters, allowing many forms of isomers including enantiomers, diastereoisomers, and epimers.

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ondary, tertiary, and higher-ordered structures assumed to be responsible for their prominent role in the chirality transformation events. The members of protein family known for chirality related functions include enzymes[III] [25], cytoskeleton molecular complex [26], amylogenic proteins [27,28], trans-membrane proteins – ligand complex [29], drugs[IV] [30,31], and antibiotics[V] [32,33]. For the purpose of our review we will restrict our attention mostly to the proteins and phospholipids.

Chirality Prevalence (Amino Acids, Sugars, Phospholipids, Water)

Most of the bio-compounds have prevalent chirality (phenomenon of homochirality).[VI]

AMINO ACIDS/PROTEINS. Among more than 700 naturally occurring amino acids only 20 are involved in the proteins synthesize. All of the alpha-amino acids are chiral (exept glicine). The essential chiral amino acids are L-configurations[VII] ("left-handed"). The amino acids stereo-chemistry is the major determinant of protein chirality. It is meaningful that the spatial configuration of amino acids in the organic world, as a rule, is governed by enzymes (i.e. proteins) [25]. The evolution known plays a pivotal role in the mechanism of protein folding. Chiral proteins, as the principal constituents of neuronal cells, provide molecular machinery for the lateralized brain cognitive functions.

SUGARS. The sugars are D-configurations ("right-handed").

PHOSPHOLIPIDS. The majority of the membrane phospholipids[VIII] is right-handed, but in the archaea (single-celled organisms) membrane they are left-handed [24,34]. Furthermore, the membrane phospholipids are right-handed [24,34] but in an archaea (single-celled organism)[IX] membrane, they are left-handed.

WATER. The water molecules (H2O) as the main constituent of the living organism are in the scope of our consideration. In a homogeneous, achiral environment, the H2O molecules possess neither a chiral center nor a helical conformation that can cause spontaneous chirality effects. Accordingly, many assume (at first glance) that water falls apart from phenomenon bio-chirality. However, this view was challenged by studies that devote more close attention to the dynamics of water structure in the chiral environment (proteins, phospholipids, polysaccharides) and dynamics of chirality. In the variety of the "inhomogeneous" situations, water molecules dynamically participate in chirality-related effects. Among such conditions, we can point on the aggregation of water molecules into clusters [38], interaction with magnetic bio-proteins [39], contact with the solid/gel/liquid surface [40], interaction with the chiral solutes [41,42], and dehydration synthesis of proteins (via covalent bonds of amino-acids). In particular, it was shown that structured water exhibits a chirality adapted from DNA [43]. The presence of hydrophobic, hydrophilic, and intermediate groups in the amino acids and phospholipids contributes to the variety pathways of spatial arrangement. The body of accumulated evidence (despite the variety of distinct pathways) suggests some common causal agent in the chain of events from the molecular chirality to the origin of body/brain morphology and function. This "universal agent" is the spatial relationships between the objects linked to the fundamental geometrical patterns of space and force fields.

Biological Evolution as a Chain of Chiral Bifurcations

The pathway of life can be perceived as an "increasing chemical and physical complexity" [44,45]. In a more particular sense, the biological evolution considered as the chain of chiral bifurcations [46].

The symmetry effects propagate from the level of molecular spatial transformations, intracellular /cross-membrane molecular transport, cell motility, to the higher hierarchical level of the spatial organization such as the cell proliferation [47], immune defense, environmental chemistry [49], motor behavior, brain cognitive functions, human psychology [50], psychiatry [48,51-53]. The symmetry effects play a critical role in food preparation [54,55], pharmaceutical industry [56,57], design of molecular devices (biosensors and information processing units. Symmetry is considered the critical issue in the theory of information processing and the design of artificial intellect[X] [58]. The hierarchy of biological structural organization arms an organism with the abilities of adequate response to environmental challenges of differential time-space ranks.

Origin of Biological Homochirality

The homochirality is usually associated with bio-molecular objects (distinct from non-biological objects). There is an objective reason for this specificity. The biological homochirality known to be essential for the molecular recognition, protein replication, post-translational modification, and degradation processes.

