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Evolution, Transposition, Transformation and Flow of Information

Evolucija, transpozicija, transformacija in informacijski tok

Marko Vitas[1,*], **Andrej Dobovišek**[2]

[1] Laze pri Borovnici 38, 1353, Borovnica, Slovenia
E-mail: vitas.marko83@gmail.com
Tel.: + 386 41 36 21 11

[2] University of Maribor, Faculty of natural sciences and mathematics, Koroška cesta 160, 2000 Maribor, Slovenia
E-mail: andrej.dobovisek@gmail.com

[*] Author for correspondence

Abstract: Modern science has still not given us a satisfactory empirical explanation of the increasing complexity in living beings through evolutionary history, though whether or not the complexity increases in biological evolution is a hotly debated topic and no agreed-upon definitions of the complexity exist. Nevertheless, this poses the question when comparing simple prokaryotic cells with more complex eukaryotic cells or comparing these with animals or plants or the most complex phenomena, e.g. consciousness and human language. The question of how life actually came into existence is definitely important in this respect. Assuming the hypothesis that in the beginning of the origins of life evolution had to first involve autocatalytic systems which only subsequently acquired the capacity of genetic heredity, we discuss in the present article the possible emergence of digital, discrete information arising from analogue information stored in the intra and intermolecular interactions throughout the molecular evolution. Explaining the origin of life is perhaps central and the most challenging question in modern science. The results of such debates and investigations might shift current biological paradigms and might also have a momentous significance for modern philosophy in understanding our place in universe.

Key words: origin of life, information, chemical evolution, complexity, genetic code, recombination.

Povzetek: Moderna znanost še vedno ni podala zadovoljive empirične razlage za naraščanje kompleksnosti živih bitij skozi evolucijski razvoj, čeprav je vprašanje, ali kompleksnost narašča skozi evolucijsko zgodovino predmet številnih znanstvenih razprav. Prav tako trenutno ne obstaja splošno sprejeta definicija kompleksnosti. To vprašanje se nam zastavi ob primerjavi preprostih prokariontskih celic z bolj zapletenimi eukariontskimi celicami ali primerjava le-teh z živalmi oziroma rastlinami ali z najkompleksnejšimi pojavi, kot sta na primer zavest in človeški jezik. V tem smislu je vprašanje, kako je nastalo življenje na Zemlji ključnega pomena. Ob privzetju hipoteze, da je moral ob nastanku življenja evolucijski razvoj najprej vključevati avtokatalitske sisteme, ki so šele kasneje pridobili sposobnost genetskega dedovanja, je v pričujočem članku predstavljen in argumentiran eden izmed možnih načinov nastanka digitalnega oziroma diskretnega zapisa iz analognih informacij, shranjenih v intra- in inter-molekularnih interakcijah skozi molekularno evolucijo. Kako je nastalo življenje je trenutno eno izmed poglavitnih vprašanj sodobne znanosti. Rezultati tovrstnih raziskav utegnejo imeti velik vpliv na sodobno filozofijo in znanost.

Ključne besede: nastanek življenja, kemijska evolucija, kompleksnost, genetski kod, rekombinacija, informacija.

> ***Problem:***
>
> *A natural system, a contradictory term. Nature does not have a system, it has, it is life and the consequence of an unknown central point towards an unrecognisable boundary. Observing nature is therefore endless and can be divided into the most individual or follow its trace in its entirety along its width and height.*
>
> *(Johann Wolfgang Goethe)*

INTRODUCTION

System Within a System and its Complexity

The hierarchical organisation of a 'system within system' is an apparent characterisation of nature. For example, cells arrange into organs that make an organism, organisms in turn add up to an ecosystem and an ecosystem to a biosphere. The nested pattern is also found when descending downwards in scale. For example, a eukaryotic cell houses cellular organelles that contain molecular complexes assembled from molecules that are, in turn, composed of atoms and so on. For many biotic and abiotic systems it is known how the nested structural and functional order builds up, yet the general principle of why matter evolves to hierarchies has remained little known to many [1-2]. The question of how life actually came into existence is definitely important in this respect. For thousands of years, philosophers and naturalists have been occupied by a quest for an answer to the intriguing question 'How did life begin?' The question on the origin of life is perhaps as old as mankind. Although modern science still has not given us a satisfactory empirical explanation of the increasing complexity in living beings through evolutionary history, though whether or not the complexity increases in biological evolution is a hotly debated topic and no agreed-upon definitions of complexity exist. Nevertheless, this poses the question when comparing simple prokaryotic cells with more complex eukaryotic cells or comparing these with animals or plants or the most complex phenomena, e.g. consciousness and human language [3-6]. However, modern technology nowadays offers various scientific approaches to this intriguing question [7].

