Mirror symmetry breaking of the bioorganic world: biogenic and abiogenic approaches

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Abstract

While inorganic nature contains equal amounts of different chirality type molecules, living nature is chirally pure. This mirror asymmetry of the bioorganic world on the molecular level is one of the unsolved mysteries of biology. A number of approaches to the solution of this problem were developed. Biogenic approaches claim that the property of chiral purity was selected in the course of biological evolution due to competitive advantage acquired by chirally pure organisms relative to racemic ones. According to the abiogenic approaches chiral symmetry was broken during the prebiotic stage of evolution either due to the presence of asymmetric factors or spontaneously.

1 Introduction

Symmetry is one of the central concepts of physics. In his article "More is Different" Nobel laureate P. W. Anderson wrote that "it is only slightly overstating the case to say that physics is the study of symmetry" [1]. Three fundamental types of symmetry are invariance relative to charge conjugation (C); space reversal or parity transformation (P); and time reversal (T). According to CPT theorem all physical laws must be invariant under combined CPT transformation. C- and P- invariance are conserved in electromagnetism, strong interactions and gravity. However C-, P-, and CP- symmetries were found to be violated in processes involving weak interaction. Apart from that life itself is a remarkable manifestation of P-symmetry violation on the molecular level. This is so because only certain types of molecules, not invariant relative to the mirror transformation, a special case of parity transformation, are incorporated into the living organisms. Strictly speaking manifestation of symmetry breaking is an absence of mirror symmetrical form of life composed of another type of molecules [2]. So two questions arise: why is bioorganic world asymmetric and how the direction of symmetry breaking was chosen. These questions are clearly closely related to the problem of emergence of life. In further discussion I will introduce the basic concepts and review some of the existing approaches to the problem.

1.1 Chirality

Chirality is a property of the object related to the mirror symmetry. Thus achiral object are invariant relative to mirror transfromation, while chiral objects are not. Another way to say this is that achiral objects have a plane or centre of symmetry while chiral objects does not. The most obvious everyday example of chiral objects are right and left hands. Right hand is a mirror reflection of the left and there is no continuous transformation that could match them.

On the molecular level an example of chiral molecules is aminoacids - fundamental structural units of proteins (Fig. 1). In fact, any molecule, containing an atom with four different substituents, is chiral. Such an atom is called a chiral center. Two chiral molecules, that are reflection images of each other, are called enantiomeres or optical isomers. In general, molecule can have more than one chiral centre. In that case situation becomes more complicated - chirality of the whole molecule will depend on the symmetry between chiral centers. Molecule with N chiral centers will have 2^N optical isomers and 2^{N-1} pairs of enantiomers. For example sugar pentose can have 4 asymmetric atoms, and thus 16 possible optical isomers, that can be divided into 8 pairs. Two of them - L- and D-ribose are shown on Fig.2. Nucleic derivatives of ribose and deoxiribose serve as a building blocks of DNA and RNA - the most important molecules of life.

In symmetric evironment enantiomers have identical physical and chemical properties. A distinctive property of chiral molecules is their optical activity. Enantiomeres rotate polarization plane of light in the opposite directions. They also usually behave differently when interacting with other chiral, or enantioselective structures. There are several classifications allowing to differentiate between enantiomers. The conventional one - L-, D- classification is determined according to the order of substituents and is illustrated on the Fig. 1.

Not only molecules themselves, but medium composed of chiral molecules is optically active as well if it contains the excess of one enantiomer over the other. Enantiomeric excess, which can be considered as an order parameter of the system, is calculated as $\eta = (L - D)/(L + D)$, where L and D stand for concentration of L- and D-enatiomers correspondingly, and is used to characterise chiral purity of the medium. When medium contains equal amounts of enantiomers of each kind, $\eta = 0$, medium is optically inactive and is called racemic. When it contains only one type of enantiomer,$\eta = 1$, and it is called chirally pure.