The origin of homochirality in biology is the subject of much debate. The emotional view on bio-chirality is frequently associated with an expression such as a symmetry breaking,[XI] enigma, puzzle, or mystery. More rational scientific approaches exhibit some degree of uncertainty, but always are ready to move forward along with the newly-coming objective evidence. After works of Prelog, the discussion of an origin and maintenance of homochirality was shifted from the intuitive, emotional domain to the ground of scientific facts [59]. The cumulative advance in chiral physics, chemistry, and mathematics sheds light on the phenomenon of chirality in general and on biological homochirality in particular. Several decades ago Frank developed the mathematical model[XII] for the spontaneous autocatalytic reaction as the mechanism for the evolution of homochirality [60,61]. Recently it was shown that the origin of molecular homochirality could be attributed to the non-equilibrium state of biological systems. The Vester-Ulbricht hypothesis, based on the interaction of the left-handed electrons (present in beta-radiation) with biological materials which preferentially destroyed one of the two enantiomer, was the first step in the right direction [62,63]. This hypothesis was successfully tested experimentally [64]. The sensitivity of molecular chirality to external determinants becomes one of the most productive ideas. The classic experiment of Viedma reveals that the bulk and dispersed solid state crystals show different dynamics of solid-liquid phase transition, which, under certain conditions, can be utilized to achieve an enantiomeric preference [65]. The following studies of the chirality dynamics in the solid-liquid phase system leads to several models presumably providing the mechanism implicating for the origin of biochirality. Among them is the model based on the different solubility of homochiral and heterochiral crystals [66] and "chiral amnesia" model [67,68]. The review of current hypothesizes on the biological homochirality in connection with the recent discovery of the interstellar chiral molecule can be found in multiple sources [10,44,69-71]. The new finding reveals the fundamental significance of the symmetry transfer (1) and symmetry-associated phase transitions (2) in resolving the origin of biological homochirality [44,70,72]. Among them are the chiral recognition/selection during the self-assembly of protein-mimic macro-anions [73], chiral recognition in the transmitter-receptor interactions [74], the chirality-induced conformation of the cell membrane lipid rafts[XIII] [75,76], and the phase-transfer chiral catalysis[XIV] [77]. The chiral catalysis is productively utilized for symmetry-asymmetry

[III] The enzymes determine the crystallization of chiral amino acids [25] and the "handedness" (chirality) of the proteins during catalytic synthesis.

[IV] The enantiomers of a drug, as a rule, are differing in potency, toxicity, and behavior in biological systems.

[V] The advance in enantio-separation of the antibiotics reveals the significance of chirality in their biological activity [32,33].

[VI] Phospholipids and cholesterol both contain chiral carbon atoms and could themselves mediate stereoselective effects [35].

[VII] Brain tightly regulates the balance between the levels of right- and left-handed amino acids for proper structure of functional proteins [22,36,37].

[VIII] It is essential to know that homochirality is always relative (not absolute). There are many examples in nature where polypeptide topologies use both: L- and D-amino acids [36,37]

[IX] Archaea are classified as microbes (single-celled prokaryotes).

[X] It is notable that the design of an intelligent human-made sensing system is based on the discrimination of the object chirality and the use of chiral shape-defined polymers such as the dynamic helical polymers [58].

[XI] At the molecular level, the term "symmetry breaking" refers to the imbalance between two enantiomers.

[XII] The main idea is that a substance acts as a catalyst in its own self-production and at the same time acts to suppress synthesis of its enantiomer.

[XIII] It has been suggested that the chiral nature of cholesterol plays a role in the process of the bud formation [85].

[XIV] The variety of intracellular chemical reactions is mediated by seospecific enzymes. Many catalytic mechanisms require stereospecific deprotonation and reprotonation steps [77]. The L-amino acid active center is the primary determinant of catalytic activity. Thus, L-amino acid actively transfer chirality to the stereospecific enzyme activities [77].

transformations in biochemistry [78]. The phenomenon of chirality is common to all aspects of animal life and body/brain morphology, including the internal organs, the sensory systems, the central nervous system, and behavior. In particular, it pertains to sensory perception [79], motor-behavior [80], and food consumption [54]. All of the arguments related to the origin of the biological homochirality, including terrestrial [44] and extraterrestrial [81,82] are based on the common and experimentally proved effects. The sensitivity of chiral molecules to the internal, external, and mutual (internal-external) physical (objective) parameters [83]. While you can find discussions of the many particular local physical parameters, in the majority of current reviews, you will almost never find discussions about of the global parameters, such as the chirality of space-time evident in the physical systems [83,84].

Transformation of Bio-Chirality

Symmetry transformation is traditionally considered to be the spontaneous processes accompanying all of the molecular interactions (phase separation and phase transition), including symmetry breaking and molecular folding in relation to information minimization or symmetry maximization [86]. The symmetry dynamics at the molecular level are frequently considered to be the mechanism responsible for the laterality of cognitive functions. Thus, the laterality and hemispheric asymmetry should be regarded as the indispensable attributes of the brain. The molecular basis of the symmetry evolution in biological systems is the question of interest. Current evidence suggests that integration of the internal and external determinants [84], as well as global and local signaling pathways, is necessary for orienting the diverse levels of structure with respect to the body/brain axes [87-89]. In particular, the integration is evident in the hierarchical chirality transformation accompanying the planar cell polarity[XV] in the epithelium, sensory organs [90],[XVI] and the brain morphology [89].