"Primeval soup" and Two Schools on the Origins of Life

More than 100 years before the duplex structure of DNA was proposed, Charles Darwin imagined a chemical rich "warm pond" from which evolution originated [8-9]. Later, in 1924, the Russian biochemist Aleksander Oparin introduced his thesis that the development of living creatures in its initial phase should have been the subject of a purely chemical evolution. Under the influence of various natural circumstances, such as, for example, electrical discharges, the first complex organic substances were synthesised from the various inorganic substances, which lead to the creation of the so called "primeval soup" that was composed of substances which represented the basic building blocks for the creation of the first living cells [10-11].

Contemporary efforts in the area of life's origin are focused around two schools that are trying to resolve the question of what occurred first; replication or metabolism. In this respect different authors write about functional circuits, in particular, on metabolic networks ("metabolism first" hypotheses) and self-replicating nucleic acids (e.g. RNA) or their predecessors ("replication first" hypotheses) [12-15]. In other words, theories of the Origin of Life can be categorised as 'template replication first' and 'metabolism first' [16].

The seminal observations of Orgel, Ferris [17 and given references], and others clearly suggested that something like RNA might have been the first polymer to be associated with life processes. Additional evidence was provided when Thomas Cech and Sidney Altman [17] found that certain types of RNA had catalytic properties, Such RNA molecules, now referred to as ribozymes, can make and break specific chemical bonds within their own structure rather than depending on protein enzymes. The discovery of catalytic RNA led Walter Gilbert to propose an "RNA World," positing that life did not begin with the complex systems of DNA, RNA, and proteins that characterize all life today. Instead, RNA molecules could have served as catalysts as well as storing and transmitting genetic information [8, 17]. The "Replication first" hypotheses can explain the adaptive evolution of primordial systems via random mutations and natural selection, however, there are many problems that an RNA world scenario creates in terms of an "impossible" chemistry [13-14, 18 and given references; 19-20], like catalytic RNA (ribozymes) in an RNA World must have been synthesized without templating, i.e. they had to have originated by a random process. The synthesis of longer polymers requires a synthetic reaction whose efficiency approaches 98–99%. In addition even small RNAs do not release their complementary strand very efficiently, which makes any template-dependent growth mechanism difficult. Generally RNA is a very unstable molecule. Furthermore, nucleotides are complex molecules and the probability of their spontaneous synthesis is very low. Actually, even if the abiotic synthesis of genetic polymers was possible, the question would not be solved as the issue is not to synthesize specific molecules but the need of the spontaneous emergence of non-equilibrium self-organizing systems with an evolvable capacity.

In contrast to that, the "Metabolism first" hypotheses imply that autocatalytic networks can be assembled from mixtures of interacting organic molecules not capable of template-based replication. Such autocatalytic networks represent the primordial process in evolution history. An organism ("a metabolist") supposedly later acquired the competence of genetic information storage, genetic control and cellular organisation [21-22]. This scenario has been criticized from the biochemical point of view [23]. However, even if the chemistry of the cycle worked properly, it is not clear how this network could evolve via mutations and selection because it was not enclosed in a proto-organism [13] and the approach of open non-equilibrium self-organizing systems without resorting to genetic polymers is confronted with the problem of heredity, i.e. the need for the systems to acquire heritable structure/function properties [14]. However, epigenetic mechanisms based on structural inheritance systems are available in present organisms [24-25]. In this respect, two intriguing questions which arise from the sequencing of the human genome should also be considered; how can some of 25,000 genes generate such a rich complexity in the human phenotype and what are the theoretical reasons for the vastly greater phenotypic complexity of humans compared to a round worm *Caenorhabditis elegans*, with about 20,000 gene coding sequences [26]. In other words, the number of human genes is far fewer than we expected [7]. Assuming the hypothesis that in the beginning, in the origins of life evolution had to first involve autocatalytic systems, which only subsequently acquired the capacity of genetic heredity; we discuss in the present article the possible emergence of digital, discrete information arising from analogue information stored in the sets of intra and intermolecular interactions throughout the molecular evolution.

DISCUSSION

Were Metabolic Networks and Circles Able to Evolve?

According to evolutionary theory concepts, variations and errors are crucially required in the development of new functions and species by natural selection. As we have assumed the primary role of the autocatalytic systems in the origins of life before they acquired the capacity of template-directed heredity, this question poses itself as a fundamental one and needs to be addressed first before we proceed with our discussion. Metabolism conforms to thermodynamic laws, precluding the strict accuracy of the catalysed reactions. Hence, in extant organisms, for each regular pathway, a wealth of variants inputs and produces metabolites that are similar to but not exact replicas of the core metabolites. Macromolecule modification results in the alteration of the enzymatic catalysed reactions. A further source of non-standard metabolites results from inaccuracies in the enzyme catalysed reactions. Paralogous metabolism, named and reviewed by Danchin and Sekowska [27], i.e. variants of metabolism, with variants of regular metabolites included, are continuously emerging in living organisms.

