

REVIEW**Physico-Chemical and Evolutionary Constraints for the Formation and Selection of First Biopolymers: Towards the Consensus Paradigm of the Abiogenic Origin of Life**by **Armen Y. Mulkidjanian**^{*a)}^{b)}, and **Michael Y. Galperin**^{c)}^{a)} School of Physics, Universität Osnabrück, D-49069 Osnabrück

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Dedicated to the memory of *Stanley L. Miller*

During the last two decades, the common school of thought has split into two, so that the problem of the origin of life is tackled in the framework of either the ‘*replication first*’ paradigm or the ‘*metabolism first*’ scenario. The first paradigm suggests that the life started from the spontaneous emergence of the first, supposedly RNA-based ‘replicators’ and considers in much detail their further evolution in the so-called ‘RNA world’. The alternative hypothesis of ‘metabolism first’ derives the life from increasingly complex autocatalytic chemical cycles. In this work, we emphasize the role of selection during the pre-biological stages of evolution and focus on the constraints that are imposed by physical, chemical, and biological laws. We try to demonstrate that the ‘*replication first*’ and ‘*metabolism first*’ hypotheses complement, rather than contradict, each other. We suggest that life on Earth has started from a ‘*metabolism-driven replication*’; the suggested scenario might serve as a consensus scheme in the framework of which the molecular details of origin of life can be further elaborated. The key feature of the scenario is the participation of the UV irradiation both as driving and selecting forces during the earlier stages of evolution.

Introduction. – For the most part of the 20th century, up until the late 1970s, scientific approaches to the origin of life developed in the framework of one mainstream paradigm. This paradigm was based on a series of theoretical papers that described tentative events that could lead to the origin of life (see the original works by *Oparin* [1], *Haldane* [2], *Horovitz* [3][4], or recent reviews [5][6]. These theoretical papers developed into a widely accepted paradigm largely thanks to the pioneering experimental studies by *Stanley Miller*, to whose memory we dedicate this paper [7]. *Stanley Miller* and his colleagues showed that simple building blocks, such as amino acids, nitrogenous bases, and carbohydrates, could be formed from inorganic compounds, such as hydrogen, nitrogen, and carbon monoxide, under reducing and/or neutral conditions imitating the primordial atmosphere, as long as energy was provided in the form of electric discharges or UV light (reviewed in [8][9]. Accordingly, it was suggested that the accumulation and interaction of increasingly

complex compounds, formed under primordial conditions, could eventually lead to the origin of life. This initial paradigm did not contain much detail on the particular chemical routes involved.

Experimental studies of the 1980s and 1990s, including the discovery of the catalytic RNA molecules, ribozymes [10][11], prompted a transition to the more detailed, mechanistic approaches. As a result, the common school of thought has split into two, so that, currently, the problem of the origin of life is tackled in the framework of either the ‘*replication first*’ paradigm or the ‘*metabolism first*’ scenario (see, e.g., [12]). The first paradigm suggests that the life started from the spontaneous emergence of the first, supposedly RNA-based ‘replicators’ (see, e.g., [13–19]). This concept does not provide details on the origin of these replicators but considers in much detail their further evolution in the so-called ‘*RNA world*’ (it is generally accepted that RNA preceded DNA in evolution). The alternative hypothesis of ‘*metabolism first*’ derives the life from increasingly complex autocatalytic chemical cycles presumably developed at the surface of ancient minerals; here, replication is considered a later invention (see, e.g., [20–23]).

Although these two paradigms do not directly contradict each other, they are usually considered as alternatives [12]. This apposition results in the absence of a consensus scientific opinion on the problem of abiogenic origin of life. Absence of a consensus among the members of the scientific community is causing problems outside science by opening the window for the proponents of the ‘*intelligent design*’ as another, supposedly equally plausible hypothesis of origin of life.

Therefore, we see an urgent task to formulate a consensus scenario for the abiogenic origin of life that 1) would be scientifically plausible, 2) could serve as a common basis/paradigm for the scientists with different views, and 3) could eventually be offered to the general public.

Obviously, the number of hypothetical scenarios for the origin of life is virtually unlimited. Still, the space of possibilities can be dramatically restricted by invoking certain external constraints. The geological constraints on the origin of life were, in particular, formulated by *Shock* [24]. In this work, we focus on evolutionary constraints, and on the constraints that are imposed by physical and chemical laws. Using this approach, we try to demonstrate that the ‘*replication first*’ and ‘*metabolism first*’ hypotheses complement, rather than contradict, each other. Further, we suggest that life on Earth has started from a ‘*metabolism-driven replication*’ and attempt to reconstruct the conditions under which such a replication could have occurred.