Dynamic Organic Reactions

The spatial interpretation of molecular structures was advanced (1874) by the concepts of the tetrahedral orientation of carbon's four bonds by Van't Hoff and optical isomerism by Le Bel [91,92]. These ideas, in turn, gave rise to the stereochemistry of chiral stereoisomers. It was realized that the spatial orientation of different functional groups governs the patterns of specificity in chemical reactivity [93]. The interaction between the chiral and achiral components was widely studied in the biological organic reactions. The dynamics of organic reactions (in particular those that take place within the spatially ordered environment of an enzyme protein interaction) exhibit stereoselectivity and stereospecificity. The excellent review of the stereo-dynamic of chiral objects, including natural molecular structures and artificial molecular devices, can be found in [94]. It is notable, that both the stereoselectivity and stereospecificity are based on the recognition of the symmetry-related characters (such as polarity, chirality, and helicity). Thus, a conclusion such as "chiral recognition is the fundamental property of many biological molecules" is not surprising [7].

Diversity of Stereospecific Phenomena

The diversity of stereospecific (chiral) phenomena was observed in molecular structures including chirality recognition/sensing [95,96], chirality transfer [97], chirality/helicity induction [98-101], chirality amplification [102-104], chirality breaking [61,105], chirality conflict [106,107], helicity inversion [108-110], and chiral phase transitions[XVII] [111-114,116]. Progress in the studies of molecular chirality transformation is helpful in resolving three questions. First, what kind of determinants can provide a favor in the production of one enantiomer over the other? Second, what is the mechanism of intermolecular propagation and preservation of chirality? And third, what is the mechanism of chirality propagation from the molecular level to a higher degree of biological organization?

Chiral Phase Transitions in Relation to Chirality Transfer

Physical System

Among the variety of the topological phase transitions [120-123] several sub-categories, including the order–disorder [118], chirality-related [119] and geometry-induced [120,123] transitions, were discovered. In condensed matter physics, phase transitions exhibit sensitivity to external physical parameters (pressure, fields, electro-magnetic radiation, sonication,[XVIII] and doping). The systematic study of these phenomena has revealed a new class of phase transitions, called "quantum phase transition (QFT)". Spontaneous QFTs take place at the mesoscopic level at zero temperature and are driven by the quantum fluctuations[XIX] (according to Heisenberg's uncertainty principle). For the two above facts, the sensitivity to external physical parameters and the concept of the spontaneous phase transitions are of great importance.

Biological Systems

In relation to the biological systems, the chirality of the sub-cellular structures (such as hair bundles) was observed in auditory and vestibular sensory neurons of vertebrates [87,118]. The phase transitions are the common effects, observed in the chiral molecules with pyramidal atomic centers such carbon and nitrogen. The frequency of a pyramidal inversion (tunnel quantum-mechanical effect) depends on the value of the energy barrier and set of external physicochemical factors. Chirality transfer from molecular to morphological level is observable in a diversity of physical objects as well as biochemical and synthetic materials [124,125]. The hierarchical propagation of chirality was found between the objects of different size, shape, and dimensionality [126]. The chirality breaking in the nonequilibrium systems (Bloch walls) was studied in magnetic materials [127]. Recent progress in the development the concept of "active fluids" reveals the chiral behavior of a class of nonequilibrium systems, which include bacterial suspensions of a bacteria, cytoskeleton proteins, and biological tissues. Even relatively simple combination of chiral and achiral stresses, leads to an "unprecedented range of complex motilities, including oscillatory swimming, helical swimming, and run-and-tumble motion" [128].

Chirality Transfer

Variety of Spatially Related Events

Among the variety of spatially related events, the phase transitions and the symmetry transformations are known as the most closely associated. We will focus mostly on the phenomena of the chirality transfer. The chirality transfer from the molecular to morphological scales was documented in nano-materials [124] and polymers [125]. The studies of the plant's growth reveal the "hierarchy of chirality" which transfers from the molecular (lower) levels to the macro-morphological (higher) level [130]. In our review, we explore what is currently known about how the molecular chirality is transformed into to the laterality of cognitive functions.

Sensitivity of Chirality Transfer to Internal, External, Local and Global Conditions

Symmetry transformation arising from chemical and physical origin is one of the hottest issues in the field of molecular chirality [5-8]. Before the further consideration it is essential to emphasize that hypothesis about the distinction between internal and external determinates in the living organism being very productive could become irrational in the form of an absolute opposition. The most convincing example of the link between external and internal factors is the function of a digestive system, which permanently transforms the external factors into the very internal. Pasteur (1861-1887) was the first who introduced an idea regarding an interaction between the polar physical fields (electrical, magnetic, electromagnetic, gravitational/mechanical) with atomic/molecular chirality [131]. He

[XV] Planar cell polarity (PCP) "is driven by multiple global cues, including gradients of gene expression, gradients of secreted ligands, and anisotropic tissue strain" [117].