Ancient enzymes were fuzzy in the way they recognised their substrates [28]. In the course of evolution they progressively became more and more specific [29]. Therefore we may frankly assume that primordial metabolic networks were prone to errors and alternative autocatalytic networks and cycles may have arisen at the early stages of chemical evolution. It was shown that autocatalytic sets are capable of evolution by natural selection, even in the absence of specific information-carrying molecules [30]. Large, complicated and extremely complex early prebiotic metabolisms have been proposed [31-32]. The system of autocatalytic reactions struggles to use its power to dominate the whole space and out-compete other systems or absorb them. If we consider the division of the system in its broadest sense so that the division does not necessarily include the creation of identical parts, then we can treat it as the basic generator of diversity. As a partition network into potentially growing sub-networks could be proposed and it is also known that natural selection acts on the variation in any mechanism that consumes energy from the environment [26] which in turn includes molecular interactions and metabolism [33], we can suppose that evolutionary development is possible on the Darwinian paradigm of the networks of autocatalytic reactions that occurred in the primordial world, without having information stored in template homopolymers e.g. DNA or RNA.

Peptide Chains Refined Substrate-Specificity of Early Catalysers

Coenzymes likely represent the oldest metabolic fossils within a cell, as suggested by their presence and essentiality in all realms of life and the autocatalytic nature of their biosynthetic pathways. Coenzymes are often considered as the remnants of primordial metabolism. The autocatalytic nature of coenzymes also speaks in favour of an ancient metabolic history [13, 15, 34], while some other authors give preference of the primordial role to metal catalysts such as iron, nickel, cobalt molybdenum, and tungsten. Abiotically synthesised peptides would soon stabilise and begin to optimize metal-based catalysts as well as to introduce substrate-specificity [35]. Can this assumption be logically extended to coenzymes and could the origin of the genetic code and homochirality be explained by the acquisition of substrate-specificity with the acquirement of peptide chains, where owing to kinetic reasons homochiral reaction systems outcompeted heterochiral ones. It should also not be overlooked that some coenzymes, including NAD, FAD, coenzyme A and adenosyl-cobalamin, share a ribonucleotidyl group, even though they have completely different biochemical roles. Indeed, in none of them does the ribonucleotidyl moiety participate directly in the coenzymatic function [15]. Thus, this ribonucleotidyl moiety might serve us as a clue for looking at the origin of the genetic code. The origin and evolution of the genetic code is supposed to be a critical transition in the evolution of modern organisms [4]. The canonical genetic is one of the most dominant aspects of life on this planet, and thus studying the origin of the genetic code is critical to understanding the evolution of life [36], including the origin of life. In this sense it is possible to view the ribosome as a digital-to-analogue information converter [37], which intuitively is leading us to the next question.

Did Metabolic Cycles and Networks at the Time of the Origins of Life Possess Heredity?

A sudden transition in a system from an inanimate state to a living state - defined on the basis of present day living organisms - would constitute a highly unlikely event hardly predictable from physical laws [38]. Very probably such living matter from the time of the origins of life would be at the present day instantly devoured or absorbed, which would not have been the case before living creatures were formed [8], which makes difficult to guess what kind of molecules were the carriers of the information in prebiotic organisms. Life is a palimpsest [39-40]. Surprisingly, the number of discovered human genes is far fewer than expected, therefore our knowledge of the epigenetic coupling with the environment might radically change our view on heredity [7], which will be discussed later on. In present organisms, the information defining the richness of phenotypic complexity is stored digitally, discrete in the nucleic acids and are contained in a more analogue way in the proteins. Discrete information stored in the nucleic acids is the only information that can be unambiguously read and copied, while proteins are more analogue in their physicochemical engagement. Since in some conformational span the enzyme molecule is able to perform a catalytic function and every infinitesimal change in conformation has an impact on the kinetics of the catalysed reaction, we can describe this information as analogue. Protein folding into compact domains is a kind of self coding [41]. There are also some other post-translational modifications, like proteolytic editing and glycosilation which should be mentioned in addition to DNA methylation as a heritable epigenetic modification involved in the regulation of a variety of processes ranging from development to genomic imprinting, gene regulation and transposon silencing [42]. Therefore the digital genome is only one part of the informational story and proteins define another form of heredity, one that lies outside of the genetics (epigenetics). Moreover, according to Kurland [41], self folding and proteolytic editing might be just good enough to create a prebiotic chemical platform from which a cellular genetic system might take off. Active sites of protein enzymes generally function as part of a larger structure that holds them in proper alignment. The backbone of protein polymers, for which sequence the information is stored digitally in nucleic acids, is invariable, while their side chains can be arranged in an unlimited variety of combinations. In general, therefore, no predictions of tertiary protein structure are possible from the information contained in the DNA sequence alone [26]. Each amino acid side residue with its side-chain has a specific influence on the protein folding into the tertiary structure. This specific impact is heritable. Certainly this view must however reckon with the physicochemical constraints like temperature, pH and interactions with other macromolecules within the micro-environment. Besides, taking into account that Freeman Dyson [43] had convincingly established [40] that information propagates by metabolism which reproduces (makes a similar copy), while programme replicates (makes an identical copy), it is possible to assume the primeval occurrence of analogue information within autocatalytic networks and cycles and before replicating templates.

