

Review

The origins and physical roots of life's dual – metabolic and genetic – nature

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ABSTRACT

This review paper aims at a better understanding of the origin and physical foundation of life's dual – metabolic and genetic – nature. First, I give a concise 'top-down' survey of the origin of life, i.e., backwards in time from extant DNA/RNA/protein-based life over the RNA world to the earliest, pre-RNA stages of life's origin, with special emphasis on the metabolism-first *versus* gene/replicator-first controversy. Secondly, I critically assess the role of minerals in the earliest origins of both metabolism and genetics. And thirdly, relying on the work of Erwin Schrödinger, Carl Woese and Stuart Kauffman, I sketch and reframe the origin of metabolism and genetics from a physics, i.e., thermodynamics, perspective. I conclude that life's dual nature runs all the way back to the very dawn and physical constitution of life on Earth. Relying on the current state of research, I argue that life's origin stems from the congregation of two kinds of sources of negentropy – thermodynamic and statistical negentropy. While thermodynamic negentropy (which could have been provided by solar radiation and/or geochemical and thermochemical sources), led to life's combustive and/or metabolic aspect, the abundant presence of mineral surfaces on the prebiotic Earth – with their selectively adsorbing and catalysing (thus 'organizing') micro-crystalline structure or order – arguably provided for statistical negentropy for life to originate, eventually leading to life's crystalline and/or genetic aspect. However, the transition from a prebiotic world of relatively simple chemical compounds including *periodically* structured mineral surfaces towards the complex *aperiodic and/or informational* structure, specificity and organization of biopolymers and biochemical reaction sequences remains a 'hard problem' to solve.

KEY WORDS: Origin and nature of life; Metabolism; Genetics; Crystallinity; Mineral surfaces; Thermodynamic and statistical negentropy.

INTRODUCTION AND ARTICLE OUTLINE

"What is life?" is arguably the most fundamental question that can be asked in biology, as it concerns the 'physical nature' of life and herewith the very foundation of biology within the broader and more fundamental field of physics.¹⁻³ Living cells and organisms are complex physical systems constituted by (i) metabolic network organization which is pervaded by functional gene products (i.e., functional RNAs and proteins) and, thus, by genetic sequence information derived from (ii) the aperiodic crystalline structure of nucleic acid sequences.⁴ In the present paper, I aim at a better understanding of the origin and physical foundation of this 'dual' or 'twofold' nature of life on Earth. One of the most enduring controversies in the origin-of-life research is that between a 'metabolism-first' *versus* 'gene/replicator-first' origin. Here, the weakness of the two scenarios is outlined, while the recent tendency by both camps to approach and to integrate the two models is supported. That is, it is argued that both metabolism and genetics run all the way back to the very dawn and physical constitution of life on Earth.

First, in section 2, relying on a concise 'top-down' review of the origin-of-life research – backwards in time from extant DNA/RNA/protein-based life over the RNA world to the earliest, pre-RNA stages of life's origin – I explore to what extent life's dual nature, i.e., metabolic network dynamics and crystalline genetics, would already have been present in the RNA world or even

earlier in pre-RNA stages.

Then, in section 3, I discuss the role of mineral catalysts (crystalline mineral surfaces) in the earliest stages of life's origin and their bearing on life's dual nature. Based on the current state of research on the origin of life on Earth, I conclude that, while *sources of thermodynamic negentropy* [which could have been constituted by solar radiation (UV light and heat) and/or geochemical sources (heat and mineral reducing power)] were crucial for the emergence of life's combusive and/or metabolic aspect, the abundant presence of mineral surfaces on the prebiotic Earth – with their selectively adsorbing and catalysing (thus 'organizing') micro-crystalline structure or order – arguably constituted an important *source of statistical negentropy*, eventually leading to life's crystalline and/or genetic aspect. That is, both metabolism (or more fundamentally 'combustion' as the thermodynamic aspect of life) and genetics (or more fundamentally 'crystallinity' as the statistically ordered aspect of life) are anchored in a twofold physical (thermodynamic and statistical) constitution or foundation.