Some Useful Definitions. – Before discussing the origin of life, it might be appropriate to define what the life is. As noted by many authors, a rigorous general definition of life is hardly possible, since we do not know how the life might be organized elsewhere in the universe (see, e.g., [25]). On the other hand, the ‘*life on Earth*’ can be acceptably defined by ‘working’ definitions, such as ‘*Life is a system capable of evolution by natural selection*’ suggested in [26], or ‘*Life is a self-sustained chemical system capable of undergoing Darwinian evolution.*’ [27][28], which is the definition used by NASA. According to these definitions, life started simultaneously with biological evolution. This implies that the events that accompanied the origin of life could be tentatively reconstructed by tracing the evolution as far back as possible. Therefore, physico-chemical and geological constraints on the origin of life can be

supplemented by evolutionary constraints. In other words, physical and chemical conditions that permit origin of life must also facilitate evolution of the life forms. Accordingly, changes in the environmental conditions can be considered among the driving forces for the evolution of the life forms.

Physico-Chemical Constraints on the Origin Life. – There are several obvious physico-chemical constraints on the origin of life. Thus, temperature and pressure had to be such as to permit formation and maintenance of complex organic molecules, meaning that life was unlikely to emerge until the Earth cooled down to less than 400°. Other constraints include presence of liquid water, all biotic elements, simple inorganic molecules, such as hydrogen, hydrogen sulfide, ammonia, carbon monoxide, and carbon dioxide, and the availability of sources of energy [29]. The latter point requires some clarification. Many researchers, most recently in [29], list various ‘sources of energy, *i.e.*, solar light, lightening, cosmic rays and heat, which induce the formation of building blocks of biomolecules (amino acids or nucleobases) from simple molecules’. We would like to emphasize that formation and maintaining of increasingly complex biopolymers could proceed only if supported by a *constant flow* of utilizable energy. This consideration severely constrains otherwise plausible hypotheses of origin of life under impact bombardment [30] that tend to treat emergence of life as a one-time event. In addition, it rules out such single events as lightening, electric discharges, volcanic explosions, and so on. The second law of thermodynamics imposes an additional, less obvious constraint on the origin of life, namely, that heat cannot be used as an energy source for the formation of increasingly complex chemical compounds. Hence, the ultimate source of energy must be external and constant, which effectively leaves solar radiation as the most likely candidate (see also below).

An important chemical constraint, which often remains unrecognized, is the reversibility of most (bio)chemical reactions. Therefore, any scheme that explains biopolymer formation under certain environmental conditions should also be able to explain why the synthesis of the given biopolymers would not be followed by their immediate hydrolysis. One cannot help noting that, in virtually all papers describing origin of life, the corresponding schemes contain unidirectional arrows, instead of bidirectional ones. However, the mechanisms that underlie that unidirectionality are almost never described. In a way, the mechanisms for formation and maintenance of biopolymers require some kind of *Maxwell’s Demon* that would allow the reaction to go in the direction of increasingly complex compounds. Such a demon is hard to imagine, which serves as fertile ground for ideas of some kind of Supreme Being that was needed to ‘breathe life’ into disorganized organic matter. The simplest substitution for this kind of *Maxwell’s Demon* would be a *Darwin’s Demon*, a selective mechanism that favors complex molecules (structures) over simple ones. Obviously, it would require external source(s) of energy. However, such a selective mechanism acting for a sufficiently long period of time appears to be a necessary condition for sustaining abiogenic evolution that could have produced a variety of pre-biological molecules and eventually brought about the first living organisms.

Evolutionary Constraints on the Origin of Life. – The postulate that life is intrinsically linked to evolution imposes surprisingly strict constraints on the origin of

life. To better understand these constraints, it might be useful to formulate those traits of the evolutionary process that might be instrumental for the reconstruction of the primordial events.

1) According to *Darwin*, biological evolution is driven by the selection of the fittest. Living organisms evolve because they *a*) undergo spontaneous changes and, hence, are not all identical; *b*) reproduce (replicate) themselves, and *c*) not all the progeny can survive. As a result, only those organisms that are most fit to the given environment can survive, and each next generation is more fit than the previous one.