Digital information is practically resistive to noise, while the analogue signal is sensitive to noise. Therefore, the next developmental stage for the autocatalytic network is represented by the acquisition of digital, discrete information code for the construction of a system in replicable elements (e.g. in homopolymer chains, such as RNA and DNA nucleic acids). Such a code provides additional stabilization of the system against spontaneous disintegration and simultaneously represents the very beginning of heredity as known in modern organisms [31]. It also provides a constant, stable, robust environment in terms not to be influenced by the external perturbations in order to enable more elaborated structures to develop. Natural selection can be seen as having both the role of stabilizing a species and of selecting better adapted organisms [26]. However, RNAs in primordial conditions were prone to recombination [19, 44], which is leading to delicate question, “Great Perhaps”, why the recombination of heritable material is maintained in the course of evolution, while the evolution favours the fidelity of replication. An answer probably lies in the thin borderline between permanence and the change to adapt to the ever-changing environment. Is recombination as a response to the environmental stimulus or change, a relic from the ancient evolutionary past?

Various Definitions of Life Exist in Contemporary Science

As it is troublesome and elusively difficult to define a living state as such, vis-à-vis to non-living matter, consequently various definitions of life exist in contemporary scientific conceptions [14, 45, 46] and simultaneously taking into account the hierarchical organisation of irreversible processes "system embedded within system" that life certainly is [47], it is worth considering a "heterotroph" – "organotroph" type of organism bordered with a membrane which depended on and was as a part of the broader autocatalytic network at the beginning of the cellular life on earth. In general, interactions are effectively weaker over increasingly longer distances. The strongest forces adhere to the smallest systems. For example, the chemical reactions in a cell are faster than intercellular trafficking in an organism. This is the reason for the characteristic asymmetry about the boundary between a larger system and its submerged smaller systems [1]. Therefore it can be proposed that encapsulation into a membrane occurred and evolved where the strong interactions were needed. However, such a "heterotroph" organism is not supposed to be a simple prokaryotic organism, but rather a far more complex one e.g. like a eukaryote. At this point, it is necessarily to take into consideration the matter of fact that higher organisms often return to their unicellular origins during their life cycle in the form of zygotes or gametes [48]. This process is commonly accompanied by recombination and has evolved perhaps for entropic reasons. Unicellular organisms reproducing through binary fission are like DNA and RNA homopolymers "immortalized" and therefore lack an important attribute of life. In contrast to RNA and DNA homopolymers, unicellular organisms possess a metabolism. According to Kurland [41] the eukaryotes are the ancestral lineage from which the divergence of Archaea and Bacteria are thought to have been driven by reductive pressure. Bacteria and Archaea are not identifiable as ancestors to eukaryotes. Instead they diverge from a common ancestor independently of the eukaryotes as highly specialised, fast growing unicellular organisms that have evolved efficient simplicity as the hallmarks of their cellular architectures and to survive predation by their relatively complex eukaryote cousins [49]. Therefore some other aspects of the transformation of chemical information need to be considered.

Flow of Information

As it was mentioned earlier it is troublesome and elusively difficult to define living state, one is for sure; living organisms tend to keep their internal processes far from thermodynamic equilibrium and under relatively stable conditions. In a good approximation, living organisms can be viewed as open systems in a stationary non-equilibrium state.

If an organism is to be considered live, it must export entropy to its environment, which would enable it to avoid the state with maximal entropy – equilibrium state. The export of entropy of an organism to its environment seems to be of central importance when we discuss about living matter and one of the fundamental characteristics of life [50]. On the other hand, entropy is in tight connection with information, since information is defined as the difference between the maximum and actual entropy of the system [20]. Therefore, together with the flow of entropy, the flow of information between an organism and its environment also exists. Since the flow of entropy is directed from the organism to the environment which enables the organism to lower its internal entropy, information must flow in the opposite direction – from the environment to the organism. In other words, in order to be considered living, an organism must be able to maintain information – organisms are able to stay away from the state of maximum entropy arbitrarily longer [20]. Entropy production and information accumulation are two sides of the same coin [51].