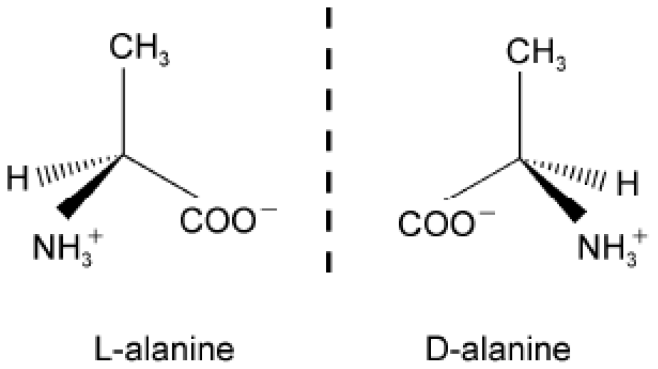

Figure 1: L- and D- Alanine

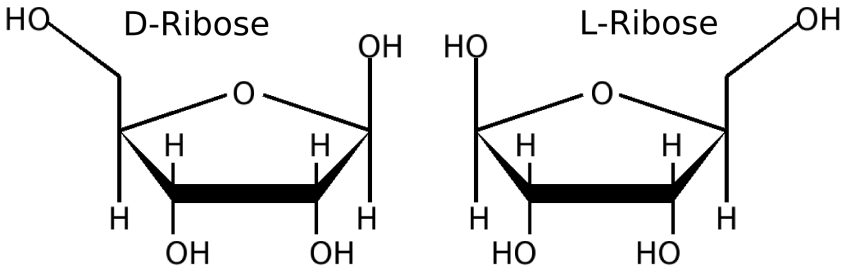

Figure 2: L- and D- Ribose

1.2 Classification of existing approaches

As I have already mentioned before, bioorganic nature presents a remarkable example of mirror symmetry breaking on the molecular level. All living organisms are composed of L-type aminoacids and D-sugars[1]. Being one of the key properties of living nature, chiral purity is closely related to the problem of emergence of life on the Earth. Despite the number of developed approaches, emergence of homochirality still remains one of the unsolved mysteries of biology.

All the existing approaches can be subdivided into several groups by the type of question they are trying to address. First question is, on what stage of evolution have the transition from racemic medium to medium with racemic excess occured. So called biogenic approaches suggest that chiral purity is a result of selection and interaction between first racemic organisms [3]. Avetisov and Goldansky [2, 4, 5] have carried thorough theoretical analysis that suggested that these approaches are incompatible with not only RNA world concept but with any hypothesis of origin of life involving self-replicating olygomers [2, 4, 5]. In 2005 in his review David Cline wrote that it is clear that "life cannot originate in a racemic mixture" [6]. So biogenic scenarios were abandoned and are not even mentioned in most of the recent reviews and papers on the topic [6, 7, 8, 9, 10, 11].

One of the few proponents of the biogenic scenario, Root-Bernstein presents a completely orthogonal view on the problems of emergence of life and homochirality [12, 13, 14]. He assumes that "from their very origins, living systems were complex ecologies of diverse, complementary, interactive molecules" and "selection for chirality is performed by the dynamics of the complex system itself" [13]. He suggested possible experiments to test the hypothesis and presented some experimental evidences that homochirality could have emerged simultaneously with the

[1]It is worth mentioning that other chiral molecules can be present in the cell in either enantiomeric form [2]. So strictly speaking we cant talk about chiral purity of bioorganic world, but rather about strong enantiomeric excess.

genetic code as a consequence of preferential binding between certain chirality amino acids and their codons [13, 14].