[XVI] The chirality of the sub-cellular structures (such as hair bundles) was observed in auditory and vestibular sensory neurons of vertebrates [87,118].

[XVII] The formation of supramolecular helicity is associated with the occurrence of new thermodynamic phases. The chirality related effects in thermotropic and lyotropic liquid crystals were demonstrated through the ferroelectricity [115]. The phase transitions were shown to be implicated in the effects of the chirality transformation and monochirality observed in the amino acids and proteins [119].

[XVIII] The sonication-induced chiral symmetry breaking events were observed during sol-gel phase transition [129].

[XIX] The quantum fluctuations are associated with Heisenberg's uncertainty principle.

was also the first who realize the fact of the chirality transfer from the molecular level to the level of macroscopic solid crystal [132]. The ideas were great, but the success was limited. Much later the empirical evidence of the role of the forces of nature on the chiral compounds was obtained. The early idea of Pasteur was supported by modern experimental capabilities [133,134]. Two essential facts were observed: the effect of magnetic field on the molecular chirality [135] and increased enzyme stereo specificity in the course of an enzyme/protein evolution [136,137]. Both results, accompanied by the discovery of the spontaneous [138] and induced chirality provided the tools to disclose the previously mysterious homochirality of life [139]. In particular an essential result was derived by Barron [140]. He demonstrated that supramolecular helices formed from achiral monomers have been controlled by applying the combination of the gravitational and rotational forces [140]. The transfer of stereochemical information (in the form of chirality and helicity) was observed between chiral and achiral constituents of the molecular complexes in general and of biological systems in particular [141-144]. The transfer of chirality from protein to the cellular and embryonic level was suggested in several studies [145,146]. The critical role of a molecular and cellular chirality as the determinants of LR asymmetric in the animal body, and functions has gradually emerged [8]. The explosive advance in the study of asymmetric catalysis over the last four decades has dramatically altered the view on the biomolecular chirality dynamics [147,148]. Before the era of chiral catalysis, the most common characteristic of the enantiomers was the absence or little difference in the chemical and physical properties. At present at the majority of publications related to chiral catalysis we can meet the statements like "enantiomers have different properties". Resent progress in the synthesis of the chiral compound associated with the study of the catalytic asymmetric reactions of carbonyl compounds, allow an understanding of the principles governing the dynamics of structural conformations in the amino acids and proteins of the living organisms [149]. Molecular chirality and correspondently a chirality transfer are recognized as sensitive to the broad range of modulators including the internal, external, localized, and diffused determinants. It is notable that molecular chirality exhibits sensitivity to all types of the chemical binding including ionic, covalent, and not-covalent [58].

The generation of chiral imbalance in the chiral molecular systems can occur spontaneously, due to intrinsic instability or induced by external factors [102]. In accordance with this instability, the chiral self-organization of molecular complexes is sensitive to the impact of many external factors including electrical (metal ions), magnetic, electromagnetic (photon), mechanical, and gravity force fields. The discovery of magnetically induced optical activity by Faraday was the first demonstration of the sensitivity of a molecular chirality to the physical parameters of an environment[XX] [150]. Since then, the sensitivity of the chiral objects to the environmental parameters has been explored at cosmological [151], molecular [152], atomic [57], and elementary particles levels [153]. Thus, it is reasonable to be aware that different molecular structure can have the same or different physical properties depending on the nature of the physical effect and chemical environment.[XXI] In the specific case of the stereoisomers interaction with an electromagnetic field, we have at last three different situations depending on the energy diapason (such as IR, UV and NMR spectra), and method used (such as the circular dichroism) [40]. The photons (chiral object itself) of different energy interact with the chiral components of the molecular complex (such as electron or proton) compromising its equilibrium spatial configuration. The recent discovery of the quantum chiral light–matter interaction offers fundamentally new functionalities for the charity transfer of the bio-molecular structure related to brain quantum information-processing capability [160]. The chiral molecules reveal the capability of the self-organization of the helical superstructures. The intermolecular interactions related to the modulation of chirality are the part of the supramolecular chemistry [161-165] and interfacial sciences [166,167]. The chiral sensing based on the concept of chirality transfer is of great importance.

Chain of Cirality Transfer

Several relatively new fields of science provide the bridge between dynamic chirality in solid matter physics and bio-chirality. The chirality transfer (or the transfer of handedness) is observed between organic and inorganic molecular structure [168]. The central point of these studies is the chirality transfer in the variety of forms.[XXII] Among them, we can mention the stereo-physics of liquid crystals [126] and chiral catalysis [169]. The modeling macroscopic chirality emerged from the chiral molecular elements is a challenge for theory, computations, and experiments [126]. Numerous experimental results demonstrate the transfer of chirality among different length scales ranging from dimensions of the elementary particles to the macro-scale (the length of the axon) [124]. In particular, it was shown that the chirality at the molecular scale (amino, acids, proteins, and polysaccharides) could be transferred to the macroscopic and macro-level (neurofilaments and inorganic crystals) as shown in [168]. The issue of dimensionality in the chirality transfer effects is critical for brain information processing in the brain and artificial intelligence devices.[XXIII] The examples of macroscopic chirality are found in the plant kingdom, animal kingdom and all other groups of organisms.