Successful organisms are well adapted to different conditions in their environment and, if they want to survive, they must be able to adapt successfully to changes in the environment. The latter is probably the main leading force of biological evolution. If we try to put the above-mentioned flow of information into the context of biological evolution, then we cannot overlook that such informational flow should be strongly dependent on the environmental conditions. Any changes in environmental conditions will certainly change the flow of information from the environment to the organisms. Such changes should not be too abrupt; otherwise organisms will not succeed with adaptation to new environmental circumstances and will not survive (e.g. mass extinction). However, if changes in the environmental conditions are small enough, we can expect that, at that moment, the most appropriate members of a species, with a specific pool of DNA, will survive. Due to the changes in environment, we can therefore expect that in later generations of members within some species, specific features of DNA will dominate. In this way small - analogue changes in the environment will be in some sense stored, or at least will affect digitally stored information on DNA. Organisms repeatedly "measure" their environment over generations, which lead to a cumulative record of mutations, adaptations and recombinations in the genome of surviving members of the species [52]. Digitalisation of information offers vast possibilities of precise, sophisticated regulation and control. In addition to its repository role for information to keep a record of already existing phenomena, discrete information stored in nucleic acids also serve as a sort of memory re-enacting the biochemical reactions when needed [53]. In the context of our discussion, this could not be possible without informational flow from the environment to the organisms.

As we assumed the primeval role of autocatalytic networks which contained analogue information, it is reasonable to pose a question, if the evolutionary course can also be treated as a digitalisation of molecular information. However, it's debatable how much chemical information can be practically digitalized from a minimal inventory of building blocks to support the evolutionary dynamics [7].

Whether or not complexity increases in biological evolution is a hotly debated topic. Furthermore, at least historical evidences of periods' extinction suggest that information may not always have been increasing [54]. Nevertheless, at this point of our discussion it is worth emphasising another aspect of the "order from order" theme defined by Erwin Schrödinger [50]. An externally imposed order, on whose dissipation is significantly frustrated, is needed to drive a system to disequilibrium, and potentially far enough from equilibrium that order-creating irreversible processes will arise within it. In other words, it takes order to create order [47]. The embedded system acquires information from the ordered environments. Therefore, it is indeed questionable if information is increasing through evolutionary history, if we also bear in mind the information in the embedding system. The central phenomenon is the accumulation of semantic information in the structural features of the biosphere, driven by the entropic forces [51].

While standard information-theoretic measures, such as Shannon information indices, have been proven to be useful in some biological contexts – for example, in the field of bioinformatics – more foundational questions regarding the origin and nature of biological information have been notoriously recalcitrant to consensus [7, 55]. Nevertheless, whenever the development of a trait is causally dependent on an aspect of the environment, the environment will carry information - in the bare correlational sense-about the trait [56]. The complexity of organisms over time is largely a reflection of the complexity of the environment. The information is contained in physicochemical constraints and disequilibrium system producing work i.e. order – information creating flow which leads to new structures which in turn, as everything depends on everything else, means more imposed constraints and so on. Cellular complexity (information) relies on protein to protein interaction [57] and metabolic systems, from single reactions to whole, multi-tiered pathways, are run in time and space by physical objects (enzymes) that handle chemically reactive molecules which operate in a non-homogeneous and very crowded milieu [58, 59]. Therefore, it is clear that most biological functions can only be described using a system of interacting molecules [60, 61]. Order, whose creation is dictated by the thermodynamics of far - from - equilibrium systems, is everywhere in the form of autocatalytic, work-creating engines - engines which accelerate, as active devices, the dissipation of the immense astronomy of disequilibrium with which our Universe was born [47]. On the basis of the above-mentioned references it is possible to propose the flow and transformation of information through a cascade from embedding to embedded systems.

CONCLUSIONS

The origin of life is a highly interdisciplinary field of investigation. In our discussion we have assumed a hypothesis that at the beginning, in the origins of life, evolution had to first involve autocatalytic systems, which only subsequently acquired the capacity of genetic heredity. On the basis of the published literature, we have discussed the importance of the digitalisation of information contained in the biological systems through evolutionary history, from the origins of life to the present organisms. We propose that such digitalization occurs through the flow of information from the environment to the organisms. Information flow seems to be in close connection with the non-equilibrium nature of living organisms, which must maintain information in order to be considered live. In this view, informational flow by which the embedding system influences the embedded system was emphasised.

EPILOGUE AND PERSPECTIVES

The results obtained from the origin of life research have a deep influence on contemporary life sciences. Biological evolution is an outcome of chemical evolutionary processes and continues to be influenced by it [7]. As far-from equilibrium systems are able to perform work, it was proposed that primeval autocatalytic networks and cycles behave selfishly [31], consequently the "selfish gene" metaphor defined by Dawkins in his famous popular scientific work "The selfish gene" [62] behaviour can also be extended by the alternative analogy of "selfish metabolism" [53]. There might be a shift of paradigm from the competition of genes solely to be replicated to the competition of genes also to be expressed. This could also lead to a revision of the DNA, RNA, protein central dogma flowchart [33, 53]. The results from the origins of life investigation might also influence our understanding of the Darwinian evolution by natural selection as debates have been initiated on whether the evolutionary theory needs to be revised [63]. However, it is expected that the Darwinian evolution will retain its adaptive role of natural selection as it selects better adapted species and simultaneously stabilizes them. There is no doubt that knowledge regarding the origin of life has a substantial influence on contemporary philosophical knowledge, from where we are coming from and where we are going to. Such results may also address the great challenges we face as a society and could significantly impact our future survival [7].