In case of abiogenic approach another question arise. How could enantiomeric excess emerge in the racemic primeval soup? Two possible mechanisms are usually considered [2, 4, 5, 6, 7, 8, 9, 10, 11]. According to deterministic mechanism mirror symmetry breaking is a result of some asymmetric factor acting on the initial racemic mixture of enantiomers. A number of factors are considered to be responsible for the emergence of homochirality, including but not limited to circularly polarized light; combinations of electric and magnetic fields; combination of gravitational field with rotational forces and of course the most tempting one - weak neutral currents, that could relate chiral purity of biosphere to the parity violation. Each of these factors however can create only small initial imbalance in a number of enantiomers. Theory of spontaneous symmetry breaking (chance scenario) on the other hand suggests that chiral purity of the biosphere could occur spontaneously as a result of fluctuations in the physical and chemical environment. But again due to stochastic nature of the process any excess of D-enantiomers for example created by this way will be balanced by the fluctuation in the number of L-enantiomers, unless it is somehow amplified.

So both above mentioned mechanisms require further amplification of the enantiomeric excess. Therefore inevitable question is, how this enantiomeric excess could have been amplified to lead to the current chirally pure state. The possible answers to this question seems to be less speculative as they involve much experimental evidences. Different amplification mechanisms are discussed in detail in the recent review by Blackmond et al [9].

The last question to answer is: whether homochirality has terrestrial or extraterrestrial origin (cold scenario) [6]. There are several evidences in favour of the latter one [4]. A solid one is discovery of complex organic molecules, including aminoacids, in space. More speculative argument is related to the limited duration of the prebiotic stage of evolution - $0.2 - 0.5 \cdot 10^9$ years, which was determined by dating of fossils and formation of the solid crust on the Earth. It caused some scientists to doubt that emergence of the first primitive organisms from the primeval soup could occur in such a short time interval. Most probably this scenario exclude possibility of biogenic mechanism. However other questions still have to be answered. Of course the answer to the question of whether symmetry was broken by spontaneously or resulted from action of asymmetric force, should be considered in a different physical environment. But it does not change the picture drastically: it is still chance versus determinism under low temperature and pressure.

To summarize this part, Fig. 3 illustrates my understanding of classification of the existing approaches. In this essay I will discuss in greater detail the pro and cons of biogenic approaches and abiogenic.

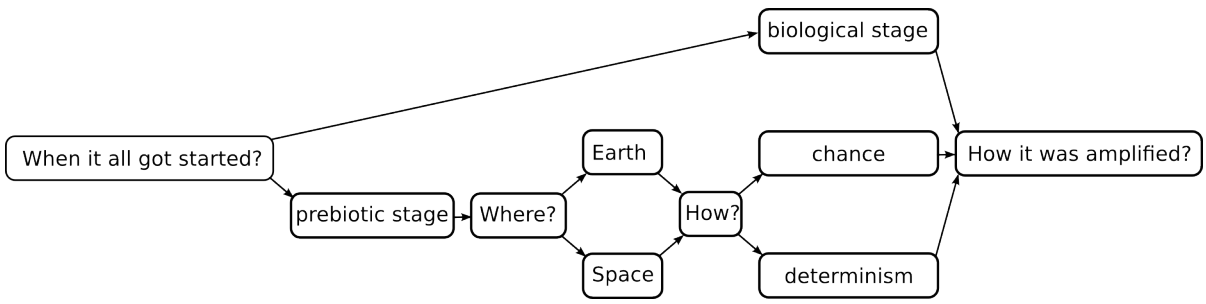

Figure 3: Schematic illustration of the existing approaches to the problem of chiral purity.