2) New functions (as well as new enzymes, organs, or mechanisms) seem to develop by co-option/modification of pre-existing entities. As *Darwin* has noted '*throughout nature almost every part of each living being has probably served, in a slightly modified condition, for diverse purposes, and has acted in the living machinery of many ancient and distinct specific forms*' [31]. In particular, new enzymes emerge routinely either after duplication of genes, followed by their separate evolution, and/or due to the rearrangement and re-shuffling of genes.

3) The principle of evolutionary continuity, succinctly formulated by *Albert Lehninger* in his *Biochemistry* textbook [32]. An adaptation that does not increase the fitness is no longer selected for and eventually gets lost in the evolution (in the current view, only those adaptations that effectively decrease the fitness end up getting lost). Hence, any evolutionary scenario has to invoke – at each and every step – only such intermediate states that are functionally useful (or at least not harmful).

4) One more empirical evolutionary rule is the one of 'chemistry conservation'. Although this principle seems to be implicitly acknowledged by biologists, we failed to find its explicit formulation. Since this principle could be especially useful for the reconstruction of the primordial conditions, it deserves to be considered in detail. The rule of chemical conservation implies that the chemical composition of living beings is more conservative than the chemical composition of their environment. Therefore, the conserved organismal chemistry can retain information about the ancient environmental conditions. The most popular manifestation of this principle is the similarity between the chemical composition of sea water and the internal liquids of multicellular animals. The latter are characterized by high sodium content even if organisms live in fresh water or on the land (*e.g.*, as human beings do). In this case, high sodium content appears to reflect the emergence of the first multicellular organisms in the sea waters. Less broadly acknowledged example of chemical conservation is the highly reduced state of the cell interior even in those organisms that inhabit oxygenated environments. The redox potential of the cell cytoplasm is very low, less than 0 mV [33] as compared to >600 mV for the redox state of oxygenated environments. The reason for this is probably that the first cells have evolved, and the principal biochemical pathways have been established, before the atmosphere became oxygenated (which was due to the activity of cyanobacteria some 2–2.5 Gy ago [34]), so that the post-modification of the whole enzyme content was not possible anymore. Hence, the organisms that live in oxygenated environments have to spend part of their resources to maintain a large redox gap relative to their environment. The principle of chemistry conservation is quite instrumental, because it helps to reconstruct the primordial environmental conditions even in those cases when no reliable geological evidence is available.

UV Light as a Selective Factor that Could Favor the First RNA-Like Oligomers. –

The standard definitions of life, as given above, imply that the life started simultaneously with biological evolution. The core of the evolution, however, is the ability of living beings to replicate. This consideration qualifies – formally – the ‘metabolism first’ concept. However, unlike the critics of this concept (e.g., [12]), we do not deny the role of autocatalytic reactions in the origin of life; on the contrary, as argued below, we suspect that at least one such autocatalytic reaction could be definitely involved. We just find it instrumental to pinpoint the origin of life to the emergence of the first replicating entities; otherwise, it is difficult to draw a borderline between the ‘non-life’ and ‘life’ while considering increasingly complex primordial (auto)catalytic cycles.

Under the first living replicating systems we understand here the RNA/DNA-based ones because they are the only ones for whom the mechanism of evolution is known. It cannot be completely ruled out that these systems were preceded by some other kind of replicators (e.g., by replicating clays [35]). Still, as we do not know anything about these hypothetical alternative replicating systems, they can hardly be treated in a framework of scientific analysis.

The hypothetical pre-RNA replicating systems were brought into play because RNA polymers were believed to be too complex to be synthesized abiotically. However, it can be argued that polynucleotides are likely to be the simplest polymers capable of replication that could emerge on the primordial Earth. Indeed, they are formed by only three types of building blocks, namely nitrogen bases (nucleobases), ribose entities, and phosphate groups. This set seems to be not incidental. Turning to nucleobases, it is worth noting that they all are unique in their ability to quench UV quanta very fast, with fluorescence life times on the order of 10^{-12} s at room temperature [36]. This means that within 1 ps the energy of trapped UV quanta is dissipated, predominantly into heat. For comparison, the fluorescence life time of tryptophan, which has a comparably complex structure, is more than 1000-fold longer, on the order of 5 ns. For nucleobases, the probability of a transition into a potentially photochemically active, long-living triplet state is quite low, at the order of 10^{-3} at room temperature [36], as compared with 0.2 for tryptophan [37]. The proficiency in dissipating the UV quanta was important, since the UV flux at the Earth surface must have been *ca.* 10–100 times larger than it is now due to the absence of the ozone layer [38][39], causing deterioration of most organic molecules. Under such conditions, the nucleobases had a major advantage: once formed, they could survive longer than other organic molecules of comparable complexity.