Physical Systems

In the quantum spin systems, the symmetry-related phase transitions [78,154,155] and the transfer of the stereospecific (symmetry) characters [XXIV] [97,156] are well-known phenomena. The recent advance in the experimental and theoretical areas of many disciplines related to stereochemistry revealed the chirality-induction effects in the various inorganic materials with mono-chiral and hybrid-chirality structures including plasmonic, semiconducting, metal oxide and silica-based compounds [170]. The most prominent among the field-induced chirality effects are the following: Coulomb (near-field, dipolar), electromagnetic, and plasmonic mechanisms [171]. The chirality transfer from the spin-quantum system of elementary particles to the atomic structure level is an essential element of basic knowledge and serves as the necessary introduction to the understanding of the chemistry and biochemistry. The nuclei of atoms and associated electron system have an innate chirality. The chemical phenomena are viewed as associated with the chirality of electron system and nuclear[XXV] constituents [172]. The molecular chirality is the consequence of the chirality transfer from the dynamic complex of elementary particles. The transfer of molecular chirality from monomers to polymeric structures has been widely explored and utilized [173]. The advanced field of chiral photon–electron /proton interaction reveals the sensitivity of chiral objects to the physical environment. As a result of such sensitivity, chiral photonelectron/proton interaction offers fundamentally new functional opportunities for information transfer technology and info-processing systems. In particular, the non-reciprocal single-photon devices allow utilizing the quantum information processing based on the superposition of two operational states in chiral spin–photon system [160]. Thus, the stereo-specific effects, including the chirality transfer, are not the unique properties of the organic world.[XXVI] Quit contrary stereospecific effects are the universal and fundamental character of both organic and inorganic materials.

Biological Systems: Basic Set of the Chirality Transfer Levels

From the physical world chiral events diversity and complexity point of view our primary concern is the chain of the chirality transfer in biological

[XX] Following Faraday's discovery [150], Pasteur tried to grow chiral crystals in the presence of magnetic field [157].

[XXI] The NMR spectra of two stereoisomers can be identical or differ depending on the chirality of an environment (solvent).

[XXII] The effect of chirality transfer is routinely used in nuclear magnetic resonance spectroscopy for the discrimination of the molecular stereoisomers absolute configurations [158].

[XXIII] The chirality transfer from monomers to a polymer is widely used in plastic engineering [159].

[XXIV] The process is frequently referred to as the chirality transfer.

[XXV] "All nuclei are innately chiral and, because electrons can penetrate nuclei, all atoms and molecules are likewise chiral" [172].

[XXVI] It is notable for the sake of our review that the spiral galaxies are the objects showing preferred chirality analogous to amino acids and sugars [175]. According to a contemporary view, the origins of the elementary particles and chemical elements are associated with the physical events at the galactic scale [176].

systems. The very essential prediction of the sequential chain of chital events in the organism was done long before the modern progress in biostereochemistry [174]. Taking the review of newly discovered facts as a basis, we will clarify the natures of elements in this chain and the hierarchy of these elements within the chain. Referring to the hierarchy of a chirality transfer, we will assume (based on the review of current publications) that it consists of several distinct levels. The basic set of these levels includes the transfer of following types:

- From the elementary particles to the atomic orbital level
- From the atomic orbital to the molecular level[XXVII]
- From molecular to macro- and supra-molecular level
- From the molecular level to the cellular level
- From the cellular level to neuronal circuits level
- From the cellular to morphological level
- From the morphological to cognitive level
- From the cognitive to the behavioral level

After reviewing the elements of the chiral hierarchy, we will examine what is currently known about the sensitivity of each of the hierarchical levels of chirality to the internal and external determinants. The chirality transfer occurs under the influence of physical and chemical determinants which play a role of the "chirality directing force." The stochastic fluctuations in parameters of an environment could result in the transient fluctuations in the relative prevalence of enantiomers [178], while long-term fluctuations will lead to permanent effects giving a chance for amplification and preservation mechanisms. Several reviews provide information about the range of chirality related events [44,45]. Finally, the degree of "stereo-sensitivity" will reveal the multi-variable pathway contributing to the evolution of the brain cognitive functions.

From Elementary Particles to Atomic Level

The chirality transfer from the elementary particles to the arrangement of atomic orbital was considered in the previous paragraphs. The energy difference (parity violation) between the ground and excited states of molecular enantiomers in the presence of weak nuclear force is predicted by theory and proved experimentally [179,180].