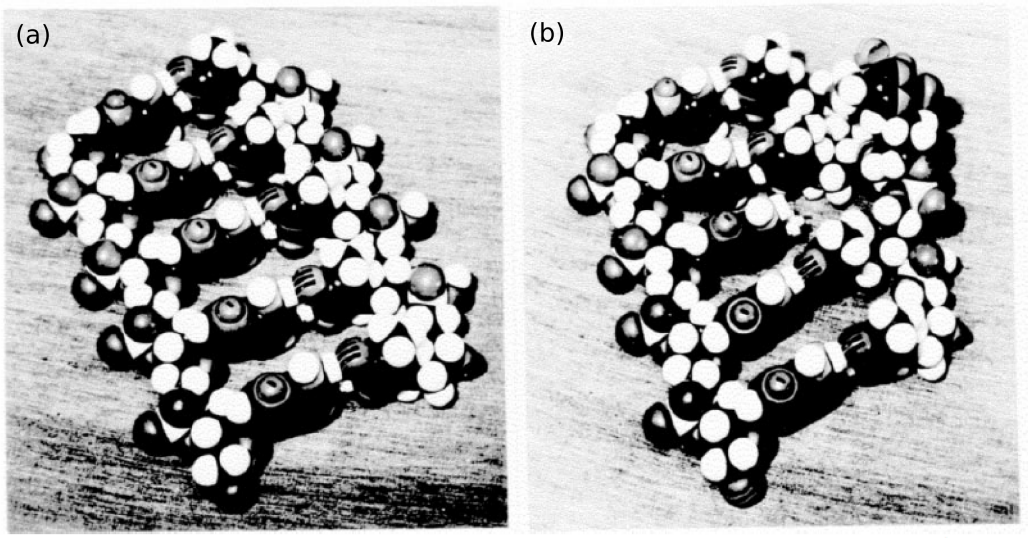

Figure 4: Double-stranded (poly-A)-(poly-T) DNA (a)-without chiral defect, (b)-with chiral defect

2 Biogenic approach vs abiogenic approach within the concept of RNA-world

The general assumption of most theories of life origin is that life started from self-replicating olygomers [15, 10]. Once established, mechanism of self-replication gave rise to natural selection and the rest is more or less known [15]. The most popular candidate for the role of the first replicator is RNA, that can both serve as a carrier of information, capable of self-replication, and is known to posess enzymatic activity [15, 10]. So the core assumption of the RNA-world hypothesis is that first life form was RNA-based. One of the most recent experimental evidences in favour of RNA was presented in 2009 by Lincoln and Joyce [16]. Authors have constructed "cross-catalytic system involving two RNA enzymes that catalyze each other's synthesis" [16]. Now, keeping this in mind let us consider pro and cons of biogenic and abiogenic approaches following works of Goldansky et al [2, 4, 5].

First of all it is important to understand that homochirality in nature has two aspects. Not only living organisms are composed of molecules of certain chirality type, but also enzymatic reactions and enzymes themselves are selective relative to the type of chirality - enantioselective [2].

If we assume that life started from replicating olygomers, than we can formulate biogenic and abiogenic approaches in the following way. According to the biogenic approach, in racemic organic medium chiral entities were formed that could nevertheless maintain evolution of complex macromolecules either by self-replication or by promoting replication. So enantiomeric excess emerged and was further amplified in the process of evolution of complex biological structures. In biogenic approach on the other hand chiral symmetry of primeval soup was broken on the chemical stage of evolution and first homochiral structures capable of self-replication were formed in this already asymmetric medium.

Now to discriminate between biogenic and abiogenic approach we need to answer several questions keeping in mind two aspects of homochirality mentioned before. Can complex chiral structures self-replicate in achiral environment and more specifically how the probability for chiral structure to emerge and further evolve depend on the chirality of the medium and complexity of the structures? How specific should be enantioselective functions to promote replication of chiral structures in an environment with different degree of chirality?

Let us consider assembly of a polymer chain in the medium with enantiomeric excess $\eta =$

$(L-D)/(L+D)$. If we assume that attachment of L- or D- type monomer depends only on its relative abundance, than relative probability of formation of L-type chiral chain of length N, $\Omega = \omega^N$, where $\omega = (1+\eta)/2$ - relative concentration of L-type monomers. In achiral medium $\eta = 0$, and polymerization results in binomial distribution of 2^N different sequences. Probability of formation of chiral chain composed of 50 monomers is already vanishingly small: $\Omega_{50} = 2^{-50}$. This lead us to a conclusion that no complex biological chiral structures can be formed in the chiral medium in the absence of enantioselective functions. Above consideration is of course oversimplified. From the experimental side it has been shown in a variety of system that distribution of sequences generated in a chiral medium departs from binomial with a higher likelyhood of assembly of chiral structures [17]. The length of structures that can be obtained in such kind of experiment still lies within only 10 monomers.