Ribose molecules, in turn, are unique in being the major products of the only autocatalytic reaction in organic chemistry that does not require enzyme catalysts, namely the formose reaction where pentoses and hexoses predominantly form from formaldehyde [40][41]. Recently, it has been argued that this autocatalytic reaction could have been additionally boosted by UV light [42].

The advantages of phosphate groups as primordial catalysts have been widely discussed in the literature (see [43][44], and refs. cit. therein). We would like to emphasize only two further points. First, the presence of a phosphate group and, accordingly, of a negative charge could serve, for a primordial organic molecule, as an ‘entry ticket’ to the ‘origin of life’ enterprise. Indeed, in the *Miller’s* experiments, as

well as in the subsequent simulations of the primordial abiogenesis, the vast majority of reaction product sedimented as a ‘tar’, *i.e.*, an insoluble organic matter of a heterogeneous composition [45]. The same could happen at the primordial Earth, so that only electrically charged, water-soluble compounds could escape aggregation and thus participate in further chemical transformations. Secondly, the key function of phosphate groups in biochemistry and their high concentration in the cell may reflect the high concentration of phosphate in the primordial waters. Routinely, the high phosphate content of the modern cells (*ca.* 10^{-1} M), as compared to the extremely low (*ca.* 10^{-9} M) concentration of free phosphate in native environments [46], is considered an evolutionary enigma. The simple solution might be that the free phosphate concentration in the environment changed with time and was higher at the beginning of times [47]. In fact, the phosphate concentration in the sea water drastically ceased only in the middle Cambrian as could be judged from the sharp decline in the fossil phosphatization [48]. Based on the above introduced principle of chemistry conservation, it is attractive to speculate that the phosphate concentration in modern cells (*ca.* 0.1M) reflects its concentration in those solutions where the first cells were formed. Accordingly, the first RNA-like polymers were likely to emerge when the phosphate concentration in water was ≥ 0.1 M.

The ribozyme chemistry implies that the first replicators, *i.e.*, oligonucleotides, that were capable of copying themselves, had to contain something *ca.* 100 nucleotides, at least [49]. Since a spontaneous emergence of such long polymers is extremely unlikely, even the tentative mechanisms of their formation has been usually skipped by the proponents of the ‘replication first’ scenario. As we have argued in more detail elsewhere, the probability of long oligonucleotide formation might be increased by many orders of magnitude if the formation of the first RNA-like polynucleotides – from nucleobases, sugars, and phosphates – were driven by selection for the most UV-stable polymers. Some authors have considered the high UV level at the primordial Earth as a major obstacle and offered several different strategies for hiding the first life forms from it (see, *e.g.*, [50–53]). Alternatively, we have argued that the UV irradiation might play a positive role upon the very origin of life by serving both as energy source and a principal selective factor in the formation of pre-biological structures [54]. Indeed, the above noted extremely efficient deactivation of the UV quanta by nitrogenous bases allows them to protect the compounds to which they are attached from the UV-induced breakage. In particular, the UV-damage to the sugar–phosphate bond was shown to decrease in the presence of adenine entity [55]; due to this phenomenon, the backbone breaks in RNA and DNA seem to happen 10^3 – 10^4 times less frequent than the UV-damage to the nitrogen bases proper [36]. Apparently, the nitrogenous bases serve as an excellent sink for the UV energy because of the lower energy of the first singlet level as compared to sugar phosphates. The backbones of RNA and DNA are thereby rescued due to the partial ‘victimization’ of nitrogenous bases [54].

It seems quite unlikely that the extremely effective UV-quenching by all five major nucleobases is just incidental. Therefore, we suggested that the nucleobases were initially recruited as UV protectors. To quantify the significance of such a UV-protection mechanism for the evolution of primordial polymers, we modeled the polymerization of sugar-phosphate monomers (*R*) in the presence of nitrogenous bases (*N*) under the conditions of UV illumination. The exact nature of the sugar moiety was

of secondary importance for the model because of approximately similar susceptibility of various sugar-phosphates to UV cleavage [36]. The set of reactions considered is schematically depicted in Fig. 1, and described in the figure caption and in [54].