From Atomic Orbitals to Molecular Level

The wavefunctions of electron orbitals are traditionally considered to be the determinants of the molecular chirality [14]. Consequently, in the stereochemistry, the spatial arrangement of the atomic orbital is the primary determinant of the chiral center's function in bio-molecules, including the amino acids, sugars, and phospholipids. At present, it is a common recognition that the electronic orbitals of the carbon atom constitute the root contributing to the molecular chirality[XXVIII] [181,182].

From Molecular to Macro-Molecular and Supra-molecular Level

The alterations of brain molecular chirality, represented in particular by the proteins or lipids constituents, are accompanied by the changes in the left/right asymmetry of the synapse (cellular chirality), asymmetry in the regional brain morphology, and laterality of brain functions in many experimental situations. In this sense the molecular chirality, is the principal initiator of the origin of the life. We will review the chirality transfer events in the order of their natural sequence. The transfer of the symmetry patterns (chirality-induced helicity or chirality-helicity transfer) from the amino acids to peptides [179] and proteins [181] is broadly studied. Four main categories of biological-macromolecules, which exhibit chirality, are proteins, lipids, carbohydrates, and nucleic acids [180,183].

PROTEINS. In the human body about 100,000 different proteins introduce the charity phenomenon for all the key physiological, perceptual, cognitive and psychological function of an organism. The chirality transfer from amino acids to proteins secondary and higher order structure is one of the most studied fields in biochemistry. The chirality of protein folding gained attention in condensed matter physics [14,184] and molecular biology [36,185]. The stereo-transformations of proteins are a highly dynamic field of science involving the most advanced analytical capabilities [146,186-196]. The protein's stereo-transformations is the area of particular interest in the neuroscience due to relevance to proteins aggregation disorders such as Alzheimer's, Parkinson's, and Huntington's disease (AD, PD, HD).

CELL MEMBRANE (PHOSPHOLIPIDS AND CHOLESTEROL). A similar mechanism is responsible for the transfer of molecular-level stereo-specificity (chirality) to the supra-molecular level (helicity) in cell membrane rafts during endocytosis [197]. The establishment of helical handedness can be formed at the macro-molecular level due to the stereo-ordering regularity of constituted chiral entities at the intra-molecular and inter-molecular interactions [198]. The chirality transfer from the molecular to the supramolecular level (nanometer and micrometer scale) and the morphological level was observed in the inorganic liquid crystals [115], polymers [198], and bio-polymers[XXIX] including cellulose, sugars, proteins, RNA, and DNA.

From Molecular to Cellular Level

The origin of cell chirality and its role in the upstream laterality are the subject of many reviews [7]. The review of current studies suggests that "molecular chirality direct whole-cell chirality [8]. The chirality transfer from the molecular (cytoskeleton proteins) to the cellular level (cell wall and cell shape) was demonstrated in the bacterium [199,200,201, 202]. Cellular chirality, in a variety of its forms, is governed by crosstalk of the internal and external determinants.[XXX] Chirality at the cellular level was first studied mostly in ciliates or single-celled protozoans. These studies reveal that molecular chirality directs whole-cell chirality[XXXI] [8]. At the cellular level, signal transduction involves the wave of chiral transformations in the protein-phospholipid interactions [204-206].

From Cellular to Morphological Level

The chirality of the biomolecules and the intrinsic cell chirality observed in various organisms appear to be a causal event for the left–right (LR) asymmetric of morphogenesis [8,130]. The multiple pathways of chirality transfer from the molecular cytoskeleton dynamics to the cellular behavior, and to organ asymmetry were found [10]. As was mentioned above, the cell-shape chirality (cell chirality) is found to be driven by an intrinsic molecular mechanism comprising from the family of chiral cytoskeleton proteins [203]. In turn, the chirality transfer from the "chiral cells" to an organ occurs by the process of "planar cell chirality" (PCC). According to the early observation of Brown and Wolpert "the spiral asymmetry, as seen in spiral cleavage and ciliates, involves the conversion of molecular asymmetry to the cellular and multicellular level" [174]. In particular, it includes climbing plants tendrils [207,208], flower petals [209], and shells [210]. In the literature, the cellular and morphological hierarchical levels of chirality transfer are frequently considered together. It is notable, that chiral morphology exhibits the prevalence of the handedness [211]. The coherent and quasi-independent role of the intracellular (gene expression and cytoskeleton dynamics) and extracellular (cilia) determinants in

[XXVII] Due to the topic of our review, we discussed very briefly (just mentioned) the two polar elements in the chain of the chirality transfer: the physic of elementary particles and space-time chirality of an environment. Actually these two elements are seemingly-polar only within our "hierarchical chain". In the nature they are inherently linked to each other by concept of space-time symmetry. Thus the linear sequence of chiral events, in this consideration, becomes a natural circle of the chiral transformations. For those who are interested in the quantum aspects of the chirality transfer we recommend to explore the "chiral effective field theory" [177].