The next question is if chiral chain formed in the racemic medium can self-replicate by polymerization. In 1984 Joyce et al demonstrated that process of Guanine polymerization on poly L-Cytosine template is much less effective for monomers of opposite handedness [18]. While in chirally pure medium containing L-Guanine chains as long as 20 monomers chains were formed, in racemic solution process of olygomerization was almost completely inhibited. Incorporation in the chain of monomer of opposite handedness leads to the termination of the process. This result becomes obvious if you consider model of double stranded nucleotide chain with a chiral defect. It is clearly seen on the Fig. 4 that monomer of opposite handedness breaks complementarity of the double chain and disrupt its matrix structure [2]. However in 2001 a group of experimentalists designed a 32-residue peptide replicator capable of effective amplifying homochiral products from racemic peptide fragments. The resulting dynamics of enantiomeric excess is shown on Fig. 5 [19].

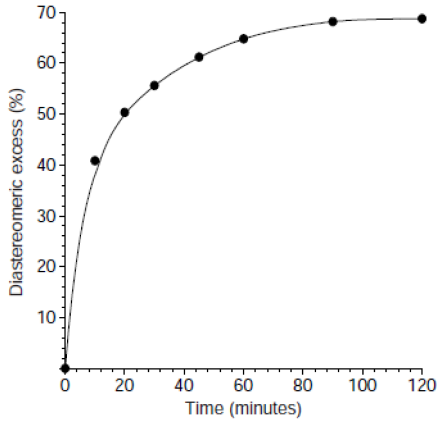

Figure 5: Increasing of enantiomeric excess as a function of time [19].

Now we can move on to the question of enanatioselectivity of the function promoting replication. This question can be answered using model of molecular quasispecies [20]. Let us consider replication of polymer chains of length $N \gg 1$, composed of monomers of two types. Each out of 2^N possible sequences S_i of length N is copied with a probability $\Phi_{ii} = p^N$, where p is a relative probability of copying a monomer. Probability of emergence of mutant sequences in the process of replication $\Phi_{ik} = q^{d(i,k)} p^{N-d(i,k)}$, where $q = 1-p$ - probability of error; $d(i,k)$- Hamming distance, minimal number of point mutations that can transfrom sequence S_i to the sequence. Lets see how relative concentrations $x_i(t) = c_i(t)/\sum_i c_i(t), i = 1, 2...2^N$, where $c_i(t)$- concentration of sequence S_i, change over time. We assume that total concentration $\sum_i c_i(t) = c_0$ is kept constant by a transport of excess substance away from the system. Dynamics of $x(t)$ is

governed by the differential equation

$$\frac{dx_i}{dt} = (A_i\Phi_{ii} - B_i - \psi_0)x_i(t) + \sum_{k\neq i} A_{ki}\Phi_{ki}x_k, \quad i,k = 1,2...2^N \tag{1}$$

where $A_i\Phi_{ii}$- copying rate, B_i- destruction rate, ψ_0- flux of sequence S_i out of the system, and $A_{ki}\Phi_{ki}$- rate of synthesis of sequence S_i due to the errors in copying sequence S_k.

In case of perfect accuracy of replication $p = 1$ and $\Phi_{ik} = \delta_{ik}$. As total concentration $\sum_i c_i(t)$ is constant over time $\sum_i dx_i/dt = 0$, then $\sum_i (A_i - B_i)x_i = \psi_0 \sum_i x_i = \psi_0$. Here $E = \sum_i (A_i - B_i)x_i$ can be considered as reproductivity of the system. Equation (1) will take form:

$$\frac{dx_i}{dt} = (A_i - B_i - E)x_i(t) \tag{2}$$

From equation (2) $dx_i/dt > 0$ if $E_i = A_i - B_i > E$, that is only those sequences S_i will multiply that have reproductivity higher than reproductivity of the system E, others will gradually decrease in number thus increasing E. In the limit of $t \to \inf$, $x_i = \delta_{ik_0}$, where S_{k_0} is a sequence with maximal reproductivity, so called master sequence [20]. In other words we observe selection of the master sequence.