As long as parameters were varied in the indicated ranges (see the figure caption), the simulation behavior of the system was qualitatively stable, with a typical example depicted in Fig. 2. In the absence of UV protection ($U=1$), the polymerization yield

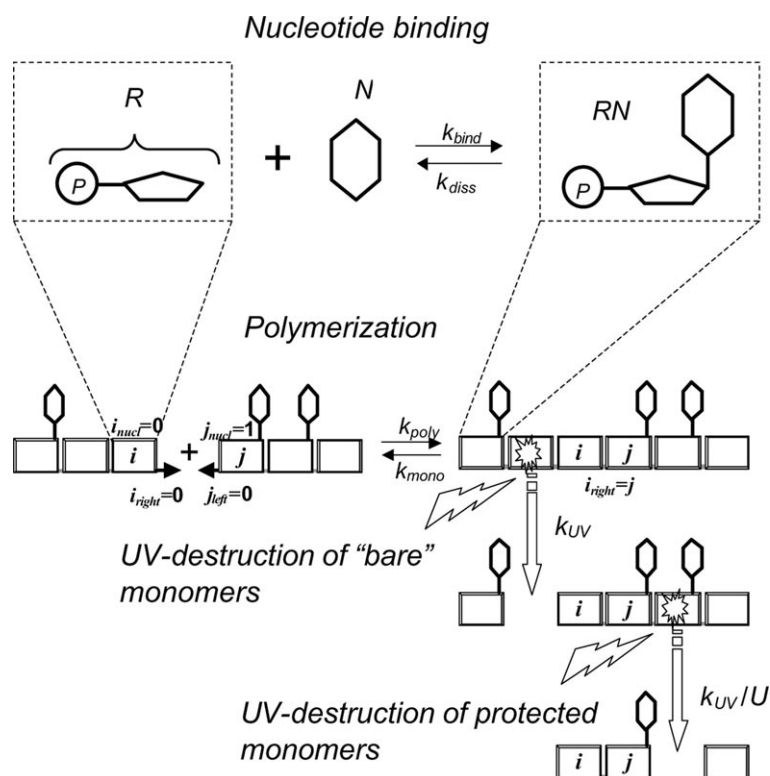


Fig. 1. The model used in Monte-Carlo simulation of the UV irradiation impact on polymerization of sugar phosphates in the presence and in the absence of nitrogenous bases (from [54], reprinted under the BioMed Central Open Access license agreement). As long as a UV quantum can split a polynucleotide chain at any point, we had to use the Monte-Carlo approach. Because the system was open, and the chains were only transient objects, the model topology was described by three pointers assigned to individual monomers. Namely, the polymerization state of monomer i was characterized by two pointers i_{left} and i_{right} defined as follows: if the left bond of monomer i was unsaturated, we put $i_{\text{left}}=0$; if the monomer i was left-bound to monomer j , then $i_{\text{left}}=j$; the same rules were used for the right pointer i_{right} . The chemical state of monomer i was characterized by an additional variable i_{nucl} that assumed values '1' or '0' when the given monomer was bound or not bound, respectively, to a nitrogenous base. The reaction dynamics was considered in discrete time steps. The interval between steps Δt was chosen appropriately small so that differential equations of chemical kinetics could be replaced by their discrete analogs. At each step, sugar-phosphate monomers were added to the reaction volume ΔV so that their total concentration remained constant. The value of ΔV was chosen so that the system contained on average *ca.* 2000 monomers.