And finally, in section 4, relying on the work of Erwin Schrödinger, Carl Woese and Stuart Kauffman, I discuss the role of both the Second and Third Laws of Thermodynamics in life's origin. I conclude that whereas the Second Law seems to have played a rather 'trivial' role, as it accompanies virtually every physical process, including biotic processes, the role of the Third Law seems to have been 'non-trivial' or 'crucial'. It played an indispensable role in providing for a relatively 'stable', 'condensed', 'solid', 'crystalline' physicochemical foundation for both genetic replication and cellular/metabolic reproduction and, herewith, for Darwinian evolution by natural selection. However, it was arguably only a 'necessary' and not a 'sufficient' condition for life to originate, as it does not explain the (still unresolved) 'hard problem' of life's origin, i.e., the transition from a prebiotic world of relatively simple chemical compounds including *periodically* structured mineral surfaces towards the complex *aperiodic and/or informational* structure, specificity and organization of biopolymers and biochemical reaction sequences.

In sum, through a systematic top-down exploration of the origin of life, it is intended to eventually penetrate into the (dual) physical nature, constitution and foundation of life on Earth as we know it and, as such, to contribute to the "what is life"-problematic.¹⁻⁶ Hence, besides providing an integrative overview of the literature, this article also aims at shedding a new and clarifying light on it.

LIFE'S DUAL NATURE (METABOLIC NETWORK DYNAMICS AND CRYSTALLINE GENETICS) DURING THE RNA/PROTEIN WORLD, THE RNA WORLD AND THE PRE-RNA WORLD

Though it has not yet attained the status of a 'fact', it is widely believed that DNA was preceded by RNA as a genetic material.⁷⁻¹⁷ More specifically, since DNA is not synthesized without the assistance of proteins, but since the latter are routinely synthesized without the help of the former (e.g., in RNA viruses),

proteins most likely existed prior to the emergence of DNA, and the extant DNA/RNA/protein world would have been preceded by a DNA-less RNA/protein world. And since proteins are not synthesized without the help of RNA, but the latter is able to act not only as a template-replicator but also as an enzyme or 'ribozyme'^{16,18,19} which is even capable of catalysing its own or other RNAs' replication,²⁰ a protein-less RNA world could have preceded the RNA/protein world. This would likely have been the case if one uses the word 'protein' *in the strict sense* like it is used by most origin-of-life researchers, viz., to refer to a class of "polypeptides assembled on ribosomes from a set of twenty tRNA-linked L-amino acids according to an mRNA-sequence".^{21(p. 79)} However, if one extends the meaning of the word 'protein' to also include other, more simple or primitive oligo- and polypeptides, then they most likely existed prior to the emergence of RNA,²¹ possibly in a kind of (pre-RNA) self-sustaining and/or self-reproducing peptide or protein world.²²⁻²⁶

The origin of RNA-assembled proteins *in the strict sense* through the establishment of the genetic code and the translation machinery is a notoriously complicated problem that is far from solved.^{7,9,27,28,29,30,31,32,33} Without entering into technical molecular-biological details; however, it is relatively safe to say that horizontal or lateral gene transfer (HGT) presumably played a decisive role in the origin of the genetic code and the translation mechanism and their universality in extant life on Earth.^{30,33-35} Pervasive HGT of RNA-elements coding for polypeptide regions and translational components would have allowed for an evolutionary shuffling and recombination among these regions and components, resulting in the (not necessarily simultaneous) optimization of both the genetic code and the translation system. Concomitant was the origin and evolution of the first true proteins and proteinaceous cells. During the RNA world, i.e., before the rise of the genetic code and the translation system, vertical/clonal reproduction of RNA-based cells was presumably less developed and less stable and robust and, hence, more blurred and obscured by HGT than it is in the present bacterial world. Indeed, whatever the nature of cell-like molecular aggregates or 'proto-cells' in the RNA world, cellular 'lineages of genealogical descent' were arguably not yet well developed.^{30,35} RNA- and ribozyme-based proto-metabolic proto-cells were possibly not yet discrete organisms, but rather like 'ecological network communities' with proto-genetic RNA-elements floating among them in an HGT-like fashion. Hence, and with regard to the issue raised in the present paper, life's dual nature, i.e., both the proto-genetic crystalline structure of RNA-elements and proto-metabolic network dynamics and interactivity, must have already played a decisive and constitutive role during this stage of the origin of life, i.e., during the origin of the genetic code, the translation system and the first true proteins and proteinaceous cells.