If on the other hand $p < 1$, concentration of master sequence S_{k_0} will decrease with error rate q and concentrations of mutant sequences S_i with Hamming distance $d(i,k_0) = 1,2,3..$ will grow. Resulting dynamics for chains with length $N = 50$ is shown on Fig. 6 [20]. You can see

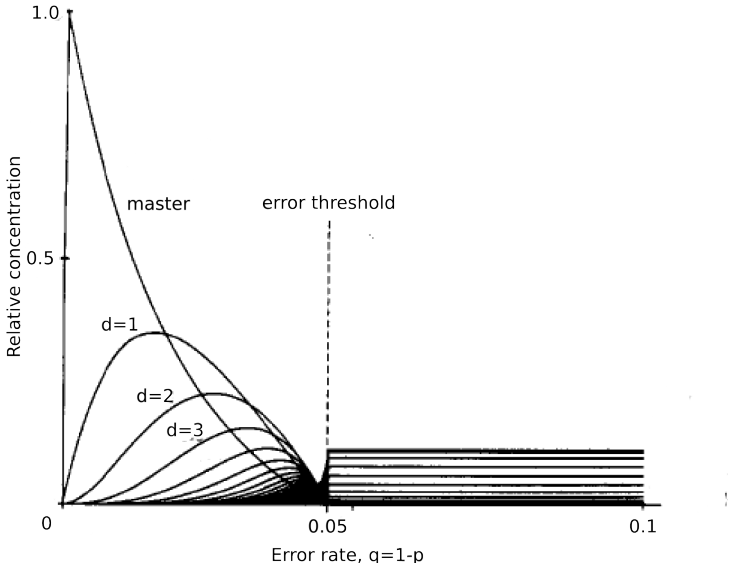

Figure 6: Relative concentration of master and mutant sequnces ($N = 50$) with $d = 1,2,3...$ versus error rate [20]

that above some critical error rate, distribution of sequences is uniform and thus no selection is possible. It is so called error catastrophe. Error threshold is estimated as $q_c = \varepsilon/N$, where $\varepsilon \sim 1$. So effective selection and thus evolution of polymer chains of length N is possible only below the error threshold:

$$q < \varepsilon/N \tag{3}$$

This condition means that the average number of errors Nq in a replica of length N, should be less than one.

We can apply above formalism to the replication of chains, composed of L- and D- monomers in racemic environment. Then, as it was shown above, sequence with a maximal reproductivity is a chiral one. It is more convenient to specify enantioselectivity as $\gamma = 1 - 2q_L$, where q_L is

probability of chiral defect, that is probability for L-type monomer to be incorporated in the D-chain. Then if there is no selectivity $q_L = q_D = 1/2$ and $\gamma = 0$. According to (3) non-zero probability to be replicated without chiral defect requires enantioselectivity $\gamma > 1-2\alpha N^{-1}$. For 50-monomers chain it means $\gamma > 0.95$. The resulting conclusion is that in racemic environment only highly selective functions can maintain replication of chiral structures. That is biogenic approach requires existence of achiral structures capable to promote highly enantioselective replication of long chiral polymers in racemic environment. To my knowledge no example of such structure has been found so far.

Now let us consider replication in a medium with enantiomeric excess $\eta = (L-D)/(L+D)$ as we did before, but taking into account enantioselectivity. That is this time probability for a L- and D-types monomer to be incorporated for example in the D-chain would be different. Relative probability of incorporating L-type chiral defect is determined as [21]:

$$q = \frac{(1-\gamma)(1-\eta)}{(1-\gamma)(1-\eta)+(1+\gamma)(1+\eta)} = \frac{(1-\gamma)(1-\eta)}{2(1+\gamma\eta)} \tag{4}$$

From (3) we have

$$\eta > 1 - \frac{\varepsilon'(1+\gamma)}{N(1-y)}, \quad \varepsilon' \sim 1 \tag{5}$$

So when γ and η satisfy (5) the accuracy of replicating is high enough to maintain selection of chiral molecules. The corresponding area of $\eta\gamma$ plane is shown on Fig. 7 [2].