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CONFLICT OF INTEREST

The authors declare no competing financial interest.

REFERENCES

1. Annila, A. and Kuismanen, E. Natural hierarchy emerges from energy dispersal. *BioSystems*, **2009**, *95*, pp. 227-233.
2. Kleidon, A. Life, hierarchy, and the thermodynamic machinery of planet Earth. *Physics of Life Reviews,* **2010**, *7,* pp. 424–460.
3. Maynard Smith, J. and Szathmáry, E. *The major evolutionary transitions*. W.H. Freeman Spectrum, Oxford, New York, **1995,** pp. 3-8.
4. Szathmáry, E. and Maynard Smith, J. The major evolutionary transitions. *Nature*, **1995**, *374*, pp. 227 -232.
5. Olson, M. V. Molecular Evolution 'When Less Is More: Gene Loss as an Engine of Evolutionary *Change. Am. J. Hum. Genet*. **1999**, *64*. pp. 18-23.
6. Adami, C. What is complexity? *BioEssays,* **2002**, *24(12)*, pp. 1085-1094.
7. Goodwin, J.T., Lynn, D. G., Burrows, C., Walker, S., Amin, S. and Armbrust, E. V. Alternative Chemistries of Life, *Empirical Approaches,* A Report from a Workshop on Alternative Chemistries of Life: Empirical Approaches. Goodwin, J.T. and Lynn, D. G. (eds.) http:// chemistry.emory.edu/home/assets/alternativechem.pdf **2014**. Accessed 24. October 2014.
8. Deamer, D. First Life, and Next Life. Synthetic Biology is a New Field, But It's Centered on an Old Question: How did Life Begin? *Technology Review*, **2009**, *112(3)*, pp. 66-73.
9. Lynn, D., Burrows, C., Goodwin, J. And Mehta, A. Origins of Chemical Evolution. *Accounts of Chemical Research,* **2012**, *45(12),* pp. 2023-2024.
10. Dixon B. *Power Unseen, How Microbes Rule the World*. W.H. Freeman Spektrum, New York, USA, **1994**, p. 5.
11. Luisi, P. L. *The Emergence of Life, From Chemical Origins to Synthetic Biology*. Cambridge University Press, Cambridge, **2006**, p. 1.
12. Pross, A. Causation and the origin of life. Metabolism or replication first? *Origin. Life Evol. Biosph.* **2004**, *34*, pp. 307-321.
13. Sharov, A. A. Coenzyme Autocatalytic Network on the Surface of Oil Microspheres as a Model for the Origin of Life. *Int. J. Mol. Sci.,* **2009**, *10*, pp. 1838-1852; doi:10.3390/ijms10041838.
14. Tessera, M. Origin of Evolution *versus* Origin of Life: A Shift of Paradigm. *Int. J. Mol. Sci.,* **2011**, *12*, pp. 3445-3458; doi:10.3390/ijms12063445.
15. Raffaelli, N. Nicotinamide Coenzyme Synthesis: A Case of Ribonucleotide Emergence or a Byproduct of the RNA World? In: *Origins of Life: The Primal Self-Organization* Editor: Egel R., Springer-Verlag Berlin Heidelberg, Germany, **2011**, pp. 185-208; DOI: 10.1007/978-3-642-21625-1_9.
16. Gordon-Smith, C. Non-Template Molecules Designed For Open-Ended Evolution. In: *Advances in Artificial Life ECAL,* Eds.: Lenaerts, T., Giacobini, M., Bersini, H., Bourgin, P., Dorigo, M. and Doursat, R. Advances in Artificial Life ECAL 2011, *Proceedings of the Eleventh Euorpean Conference on the Synthesis and Simulation of Living Systems*, Massachusetts Institute of Technology USA, **2011**, pp. 268-275.
17. Orgel, L. E. Prebiotic Chemistry and the Origin of the RNA World. *Critical Reviews in Biochemistry and Molecular Biology,* **2004**, *39*, pp. 99-123; DOI: 10.1080/10409230490460765.
18. Shapiro, R. A Replicator Was Not Involved in the Origin of Life. IUBMB*Life*, **2000**, *49*, pp. 173-176.
19. Lehman, N., Díaz Arenas, C., White W. A. and Schmidt, F. J. Complexity through Recombination: From Chemistry to Biology. *Entropy,* **2011**, *13*, pp. 17-37; doi:10.3390/e13010017.
20. Adami, C. Informatic-Theoretic Considerations Concerning the Origin of Life. arXiv:1409.0590v2 [q-bio.PE].
21. de Duve, C. Clues from present – day biology: the tioester world. In: *The Molecular Origins of Life*, Ed.; Brack, A., Cambridge University Press, Cambridge, **1998**, pp. 219-236.