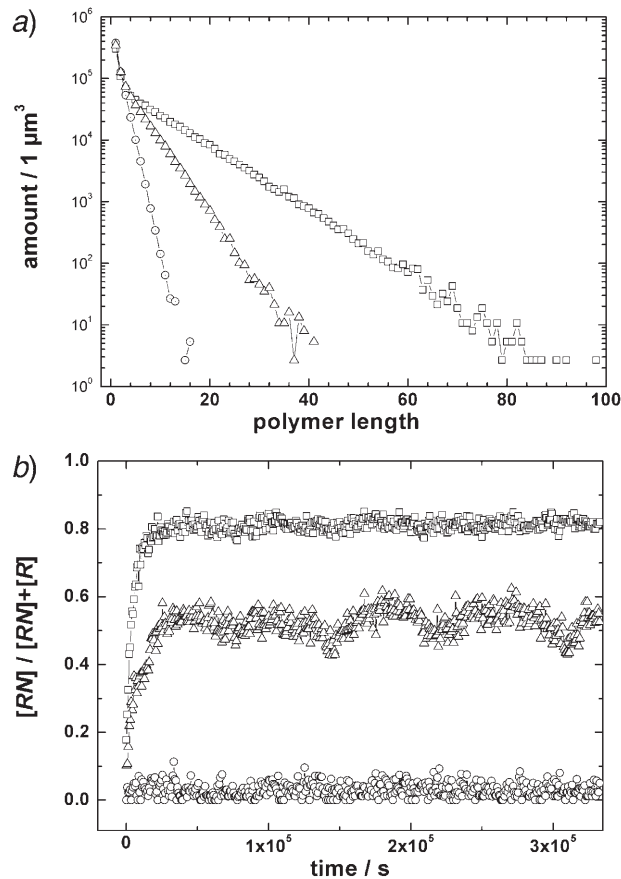


Fig. 2. Monte-Carlo simulation of the UV irradiation impact on polymerization of sugar phosphates in the presence and in the absence of nitrogenous bases (from [54], reprinted under the BioMed Central Open Access license agreement). a) Polymer length distribution at equilibrium; b) fraction of monomers protected by nitrogenous bases as a function of time. At each time step, the following reactions were considered: each monomer i with unsaturated left (right) bond ($i_{\text{left(right)}}=0$) could join a polymer chain reacting with monomer j having unsaturated right (left) bond ($j_{\text{right(left)}}=0$) under a condition that monomer j does not belong to the same chain as monomer i . The probability of such reaction was calculated as $P_{\text{poly}}(i,j) = k_{\text{poly}} \cdot \Delta t \cdot \Delta V^{-1}$. Each monomer i with saturated left (right) bond ($i_{\text{left(right)}} \neq 0$) could re-dissociate with the probability $P_{\text{mono}} = k_{\text{mono}} \cdot \Delta t$. Because the UV stability of nitrogenous bases is by a factor of 10^2 higher than that of not protected, 'bare' sugar-phosphates (see above), the former were assumed to be present in excess. Then, each R monomer could bind nitrogenous base with the probability $P_{\text{bind}} = k_{\text{bind}} \cdot \Delta t$ and each RN nucleotide could dissociate with the probability $P_{\text{diss}} = k_{\text{diss}} \cdot \Delta t$ independently of the polymerization state. The ratio of the rate constants k_{bind} and k_{diss} reflects the thermodynamic equilibrium of the nucleotide binding reaction: $k_{\text{bind}}/k_{\text{diss}} = K_{\text{nucl}}^{\text{eq}} = \exp(\Delta G_{\text{nucl}}/kT)$. The probability of UV decomposition for 'bare' sugar-phosphate monomers was $D_{\text{UV}} = k_{\text{UV}} \cdot \Delta t$ independently of whether they were part of a polymer chain or not. A nitrogenous base protected the sugar-phosphate to which it was bound from UV degradation by a factor U so that the probability of its decomposition was $D_{\text{UV}} = U^{-1} \cdot k_{\text{UV}} \cdot \Delta t$. On simulation, we assumed, for simplicity, that each monomer is hit by a UV quantum once per second. On picking the values of polymerization rate constant k_{poly} , we assumed, in line with experimental observations [56–58], that this reaction was slow. The experimental observation of the formation of oligonucleotides of up to 50 units on clays [57] implies an equilibrium constant of an inorganic template-guided polymerization $K_{\text{poly}}^{\text{eq}} = k_{\text{poly}} \cdot [R]/k_{\text{mono}} > 1$. In contrast, nitrogenous base binding was assumed to be thermodynamically unfavorable, with a respective equilibrium constant $K_{\text{nucl}}^{\text{eq}} = k_{\text{bind}}/k_{\text{diss}} \ll 1$. The values of the UV-decay rate constant k_{UV} and of the UV-protection factor U were varied around their experimentally established values of 10^{-1} – 10^{-3} and 10 – 10^3 , respectively (see [54] for details).

was marginal (*Fig. 2, a*, circles), and the extent of nitrogenous base incorporation in the polymers was close to zero (*Fig. 2, b*, circles). With the UV protection ‘switched on’ ($U > 1$), the length of formed polymers increased dramatically (*Fig. 2, a*, triangles). Even more importantly, under these conditions the fraction of nitrogenous-base-carrying sugar-phosphates increased significantly (up to *ca.* 0.5 in the case presented in *Fig. 2, b* by triangles). Thus, in the simulation, the UV selection caused a strong relative enhancement in oligonucleotide-like polymers even under conditions where the binding of nitrogenous bases to sugar-phosphate moieties was thermodynamically unfavorable.