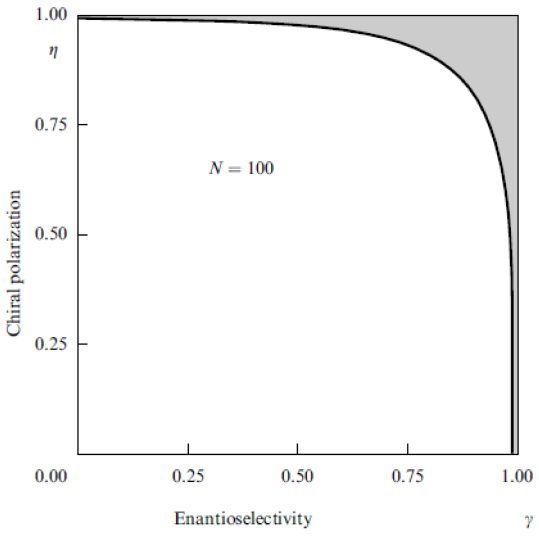

Figure 7: Enantiomeric excess η versus enantioselectivity γ [2].

Thus we can conclude that to avoid eror catastrophe during replication of complex organic molecules on both prebiotic and biological stages of evolution we need either chiral purity of the media (biogenic approach) or enantioselective functions that can maintain selective replication of these molecules (abiogenic approach) [2].

3 Alternative chemistry of life

Now let us consider completely different view on the problem suggested by Root-Bernstein. In his highly phylosophical paper about role of molecular complementarity in the origin and evolution of life he proposed scenario of life origin alternative to generally accepted RNA-worls concept [12]. He defines life as self-organizing systems, existing away from thermodynamic

equlibrium and directed by complimentarity. Such systems evolve by hierarchical ordering of subsystems and have homeostatis both in space and in time[2]. Note that an abiblity to replicate is not considered as an essential property of living organism. It is assumed that "metabolic life preceded genetic life but, nonetheless contained within itself information storing processes that made possible the emergence of genetics" [12].

In the absence of replication chiral purity is not a prerequisite for the emergence of life. So first life was evolving in the racemic environment containing amino acids, peptides, nucleotides and polynucleotides [13]. The core assumption is that choice of amino acid and nucleotide chirality, emerged simultaneosly with the genetic code and its preffered directionality [13]. This process involved a set of selective interactions, that is "of all the possible DNA/RNA bases/amino acids, those that could pair with each other and with RNA/DNA bases,as well as perhaps with amino acids or short peptides would have been selected". The next assumption is that each L- or D-amino acid should not only preferentially bind a codon of certain chiral form, but this binding should be directionally sensitive. Thus if L-Valine prefers to bind to its codon D-GUA, then D-Valine should bind preferentially to mirror image of D-GUA, that is L-AUG (Fig. 8). And similarly if L-Methionine prefers to bind to its codon D-AUG, then D-Methionine would bind to L-GUA (Fig. 8).

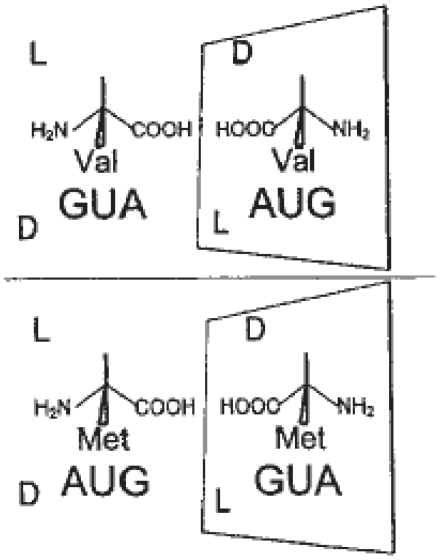

Figure 8: Example of codon-amino acid pair for Valine and Methionine [13].