22. Wächtershäuser, G. Origin of life in an iron – sulfur world. In: *The Molecular Origins of Life*, Ed.; Brack, A., Cambridge University Press, Cambridge, **1998**, pp. 206-218.

23. Orgel, L. E. The Implausibility of Metabolic Cycles on the Prebiotic Earth. *PLoS Biol* **2008** *6(1)*: e18. doi:10.1371/journal.pbio.0060018.

24. Baverstock, K. and Rönkkö, M. Epigenetic regulation of the mammalian cell. *PLoS* One *3*, e2290, **2008** doi:10.1371/journal.pone.0002290.

25. Baverstock, K. Life as physics and chemistry: A system view of biology. *Progress in Biophysics and Molecular Biology,* **2013**, *111*, pp. 108-115; http://dx.doi.org/10.1016/j.pbiomolbio.2012.09.002.

26. Annila, A. and Baverstock, K. Genes without prominence: a reappraisal of the foundations of biology. *J. R. Soc. Interface,* **2014**, *11*: 20131017; http://dx.doi.org/10.1098/rsif.2013.1017.

27. Danchin, A. and Sekowska, A. The logic of metabolism and its fuzzy consequences. *Environmental Microbiology,* **2014**, *16(1)*, pp. 19-28.

28. Kajander, T., Kellosalo, J., and Goldman, A. Inorganic pyrophosphatases: one substrate, three mechanisms. *FEBS Lett.*, **2013**, *587*, pp. 1863–1869.

29. Nam, H., Lewis, N.E., Lerman, J.A., Lee, D.H., Chang, R.L., Kim, D., and Palsson, B.O. Network context and selection in the evolution to enzyme specificity. *Science,* **2012**, *337*, pp. 1101–1104.

30. Vasas, V., Fernando, C., Santos, M., Kauffman, S. and Szathmáry, E. Evolution before genes. *Biology Direct,* **2012**, *7:1;* http://www.biology-direct.com/content/7/1/1.

31. Vitas, M. On the Theory of Species Evolution Through Natural Selection; Original Title: O teoriji razvoja vrst a pomočjo naravne selekcije. *Apokalipsa: revija za preboj v živo kulturo,* **2011**, *152*, pp. 113-122; http://www.dlib.si/?URN=URN:NBN:SI:DOC-UY4WVSCK.

32. Virgo, N. and Ikegami, T. Autocatalysis Before Enzymes: The Emergence of Prebiotic Chain Reactions. In: *Advances in Artificial Life ECAL 2013*; Eds.; Lio, P., Miglino, O., Nicosia, G., Nolfi, S. and Pavone, M.; *Proceedings of the Twelfth European Conference on the Synthesis and Simulation of Living Systems*, **2013**, pp. 240-247; DOI: http://dx.doi.org/10.7551/978-0-262-31709-2-cho36.

33. Kupiec J. J. *The Origin of Individuals.* World Scientific. New Jersey, London, Singapore, Beijing, Shanghai, Hong Kong, Taipei, Chennai, **2009**, p. 65, 106 and 137.

34. Jadhav, V.R.; Yarus, M. Coenzymes as coribozymes. *Biochimie;* **2002**, *84*, pp. 877-888.

35. Nitschke, W., McGlynn, S. E., Milner-White, E. J. and Russell, M J. On the antiquity of metalloenzymes and their substrates in bioenergetics. *Biochimica et Biophysica Acta,* **2013**, *1827* pp. 871–881; http://dx.doi.org/10.1016/j.bbabio.2013.02.008.

36. Johnson, D. B. F. and Wang, L. Imprints of the genetic code in the ribosome. *PNAS,* **2010**, *107 (18)*, pp. 8298-8303; doi: 10.1073/pnas.1000704107.

37. Goodwin, J.T.; Mehta, A. K. and Lynn, D. G. Digital and Analog Chemical Evolution. *Acc. Chem. Res., 45(12)*, **2012**, pp. 2189-2199; DOI: 10.1021/ar300214w.

38. Pascal, R., Pross, A. and Sutherland, J. D. Towards an evolutionary theory of the origin of life based on kinetics and thermodynamics. *Open Biol.* **2013**, *3, 13015,;* http://dx.doi.org/10.1098/rsob.130156.

39. Cairns-Smith, A.: *Genetic takeover and the mineral origin of life*. Cambridge University Press, Cambridge (UK), **1982**.

40. Danchin, A. The emergence of first cells. In: *Encyclopedia of Molecular and Molecular Medicine.* 17, Ed.; Mayers, R.A. Wiley, **2014**, pp. 1-25.

41. Kurland, C. G. The RNA dreamtime. *Bioessays* **2010**, *32,* pp. 866–871.

42. Montanini, B., Yang Chen, P., Morselli, M., Jaroszewicz, A., Lopez, D., Martin, F. Ottonello, S., and Pellegrini, M.. Non-exhaustive DNA methylation-mediated transposon silencing in the black truffle genome, a complex fungal genome with massive repeat element content. *Genome Biology,* **2014**, *15:411;* http://genomebiology.com/2014/15/7/411.