[XXVIII] Molecular level of the chirality transfer cover the broad range of molecular structures from small molecules (such the amino acids) to the large complexes including polymers (such as proteins) and globular molecules.

[XXIX] Among the biopolymers, we will mostly concentrate on the proteins.

[XXX] Support of this statement speaks to the fact that the cells isolated from developing organism undergo the symmetry transformation even in the absence of the external signals [8].

[XXXI] Several chiral compounds exhibit capability to block cell proliferation suggesting their relation to issue of the cancer treatment [47].

the initiation of the embryonic asymmetry were studied in Caenorhabditis elegans, Xenopus, snails, Drosophila,[XXXII] frogs, chicks, and mice [8,212]. The interaction of proteins and phospholipids chirality at cellular level finally result in the asymmetrical distribution of major CNS receptors[XXXIII] between left and right cerebral cortex [213].

From the Morphological to Cognitive Level

The chiral, spiral or helical shapes are seen in the morphology of many biological systems, including the spiraling of plants, and shape of the mammalian cochlea [18]. During animal development, chirality transfer repeatedly occurs at the different levels and scales of spatial organization. As we will see later, each lower-level (in the hierarchy of symmetry transformation) generates the higher level of the morphological and functional specialization. The functional specialization of the nervous system at the molecular (intracellular) level is always under impact of the extracellular events. The functions on the cellular and organ (brain) level, in turn, are always under the acute influence of evolutionary preserved behavioral paradigms. The studies of the association of brain function with the body's reflexive reactions and goal-oriented movement were initiated by works of Pavlov in relation to the conditioned and unconditioned reflexes [214]. The ideas of Pavlov resonate with the earliest thoughts of Plate and Aristotle regarding the succession of memory events and modern theories of cognitive association. Brain asymmetry at the structural level begins to be apparent in the fetal brain in humans and nonhuman primates [215]. Brain laterality at the functional level is considered to be a result of morphological laterality [216]. The higher-order cognitive functions are associated with the spatially distributed activity of cerebral cortex. The anatomical asymmetry of the human cerebral cortex is exhibiting a three-partial differentiation. First-the torque {right frontal and left occipital areas are more prominent in size} [217]. Second-the leftward volumetric dominance in language-related areas [218,219]. Third-the left-right asymmetry in cortical thickness (right biased in frontal and left biased in parietal regions [220-222].

The discrimination between sleep and evoke brain activity with fMRI and EEG techniques demonstrates objective (and now trivial) link of the quantum dynamics of proton and electron with the faculties of space perception,[XXXIV] and consciousness [223,224]. The chirality transfer from the morphological level to functional brain laterality is considered in the plenty of the articles, reviews, and monographs [44,224-226].

From Cognitive to Behavioral Level

Chiral information is used for social communication in the variety of species from insect[XXXV] to human[XXXVI] {face expression and perception} [228,229]. Diverse explanations have been proposed for the origin of the behavioral laterality including space constraints [230], as well as genetic, and ecological determinants. The link between the molecular, functional, and behavioral laterality is the focus of many studies. It is known that lateralized expression of the neuro-receptors serves as internal positional markers (compass) to distinguish the left and right hemisphere. Long time ego these markers were hypothesized to be necessary during ontogenesis for bilaterally-symmetrical brain formation and performance the hemisphere-specific perceptual and cognitive functions [231]. In particular, it was shown that the circle rotation of animal, which is mediated by several neurotransmitting systems, significantly contributed by an asymmetric expression of the hypothalamic neurohormones (such as somatostatin, substance P, and others [232]. Thus behavioral studies support the idea of a hierarchical chain of the chirality transfer.

Biological Transport, Information Processing, and Cognitive Systems

It is reasonable to mention here that the chirality transfer is relevant to three essential issues associated with space topology: the biological transport, information processing, and principle of cognition. A wide range of the coordinated motions, including the locomotion of organisms, spatial displacements at morphological (muscle fibers), cellular (flagella, cilia, synaptic spine) and molecular levels (protein fold, lipid chirality) are based on the principles of the chiral dynamics [91]. It has become clear that the evolutionary design of biological molecular motors acts upon the chirality transfer from the amino acids to the helical chirality of proteins. The biological molecular transport systems consist of two major parts: the cytoskeleton and motor proteins [233,234]. The functions of intracellular motor-proteins inspired the engineering molecular motors [235,236]. The advance in the design of artificial molecular motors promotes the understanding of the mechanism of intracellular transport [112,202,237, 238]. Thus not only the lower level biological features like the molecular transport, neuronal signaling, but also the higher level features such as sensory perception, brain information processing, and cognitive functions in general are related to the modality of chirality transfers.