From the above it follows that two genetic codes should have occured differing only by chirality of amino acids, their codons and directionality of its transcription. According to Root-Bernstein this did not happen because of different concentrations of amino acids, nucleotide precursors and affinities of binding. Thus on the prebiotic Earth Valine was likely present in a higher concentration than Methionine, then in binding D-GUA L-Valine would out-compete D-Methionine, and in binding L-AUG D-Valine would out-compete L-Methionine. In order for the modern genetic code to win D-AUG should have higher affinity for L-Methionine than for D-Valine.

The hypothesis was tested experimentally in a later work [14]. To do this four oligonucleotides were synthesized: D-RNA-oligonucleotides D-CGUA and D-AUGC and their corresponding L-RNA-oligonucleotides L-CGUA and L-AUGC. Their affinity for eleven pairs of L- and D-amino acids was measured using UV spectroscopy. According to the above assumption, for example olygonucleotide D-CGUA coding L-Arginine (CGU) and L-Valine (GUA) should

[2]Here homeostasis is a property of a system to return to its equilibrium after being pushed away [12].

manifest stronger binding to these amino acids. The assumption was confirmed only partially (Table 9). Thus it was shown that only amino acids, encoded by synthesized olygonucleotides, and Phenilalanine, demonstrated significant binding constants; and binding of amino acid to codons is indeed sensitive to chirality and directionality, but not always in the predicted way. In general there was "two- to three-fold preference of encoded D-amino acids for L-codons and L-amino acids for D-codons" with the exception of D-Cysteine (Table 9) [14]. Preference for their codons was also demonstrated only for some amino acids (Table 9). These results though very encouraging are somewhat controversial and further experimental studies are required to justify the theory of co-evolution of homochirality and genetic code.

200 nm	D-CGUA	L-CGUA	D-AUGC	L-AUGC
L-Arginine	**1.3×10^{-7}**	3.8×10^{-7}	2.6×10^{-7}	2.7×10^{-7}
D-Arginine	5.0×10^{-7}	4.0×10^{-7}	4.0×10^{-7}	**1.9×10^{-7}**
L-Methionine	**7.5×10^{-7}**	3.4×10^{-6}	1.0×10^{-6}	3.2×10^{-6}
D-Methionine	6.0×10^{-6}	**2.2×10^{-6}**	4.5×10^{-6}	4.0×10^{-6}
L-Cysteine	8.0×10^{-5}	4.0×10^{-5}	**1.8×10^{-5}**	3.0×10^{-5}
D-Cysteine	**3.0×10^{-6}**	4.5×10^{-6}	1.2×10^{-5}	6.5×10^{-6}
L-Valine	6.0×10^{-4}	7.5×10^{-4}	**3.7×10^{-4}**	9.0×10^{-4}
D-Valine	2.0×10^{-4}	3.0×10^{-4}	2.0×10^{-4}	2.0×10^{-4}

Figure 9: Binding constants determined by UV spectroscopy for different combinations of L- and D-amino acids with L- and D-olygonucleotides [14].

4 Conclusions

The main conclusion I could draw for myself is that despite a large amount of both theoretical and experimental efforts put into the problem, emergence of homochirality of bioorganic world still remains an open question. Of cource some aspects are more controversial than the others. To me it seems highly unlikely that the question of terrestrial or extraterrestrial can be ever resolved unambiguously. The question of amplification of the enantiomeric excess on the other hand seems more straightforward, as it was experimentally demonstrated in a number of systems [9]. Discussion presented in this essay is just the tip of the iceberg. Due to the lack of space and time I was not able to consider here chance and deterministic scenarios of symmetry breaking (Fig. 3), different mechanisms of amplification of chiral excess as well as hypothesis of its extraterrestrial origin.

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