What about the earlier major transition in the origin of life, i.e., the origin of the RNA world itself? Although some recent progress has been made,³⁶ the *de novo* synthesis of RNA under prebiotic conditions poses a considerable riddle, as even single nucleotides and small RNA-oligomers are already very complexly structured molecular aggregates compared to abiotic chemical

standards.^{12-15,37,38} Furthermore, did the RNA world emerge as a 'pure' RNA world with auto- and cross-catalytic RNA fulfilling the role of both genetic template-replicator and enzyme catalyst or ribozyme, thus without the help of other organic molecules or proto-metabolic reaction networks?^{10,39} Or was RNA already from the start assisted by small-molecule cofactors such as amino acids, oligo- and polypeptides and/or other organic molecules?^{21,26,40,41} Or even more, by a proto-metabolic reaction system?^(footnote 1)^{140,42-51}

To circumvent the difficulties surrounding the *de novo* emergence of RNA under prebiotically plausible conditions, some researchers working in the 'gene/replicator-first' framework have proposed simpler precursors to RNA which are also capable of catalysing their own replication, such as threonucleic acid (TNA) and peptide nucleic acid (PNA)^{12,13,15} and even self-replicating peptides.²³⁻²⁵ Experimental research in the relatively new field of 'systems chemistry' has shown that non-enzymatic autocatalytic template-replication is possible in synthetic reaction systems designed under laboratory conditions⁵²⁻⁵⁴ and that *networks* of auto- and cross-catalytic replicative oligomers, including replicating peptide and nucleic acid networks, can be generated.⁵⁵⁻⁵⁷ While possible and even mutable and hence evolvable to a (very) limited extent, an exclusively *auto* catalytic template-replicator, i.e., an oligomer or polymer only catalysing its *own* replication, is not regarded as a plausible starting point for life, since such replication reactions turn out to cease quickly even when feedstock for further replication is constantly provided.^{5,20} On the other hand, two or more *cross*-catalytic oligomeric template-replicators, like peptides^{24,25} or nucleotide-based oligomers,^{20,58} may constitute a *network which autocatalytically replicates or reproduces as a whole* and which is – due to its network properties – much more self-sustaining and evolvable.^{5,17,20,55,56} The gene-first approach assumes that life started with the emergence of such auto- and cross-catalytic replicator-based network systems, and that the first metabolic reaction sequences gradually evolved within such systems.^{5,12,13,59-63} That is, it is assumed that there was a gradual evolution, driven by a kind of chemical natural selection possibly in combination with HGT, towards *more efficient catalysis* of the replication processes, i.e., more efficient catalysis of (proto-metabolic) reactions that turn environmental resources and building blocks into template-replicators and eventually into cell structures.

The 'metabolism-first' or 'small molecules' approach, on the other hand, sees the order of events differently: it claims that template-based molecular replication must have evolved within a kind of pre-existing proto-metabolic reaction system.^{40,42-51} It has the advantage over the gene-first approach that it does not require, as a starting point, an already complex environment of activated building blocks giving birth to complex oligomeric 'aperiodic crystals' capable of auto- and cross-catalytic template-replication. The term 'proto-metabolism' refers to a robust set of thermodynamically driven chemical reaction sequences capable of being maintained in a prebiotic environment of relatively

small molecules such as minerals, amino acids and small peptides, gradually giving rise to larger molecules including oligomers capable of template-replication. It is argued that no replicative pre-RNA or RNA world could have originated 'naked', i.e., without the thermodynamic and chemical underpinning by a robust set of reactions prefiguring the metabolic reactions that sustain and allow for genetic replication in extant life. Gene-first adherents, in turn, have responded that proto-metabolic reaction sequences, while admittedly relying less on *molecular* complexity, require too much *reaction sequence* specificity and complexity to have self-organized spontaneously under prebiotic conditions.^{60,61,63} In fact, both approaches seem to suffer from a similar weakness: they cannot prove but only assume the 'spontaneous', i.e., thermodynamically and statistically favoured, emergence in the prebiotic world of complex physicochemical order or negentropy either at the *crystalline oligomeric* level in the case of a gene-first scenario or at the *reaction sequence* level in the case of a metabolism-first scenario. So the jury is still out on which of the two frameworks most closely approaches what really happened at the dawn of life on Earth.