43. Dyson, F. J. *Origins of life*, Cambridge University Press, Cambridge (UK), **1985**.

44. Nechaev S. Y., Lutay, A. V., Vlassov, V. V, and Zenkova, M. A. Non-Enzymatic Template-Directed Recombination of RNAs. *Int. J. Mol. Sci.,* **2009**, *10*, pp. 1788-1807; doi:10.3390/ijms10041788.

45. Egel, R. On the Misgivings of Anthropomorphic Consensus Polling in Defining the Complexity of Life. *Journal of Biomolecular Structure & Dynamics,* **2012**, *29(4)*, pp. 615-616.

46. Tessera, M. Is A n + 1 Definition of life Useful?

Journal of Biomolecular Structure & Dynamics, **2012**, *29(4)*, pp. 635-636.

47. Russell, M. J., Nitschke, W. and Branscomb, E. The inevitable journey to being. *Phil Trans R Soc B,* **2013**, *368*: 20120254; http://dx.doi.org/10.1098/rstb.2012.0254.
48. Torday, J. S. Evolutionary Biology Redux. *Perspectives in Biology and Medicine,* **2013**, *56(4)*, pp. 455-484.
49. Harish, A., Tunlid, A. and Kurland, C. G. Rooted phylogeny of the three superkingdoms. *Biochimie,* **2013**, *95*, pp. 1593-1604.
50. Murphy, M. P. and O'Neill, L. A. J. What is Life? The next fifty years. An introduction. In: *What is Life? The next fifty years*, Eds.: Murphy M. P. and O' Neill L. A. J. Cambridge University Press, Cambridge, **1997**, p. 2.
51. Herrmann-Pillath, C. Revisiting the Gaia Hypothesis: Maximum Entropy, Kauffman's 'Fourth Law' and Physiosemeiosis. *Frankfurt School – Working Paper Series 160, Frankfurt am Main: Frankfurt School of Finance & Management*, **2011**.
52. Binder, P. M. and Danchin, A. Life's demons: Information and order in biology. *EMBO reports,* **2011**, *12(6)*, pp. 495-499.
53. de Lorenzo, V. From the selfish gene to selfish metabolism: Revisiting the central dogma. *Bioessays,* **2014**, *36,* pp. 226–235.
54. Mirmomeni, M., Punch, W. and Adami, C. Is information a selectable trait? arXiv:1408.3651v1 [q-bio.PE].
55. Lean, O. M. Getting the most out of Shannon information. *Biol. Philos.* **2013**; DOI 10.1007/s10539-013-9410-2.
56. Griffiths, P. E. and Gray, R. D. Developmental Systems and Evolutionary Explanation. *The Journal of Philosophy,* **1994**, *91(6)*, pp. 277-304.
57. Woese, C. R. A new biology for new century. *Microbiol. Mol. Biol. Rev.* **2004**, *68,* pp. 173-186. doi:10. 1128/MMBR.68.2.173-186.2004.
58. Weiss, M. Crowding, Diffusion, and Biochemical Reactions. *International Review of Cell and Molecular Biology* **2014**, *307*, 383-417; http://dx.doi.org/10.1016/B978-0-12-800046-5.00011-4.
59. de Souza, T. P., Steiniger, F., Stano, P., Fahr, A. and Luisi, P. L.: Spontaneous Crowding of Ribosomes and Proteins Inside Vesicles: A Possible Mechanism for the Origin of Cell Metabolism. *ChemBioChem*, **2011**, *12*, pp. 2325-2330; DOI: 10.1002/cbic.201100306.
60. Perica, T., Marsh, J. A., Sousa, F.L., Natan, E., Colwell, L. J., Ahnert, S. E. and Teichmann, S. A. The emergence of protein complexes: quaternary structure, dynamics and allostery. *Biochem. Soc. Trans.* **2012**, *40,* pp. 475–491; doi:10.1042/BST20120056.
61. Marsh, J. A.: Hernández, H., Hall, Z., Ahnert, S. E., Perica,T., Robinson C. V. and Teichmann, S. A. Protein complexes are under evolutionary selection to assemble via ordered pathways. *Cell* **2013**, *153*, pp. 461-470; http://dx.doi.org/10.1016/j.cell.2013.02.044.
62. Dawkins R. *The selfish gene*, Oxford University Press, Oxford, **1978**.
63. Laland, K., Uller, T., Feldman, M., Sterelny, K., Müller, G. B., Moczek, A., Jablonka, E., Odling-Smee, J., Wray, G. A., Hoekstra, H. E., Futuyma, D. J., Lenski, R. E., Mackay, T. F. C., Schluter, D., and Strassmann, J. E. Does evolutionary theory need a rethink? *Nature* **2014**, *514*, pp. 161-164.