We have also simulated the effect of partial funneling of UV energy into the condensation reactions. In *Fig. 2*, we depict by squares a case where we accounted for a possibility of a productive binding of a nitrogenous base N by a photo-generated radical $R\cdot$. The quantum yield of such a reaction was taken as small as 9×10^{-8} . The resulting boost for the formation of oligonucleotides was remarkable concerning the length of the formed polymer chains (*Fig. 2, a*, squares), the nitrogenous base incorporation rate, and the extent of the nitrogenous bases incorporation into oligomers (*Fig. 2, b*, squares), so that polymers were built predominantly from nucleotides. After the simulation was complete, we came across the experimental data showing that the quantum yield (probability) of the compatible photo-condensation reaction was actually 10^3 times higher than we assumed in our simulation: the quantum yield of the 254-nm UV-driven AMP formation from adenine, ribose, and ethyl metaphosphate reached 10^{-4} mol/Einstein after 1 h of illumination [59]. The inclusion of the photocondensation quantum yield values compatible to those reported in [59] into the parameter set used for simulation in *Fig. 2* led to an overload because of unmanageable increase in the polymer chain length. It is hard to believe that evolution has not used the opportunity to drive the primordial condensation by energy of light, with nitrogenous bases working as light-absorbing antenna.

Biochemical condensation reactions proceed with release of water, so that the presence of the latter favors hydrolysis of biological polymers. Because of this feature, *Bernal* [4] and many researchers after him (as reviewed in [51]) advanced the view that life has begun in tidal regions, so that condensation of primordial monomers proceeded under ‘fluctuating’ conditions where the wet periods, enabling the exchange of reagents, alternated with dry ones, favoring the condensation reactions in a kind of primordial PCR reaction. This view emphasizes the importance of surfaces for primordial syntheses (see [60] and refs. cit. therein). And indeed, *Ferries* and co-workers have shown that aluminosilicate clays can catalyze the oligomerization of chemically pre-activated nucleotides. This is strong evidence in favor of surface-mediated primordial chemistry. As argued by several authors, the regular mesh of electric charges at the mineral surface can attract the reagents and even arrange them in a proper way relative to each other [20][21][60]. As argued elsewhere, the same mesh of charges should decrease the effective dielectric constant of the surface water layers [61], strengthening thus the potentially catalytic electrostatic interactions at the surface and favoring the condensation reactions.

One can argue, in the context of primordial surface metabolism, that stacking of nucleotides to each other would weaken their interaction with the surface. In the case of a UV-illuminated surface of primordial minerals, however, the nucleobase stacking should place their rings along the normal to the surface and thus decrease the number

of UV-quanta directly hitting the nucleobases proper. The interaction with the surface, at the same time, would hardly decrease the capacity of nucleobases to quench those quanta that hit the polymer backbone. Moreover, the interaction of nucleobases with surface might further attenuate the energy of UV quanta and decrease the possibility of backbone breakage.

The surface could also favor the formation of doubly stranded segments in the primordial polymers. In general, the increase in the fraction of double-stranded regions elevates the resistance of RNA backbone to UV-damage [62], as well as to hydrolysis [63]. In the primordial RNA-like polymers, an occasional formation of double-stranded segments should elevate the probability of their survival. This feature would favor those UV-protecting entities that could form pairs with each other.

In our previous paper [54], we have suggested to perform prebiological synthesis in a reactor system, which *a*) uses UV irradiation as an energy source and *b*) contains aluminosilicate clays as a polymerization template. The most recent studies indicate that surfaces that show properties of photocatalytic semiconductors are even more promising; *e.g.*, TiO₂ has been shown to catalyze the UV-powered transition of formamide into high-molecular compounds attributed to nucleoside bases [64][65].

According to the above discussed definitions of life, the formation of first RNA-like polymers preceded the biological evolution. Still, it is noteworthy that the above considered tentative mechanism of their emergence already shows some features that are typical for *Darwinian* evolution, namely:

1) *Selection of fittest*: In the UV-illuminated primordial world the probability of a UV-breakage was more than real for any compound. Correspondingly, those that succeeded to bind (trap) a UV-quencher got a selective advantage. Hence, the primordial polymerization could be driven by a mechanism that resembled natural selection, with the most UV-resistant polymers living longer.