Three decades ago, Dyson⁶⁴ and Kauffman²² provided theoretical modelling on a stage in the origin of life preceding the emergence of both template-based replication and proto-metabolic reaction cycling. Instead of working with an autocatalytic network consisting of cross-catalytic oligomeric template-replicators (see supra), their model consists of a set of two or more small molecules (e.g., small peptides) that cross-catalyse each other's synthesis *without* the involvement of template-based replication but nevertheless resulting in a cycle that *autocatalytically reproduces as a whole*. Kauffman^{65,66} argues that such 'autocatalytic sets' could be used to model the road towards template-based replicative networks as well as towards proto-metabolic reaction cycles. Freire^{67,68} too, proposes nontemplate-driven polymerization reaction cycles as a plausible origin of life.

THE ROLE OF MINERAL SURFACES IN THE EARLIEST ORIGINS OF METABOLISM AND GENETICS

Here, I want to point to the fact that, as a result of intensive research into prebiotic chemistry, on at least one thing the gene-first and metabolism-first approaches seem to have found a relative agreement during the last two decades: the key roles that *minerals* could have played in the origin of life. Small organic molecules of the kind found in the Murchison meteorite⁶⁹ and in the Miller-Urey experiment⁷⁰ and related experiments, such as amino acids, small sugars, nucleobases, lipids and alkanes, result from uncatalysed reactions synthesizing an indiscriminate array of products. *Catalysts* such as minerals; however, can select these and other products that have the potential to react and be synthesized into larger compounds. Micro-crystalline mineral surfaces are 'templates' that have the ability to *selectively adsorb and concentrate* organic molecules such as amino acids from an equimolar mix and, thereby, *catalyse and organize* the formation of stable reactions and the synthesis of small organic molecules into larger compounds such as oligomers and polymers.⁷¹⁻⁷⁵ Both gene-first and metabolism-first researchers acknowledge that,

1. For a recent in-depth exploration of the origin of the RNA world, see the Special Issue "The Origins and Early Evolution of RNA" of the journal Life. 2015; 5(4).

through selective adsorption and concentration, catalytic mineral surfaces could have played a key role as ‘organizing templates’ in the origin of life on Earth. Gene-first researchers have hypothesized that they catalytically organized the synthesis of the first oligomers capable of template-replication,⁷⁶⁻⁸⁰ while a number of metabolism-first researchers casts them as organizing catalysts for the first proto-metabolic reaction cycles^{42-44,49,81-83} and even for the assembly of the first proto-cellular membranes.⁸⁴

Both the gene-first researcher Graham Cairns-Smith^{37,85,86} and the metabolism-first researcher Günter Wächtershäuser⁴²⁻⁴⁴ went quite far in their grounding of life’s origin in mineral surfaces. Cairns-Smith hypothesized that the first genetic system might have been a mineral clay surface, that its crystalline growth constituted a kind of genetic replication, that variable sequences of point defects, layer orientation and metal cation substitutions constituted genetic sequence information, and that flaws or ‘mutations’ could occur during crystal growth/replication, resulting in differential growth (dissolution and precipitation) rate, constituting differential replication rate or ‘fitness’ and, herewith, evolution by natural selection. Wächtershäuser, on the other hand, coined the term ‘surface metabolism’ and stated that strong bonding of organic molecules to mineral surfaces was the functional evolutionary precursor of containment by cell structure, that catalytic mineral surfaces were the precursors to enzyme surfaces, that the stabilization of peptides by bonding to mineral surfaces was the precursor of protein stabilization by internal folding, and that mineral bonding was the precursor of energy coupling mechanisms in extant metabolism. However, Cairns-Smith’s hypothesis of a replicating ionic pattern in a clay mineral has never been demonstrated, and only the very first synthetic stages of Wächtershäuser’s scenario have been verified.