Conclusion

Noether's Theorem

Noether's theorem states that each conservation law[XXXVII] is associated with symmetry in the underlying physics [239]. The universal role of symmetry principles in the stereochemical configuration traditionally discussed in relations to the fundumental theorems of Noether, Ruch, and Gödel (240,241). From the platform of modern science, each of the conservation and violation laws is fundamentally associated with the preservation or alteration of the symmetry-related parameters. These universal laws are not only relevant to both nonbiological and biological objects but also are the fundamental determinants of an interaction between them. The symmetry patterns are persistently transferred between any combinations of the objects of similar or different nature.

Our Hypothesis

Utilizing the application of universal space time topology principles to the biological world, our hypothesis[XXXVIII] state that the link between molecular chirality and laterality of the cognitive function is based on the universal law of symmetry. Refraining known sentence "space and time are the primary forms of existence" we can say that the dynamic symmetry is the form of existence for the entire variety of the biological objects.

Biological molecules reveal the chirality (handedness) in a variety of fashions many of which are critical for the healthy functions of human body, brain, and mind. The observation of the sign-alternating hierarchies for DNA and proteins contribute to the structure-function link in biochemistry, neuroscience, and psychology [242]. The striking similarity in the chirality-related effects within a broad class of molecular, cellular, and morphological structures inspired researchers in many fields of stereochemistry and neuroscience. The advance in the current results reveals the fundamental significance of molecular chirality in the broad range of inter-related disciplines including an intracellular transport, neuro-development, sensory perception, motor behavior, brain cognitive functions, human psychology, and psychiatry. The helical structures of the proteins are known to be the consequence of amino acid chirality. The helicity of pro-

[XXXII] In Drosophila, intrinsic cell chirality is observed in various left–right (LR) asymmetric tissues, and appears to be responsible for their LR asymmetric morphogenesis. It is notable that the cell chirality can drive the LR asymmetric development of individual organs without establishing the LR axis of the whole embryo [8].

[XXXIII] The muscarinic acetylcholine receptors (mAChR), the prevalent receptors in the central nervous system, are asymmetrically distributed between left and right cerebral cortex with the right-side dominance [213].

[XXXIV] In Kant's view, space and time are a priory forms of sensibility, providing two windows' for empirical intuition.

[XXXV] The insects and many other animals use molecular chirality for olfactory perception. Insects, which use chiral pheromones, typically produce and respond to either a single stereoisomer or to species-specific blend of only some of the possible stereoisomers [227].

[XXXVI] The face expression and perception, which play a significant role in human social communication, both are the chirality related functions.

[XXXVII] Conservation Laws: Conservation of the Linear Momentum, Angular Momentum, and Energy.

[XXXVIII] Meaning that the hypothesis is based on the universal nature of Noether's theorem and is generated by the review of contemporary experimental facts and theoretical models.

teins, in turn, provides an opportunity for chiral biological macromolecular systems with higher hierarchical levels of symmetry and yet unknown functions [46,242,243]. The hierarchy in the chain of the chirality transfer, evident particularly from the current review, possesses several not trivial features. Each of the consequently following hierarchical levels is contributed to from the cumulative power of all lower and higher levels. Each level has its own quasi-independent internal and external determinants. The majority of the external determinants (including environmental) exhibit a chiral nature. As such, the chirality of external determinants is a critical factor in the evolution and development of the organism. The chirality is naturally imposed to the brain structure and function from the two seemingly opposite but fundamentally linked to each other sides: the nature of bio-molecular structures and from the geometry of the environment. The fundamental nature of the chirality transfer should be considered in the experimental design strategy in neuroscience, cognitive science, psychology, and pharmacology. In particular, the molecular chirality is a sensitive indicator of both: the proper protein folding and pathological aggregation. Accordingly, the chirality patterns (raging from molecular chirality to the laterality of brain function) should be considered as a new generation of the biomarkers in the spectrum of the disease conditions including neurodegenerative and psychiatric disorders [22,244]

Several recently published essential papers provide the broad review of the previous and current hypothesis of a perceptual and cognitive development in health [245], and pathology [246]. Referring to the limited progress in the current models, and the low efficiency of drug treatment, authors frequently appeal to the necessity of a new approach in the research of the cognitive functions mechanism. Notably that none of the above-mentioned review are focused on the issues of stereochemistry, and brain asymmetry which are a central point for the study of links between protein folding and brain functions. [247-249]. Even the reviews devoted to structure, function, and assembly of the visual system (which is lateralized and well-studied as one of the most asymmetrical) do not focused on the molecular substrate of sensory functions. The explosive attention to protein-brain topology demonstrated in this year's publications can be considered as a response to the "necessity calls" [250,245,251, 252].

Our review aims to contribute toward attention to the unifying direction for the studies of development, function, and decline of human perception, cognitive function, and action [252,253].

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