2) *Emergence of a new function by co-option*: In the primordial 'sugar-phosphate-centric' world, the nitrogenous bases served just as protecting units, so that the UV-quenching capacity but not their exact chemical nature was important. Accordingly, these service units were replaceable and variable. Exactly this variability could have paved the way to the variability of the future genomes. The initially stochastic sequences of UV protectors were eventually replaced by selected 'meaningful' sequences of nucleobases capable of forming more stable double-stranded segments, so that the function of UV protection was gradually complemented by the function of polymer stabilization.

3) *Evolutionary continuity*: Each step on the way from the polymers containing a stochastic set of UV protectors, *via* polymers stabilized by intra-strand interactions, towards first replicators was accompanied by increase in the UV stability of the RNA-like entities. Hence, the ability of nucleobases to form pairs was advantageous even before it became utilized upon replication.

4) *Chemistry conservation*: The ability to process promptly UV quanta, which was vital in the absence of ozone layer, is retained by modern RNA and DNA.

Emergence of the Metabolically Driven Replication. – The transition from the long RNA-like polymers to the first replicators is thermodynamically constrained. While single long polymers can form spontaneously, although with a low probability, their

replication is inevitably coupled with entropy decrease and, hence, can proceed only being driven by a metabolism of some kind. Therefore, the thermodynamically plausible mechanism of origin of life is the one of a ‘metabolically driven replication first’. The choice of potential free energy sources, which had to be constant and utilizable, is, in fact, very limited. First, as noted above, this was the solar light. By monitoring the communities of the modern hydrothermal vents, one, otherwise, can speculate that the primordial reactions could be driven by the redox potential difference between the hydrothermal waters and the environment. This is, however, unlikely from several reasons. First, the modern communities of hydrothermal vents exploit the redox-potential difference between reduced hydrothermal waters and the oxygenated ocean. In the primordial world, in the absence of oxygen, there hardly could have been any redox gap between the hydrothermal waters and the ocean bulk. Secondly, the usage of redox potential differences in the RNA world is constrained by the fact that no natural ribozymes capable of catalyzing redox reactions were discovered so far. Catalysis of redox reactions seems to be a prerogative of enzymes.

By exclusion, the remaining energy source is the UV light. No other known energy source could compete with the UV component of the solar irradiation either in ability to serve simultaneously as both selective and driving force, or in continuity, strength, and access to the whole surface of Earth. How could the UV light be utilized? It cannot be completely ruled out that the first replicators, presumably dwelling at the surface of minerals/clays, were light-driven machines. We, however, would prefer to consider a less demanding two-step primordial metabolism where the UV light contributed to the abiogenic mineral-catalyzed synthesis of rather simple organic compounds (see *e.g.*, [66]), whereas the primordial replication, similarly to the modern one, was thermodynamically coupled with the cleavage of available organics. The catalytic repertoire of modern ribozymes is compatible with this scenario; ribozymes can catalyze both the RNA cleavage and its ligation. Moreover, as first pointed by *Horowitz* [3] and as follows from our simulations (see *Fig. 2*), the spontaneous formation of a long polymer implies presence of an overwhelmingly larger amount of shorter polymers of the same kind. So, after the emergence of first entities capable of driving their self-replication by cleaving other polymers, these ‘other’ polymers become potential prey. This event started the genuine fight for survival.

Conclusions and Further Prospects. – The suggested concept of the ‘*metabolically driven replication first*’ represents a merge between the ‘*replication first*’ and ‘*metabolism first*’ concepts. The scenario does not contradict either of these concepts and might serve as a consensus scheme in the framework of which the molecular details of origin of life can be further elaborated. The key feature of the scenario is the participation of the UV irradiation both as driving and selecting forces during the earlier stages of evolution. In fact, the importance of UV illumination as energy source for the abiogenic syntheses of first macromolecules was realized already by *Haldane* who wrote in 1929 that ‘*the first living ... things were probably large molecules synthesized under the influence of the sun’s radiation*’ [2].

The suggested concept, in the same time, offers some new directions for experimental work. The experimental simulations of primordial abiogenesis were routinely carried out by using solutions imitating the modern ocean waters and, hence,

depleted of phosphate ions. As well, electric discharges were used as energy source since it has been claimed that UV light was damaging for the first life (see, *e.g.*, [52]). Here, we would like to emphasize that it might be worthy to simulate primordial condensation reactions at high phosphate concentrations, using UV light as energy source and in the presence of mineral templates. We hope that in this way the field that has been pioneered by *Stanley Miller* can progress further.

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