There are, however, three ‘certainties’ about mineral surfaces which are relevant for the origin of life:

1. Mineral surfaces were abundantly present on the prebiotic Earth.
2. There is empirical and experimental evidence that mineral surfaces have a capacity to catalyse and organize chemical reactions including the synthesis of small organic molecules into larger compounds.⁷¹⁻⁸⁰
3. From a physical point of view, mineral surfaces, having a crystalline nature, by definition have a low statistical entropy, i.e., are characterized by a relatively stable statistical order or negentropy. That is, they are a result of processes of condensation and crystallization following the Third Law of Thermodynamics.^(footnote 2)

Therefore, without going along with Cairns-Smith’s and Wächtershäuser’s speculative scenarios, it is relatively safe to say that mineral surfaces somehow served as a kind of source of

2. The Third Law of Thermodynamics states that the entropy of a perfect crystal, at absolute zero (zero degrees kelvin or 0 K), is exactly equal to zero. More specifically, the entropy change associated with any condensed system undergoing a reversible isothermal process approaches zero as the temperature approaches 0 K, where condensed system refers to liquids and solids.^{87,88}

statistical negentropy’ – as ‘organizing catalysts’ – in the origin of life on Earth.⁷¹⁻⁷⁵ Indeed, based on the current state of research on life’s origin, one can state with reasonable certainty that, apart from sources of *thermodynamic negentropy* [such as solar radiation (UV light and heat) and/or geochemical sources (heat and mineral reducing power)] being crucial for life’s origin on Earth, the abundant presence of mineral surfaces on the prebiotic Earth – with their stable micro-crystalline structure or order – provided for an important source of *statistical negentropy* for life to originate. It seems that life is metabolic network organization that – besides being fuelled by indispensable (re)sources of *thermodynamic negentropy* (e.g., solar and/or geochemical resources, ‘combustibles’ or nutrients) – originated largely on a *statistically negentropic* breeding ground of micro-crystalline order or structure of catalytic mineral surfaces, and has always remained dependent on and/or centred around the crystalline order or structure of polymeric genetic templates. That is, in light of the current emphasis in present-day systems chemistry and systems biology on life’s aspect of *system complexity*, it is important to realize that this system complexity – besides being nourished by (re)sources of *thermodynamic negentropy* (solar and/or geochemical resources, combustibles/nutrients) – also crucially, i.e., non-trivially, depends on a source of *statistical negentropy* or ‘crystallinity’: at first, organizing catalytic mineral surfaces, and later on, replicable genetic sequence-specificity. Of course, the gap between the relatively simple *periodic* structure of mineral surfaces and the much more complex *aperiodic* structure of polymeric genetic templates is a serious one that is far from solved. Not withstanding, at a given stage during the evolution towards extant life, mineral-bound proto-life must have developed a sufficiently efficient and robust set of “internally organizing and catalysing templates” – say, a set of oligomeric templates that act as enzyme-catalysts (e.g., RNA/ribozymes) or that ‘code’ for enzyme-catalysts (e.g., RNA coding for proteins) – allowing life to exist and operate on its own behalf, i.e., independently from its supporting mineral surface or ‘mother ship’.

In the next section, the physical reliance of life’s origin on two sources of negentropy (thermodynamic and statistical negentropy) is further explored and analysed.

THE PHYSICAL FOUNDATION OF LIFE’S DUAL NATURE: THERMODYNAMIC AND STATISTICAL NEGENTROPY AND THE CONSTITUTIVE ROLE OF THE THIRD LAW OF THERMODYNAMICS

The metabolism-first approach to the origin of life emphasizes the ‘combustive’, i.e., thermodynamic, aspect of life, but it has been criticized for making statistically unrealistic assumptions on the gene-less emergence of the first proto-metabolic reaction systems.⁶⁰⁻⁶³ The gene-first approach, on the other hand, emphasizes the ‘informational’, i.e., statistically negentropic or ordered, aspect of life, but it underestimates the thermodynamic requirements for the metabolism-free emergence of the first genetic replication systems.^{42,46,47} However, the realization that life is arguably the result of at least two kinds of gradients or sources

of negentropy – a thermodynamic and a statistical one (see *supra*) – pleads for a more integrative approach between the metabolic (combustive, thermodynamic) and genetic (crystalline, statistical) aspects of life. Indeed, there is a recent tendency by metabolism-first researchers to incorporate elements of genetics into their frameworks⁴⁸ and by gene-first researchers to incorporate metabolic elements into their frameworks.⁸⁹

The fact that living organization would be the self-organized net result of *two* kinds of gradients or sources of negentropy, i.e., a thermodynamic gradient (solar and/or geochemical resources, combustibles/nutrients) and a statistical gradient (mineral surfaces, genetic sequences), is not entirely at odds with other cases of self-organization in the physical world. In the Bénard-convection, for instance, the self-organized convection patterns, too, are the net result of *two* gradients or sources of negentropy: a thermal and a gravitational gradient.⁹⁰ Remove one gradient or source, and the self-organized structure will disintegrate. Both gradients or sources of negentropy are *constitutive* of the convection structure. Similarly, both a thermodynamic and a statistical gradient or source of negentropy seem to be *constitutive* of life on Earth as we know it. Indeed, the latter is difficult to imagine without both the thermodynamic (metabolic) and statistical (genetic) aspects.

The origin of life or, more specifically, the origin of complex chemical network organization on catalytic mineral surfaces under both a thermodynamic (e.g., a hydrothermal)^{42,46,81,82,83} and a statistical (e.g., a crystalline-mineral)⁷¹⁻⁷⁵ gradient can, from a physical point of view, be described as an instance of self-organization as a result of ‘cooling’, ‘condensation’ and/or ‘crystallization’ on those mineral surfaces. Cooling, condensation and crystallization involve a local decrease of both thermodynamic and statistical entropy and/or disorder, i.e., a local decrease in degrees of freedom in the configuration space, as predicted by the Third Law of Thermodynamics. The genetic aspect of life is possibly a direct ‘descendant’ from the ‘solid’, ‘crystalline’, Third-Law governed nature of mineral surfaces, although the transition from the latter’s relatively simple *periodic* structure towards genetic *aperiodicity* remains problematic. Schrödinger¹ described genetic polymeric sequences as Third-Law governed ‘aperiodic solids/crystals’ underpinning and organizing enzyme-catalysed metabolism, the latter – as a ‘combustive’ and/or ‘dissipative’ process – satisfying the overall increase of entropy as demanded by the Second Law of Thermodynamics. Woese^{34,35} has further argued that, at first, (proto-) metabolism must have been constituted by fairly loose inter- and supra-molecular aggregations or proto-cells presumably characterized by pervasive HGT of proto-genetic elements. Later on, a less loose, i.e., more ‘condensed’, ‘cooled down’ or ‘crystallized’ form of cellular organization would have evolved – with HGT occurring in a less chaotic, i.e., more ‘constrained’, ‘disciplined’ or ‘organized’ manner – due to the ‘solidification’ or ‘crystallization’ of the genetic code and the translation system (*ibidem*). These proto- or early-biotic evolutionary processes of condensation, solidification and crystallization were thus accompanied by a local decrease of entropy (as predicted by the Third Law

of Thermodynamics), but at the expense of an environmental increase of entropy (as prescribed by the Second Law of Thermodynamics) due to more efficient and robustly organized metabolism, ‘combustion’ and/or ‘dissipation’. Hence, the origin and early evolution of life would largely fall within the scope of condensed-matter physics and non-equilibrium thermodynamics.^{30,91} With the condensation and crystallization of the genetic code, the translation system and the first true proteins and proteinaceous cells, a more robust form of genetic replication and cellular reproduction would have allowed for the establishment of ‘genealogical lineages of descent’. As such, the ‘Darwinian threshold’³⁵ would have been reached and natural selection – taking over or, at least, enriching the role of the Third Law – would have become an important statistically negentropic force allowing life to further ‘climb Mt. Improbable’.⁹² It is thus important to realize that genetic replication, cellular reproduction and, herewith, Darwinian evolution by natural selection already rely on complex proto-biotic physicochemical self-organization that cannot simply be taken for granted, but that resulted from condensed-matter and non-equilibrium processes of the kind described above.

Kauffman² makes a comparison between a living cell or organism and a thermodynamic Carnot Engine capable of performing at least one work cycle. Both have in common that they are *driven* by a thermodynamic gradient or source of negentropy. A major difference; however, lies in the fact that the *organized construction* of the Carnot machine does not rely on a ‘natural’ (re)source of statistical negentropy (such as a mineral surface or a set of genetic sequences) but on a human engineer. Living cells, organisms, ecosystems and the biosphere as a whole, on the other hand, are self-organizing or self-constructing systems. Here, we suggested how at first the Third Law of Thermodynamics and later on Darwinian natural selection could explain the statistically negentropic, organized or ‘engineered’ aspect of life. Kauffman, however, doubts whether these two already long-known laws or principles suffice to explain the emergence and evolution of life. He speculates about a possible Fourth Law of Thermodynamics for self-constructing open non-equilibrium systems. As the transition from a prebiotic world of relatively simple chemical compounds including *periodically* structured mineral surfaces towards the complex *aperiodic and/or informational* structure, specificity and organization of biopolymers and biochemical reaction sequences remains a problematic gap in our understanding, such a Fourth Law might be welcome. However, as Kauffman’s proposal has remained in the margin of both physics and biology without entering mainstream science, we will not treat it further here. Restricting ourselves to the known laws and principles in science, we might conclude that the role of the Second Law of Thermodynamics in life’s origin would have been rather ‘trivial’, as it accompanies virtually all physical processes, and thus also biotic processes. That is, it is a trivial fact that the local decrease of entropy that characterizes organized biological processes is accompanied and/or compensated by an at least as large production of entropy. The role of the Third Law, on the other hand, seems rather ‘non-trivial’ or ‘crucial’: although arguably only a necessary and not a suffi-

cient condition for life to originate, it played an indispensable role in providing for a relatively ‘stable’, ‘condensed’, ‘solid’, ‘crystalline’ physicochemical foundation for both genetic replication and cellular/metabolic reproduction and, herewith, for Darwinian evolution by natural selection. Both the Third Law and natural selection are, under well-defined circumstances, able to predict the emergence of local order or statistical negentropy; both are able to predict a local decrease in degrees of freedom – a ‘selection’ or ‘sculpting’ – in the configuration space.

CONCLUSION

Life’s dual nature, i.e., metabolic network dynamics and crystalline genetics, runs very deep – arguably all the way back, via the RNA world, to the very dawn of life on Earth. It seems to be a quasi-inevitable outcome of the ‘dual’ or ‘twofold’ physical – thermodynamic and statistical – constitution or foundation of life. In contrast with the rather trivial role of the Second Law of Thermodynamics accompanying virtually all physical including biotic processes, the Third Law appears to have been a crucial ‘predecessor’ of natural selection as a statistically negentropic or ordering force or mechanism in the origin and early evolution of life. Based on the current state of research on the origin of life on Earth, it seems likely that:

1. *Sources of thermodynamic negentropy*, such as solar radiation (UV light and heat) and/or geochemical sources (heat and mineral reducing power), lie at the root of life’s combusive and/or metabolic aspect;
2. The abundant presence of mineral surfaces on the prebiotic Earth – with their selectively adsorbing and catalysing (thus organizing) micro-crystalline structure or order – provided for a *source of statistical negentropy*, thus lying at the root of life’s crystalline and/or genetic aspect.

But although crystalline mineral surfaces and the Third Law arguably served as a source of statistical negentropy in the origin of life, they appear to be *only necessary and not sufficient* to fully explain the ‘hard problem’ of life’s origin, i.e., the transition from a prebiotic world of relatively simple chemical compounds including *periodically* structured mineral surfaces towards the complex *aperiodic and/or informational* structure, specificity and organization of biopolymers and biochemical reaction sequences. Indeed, while both Cairns-Smith’s gene-first and Wächtershäuser’s metabolism-first scenarios tried to cope with this transition, there is little or no empirical evidence to support their claims. More generally, gene-first and metabolism-first approaches seem to suffer from a similar weakness: they cannot prove but only assume the ‘spontaneous’, i.e., thermodynamically and statistically favoured, emergence – in a prebiotic world of relatively simple chemical compounds – of complex physicochemical order or negentropy either at the *crystalline oligomeric* level in the case of a gene-first scenario or at the *reaction sequence* level in the case of a metabolism-first scenario. The hard problem of the origin of life and the dramatic increase of local statistical order or negentropy associated with it might only be solvable by means of both approaches joining forces.

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