

On the feasibility of nonadaptive, nonsequential abiogenesis

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Abstract

The emergence of life from non-living matter remains one of the most profound unresolved questions in natural philosophy. Classical models derived from the Oparin-Haldane hypothesis assume a gradual (sequential), selective assembly of biological precursors. Yet, for more than a century, all experimental efforts in this direction have failed in their attempt to achieve material abiogenesis. May be that this view is paradoxical when trying to explain how life arises without preexisting coordinated, complex structures – as they should be a product of selection before life itself could be able to control inheritability. Here, I elaborate on the possibility of a nonadaptive, nonsequential abiogenesis, in which life-grade complexity emerges spontaneously, ungoverned by natural selection, through contingent coalescence under excess capabilities. The Price equation, as a mathematical tool, can help assisting our thinking on the evolvability of selection itself. Selection, rather than a precondition for life, is best understood as the covariance between trait value and fitness (inheritability of fitness), a quantity that itself evolves. Prior to abiogenesis, this covariance should be effectively zero, then selection begins to govern and purify the number of feasible interactions among the primeval components. This could be achieved by a chemical system without a code. By releasing abiogenesis from gradualist idealisations, this model may provide a new theoretical foundation for interrogating life's origins.

Keywords: origins of life, nonadaptive abiogenesis, dissipative structures, Price's equation, molecular bricolage, Oparin-Haldane hypothesis, constructive neutral evolution

Introduction

Two opposed philosophical views have tried to give answer to the problematic of the origins of life. For a detailed account on the historical confrontation among vitalistic and materialistic arguments on the feasibility of this mysterious phenomenon –life emerging from inert matter–, I suggest the first chapters of Oparin’s *Origins of Life on the Earth* [1]. This is not an exhaustive review either. Instead, the purpose of this brief piece is to give, I hope, a new angle on why all our efforts to observe a material abiogenesis have failed to this day, and what could be the way forward to properly pose this never-ending question to nature.

Pasteur first demonstrated that *generatio aequivoca*, or spontaneous generation of life, was impossible – reproduction of living matter required an “egg” with instructions [2–5]. After some intense debate, the experiments were certainly replicated, and the question solved [6]. The *omnia cellula ex cellula* by Virchow [7] rendered a new meaning, and remained as a paradigmatic principle of biological reproduction (or “immortality of the protoplasm” [8]) until this day. However, although Pasteur’s discovery filled an important gap in knowledge, an intriguing question emerged: whence do living things arise, if not from inert matter? [9, 10]

Besides a subtle margin for vitalistic responses [11], many experimentalists in that era confronted the question seriously. The general materialist answer was that evolutionism, not spontaneity, led to abiogenesis [4, 8, 12–15]. They believed that only gradual chemical evolution could explain this apparent decrease of entropy of an isolated system (or the gradual accumulation of information) [16–18]. Here I argue that this generalised response reflected a false dichotomy, probably driven by a reluctance to the semantics of “spontaneity” [4], and that this historical contingency profoundly impacted every theoretical (eg. the Oparin-Haldane hypothesis [19, 20]) and experimental (see below) attempt to tackle the question. Hence, we are nowhere close to replicate abiogenesis. The standard abiogenesis model requires the chemical compounds to evolve sequentially (which led to the recurrent, confusing, and near fruitless debate on “who–first” [21–25]). Could we render some alternative models to help new experimental guidelines? For example, a separate evolution for some of the components as different systems, coalescing into one; or that part may have gradually evolved but not others; or any other model explaining the thermodynamic oddity of such unprecedented complexity [26].

Why haven’t the finest watchmakers addressed this clock yet?

Before detailing a potential new course of action, I will further justify the need for it by examining the main achievements and failures of prebiotic chemistry and synthetic biology, which are the two main fields attempting to give a mechanistic answer to a material abiogenesis.

The famous triumphs in this regard are found on the side of prebiotic chemistry. If we keep the watchmaker’s traditional metaphor, these would correspond to alchemists trying to exactly reproduce the gears and other small parts of this rare clock called life. The most celebrated surely are the Miller-Urey experiments. They demonstrated that sudden changes of potential in a recreated Earth’s prebiotic environment can produce amino acids within a brownish organic solution with acquired complexity [27]. Many more related experiments have been conducted, for example, to form nucleobases [28]. However, the production of some well-known parts of the clock does not grant us any new knowledge on how to build it, provided that the prebiotic conditions are correctly assessed [29]. These same arguments extend to the other classic experimentalists, like Joan Oró (purines from hydrogen cyanide [30]), or Cyril Ponamperuma (adenine synthesis and Urey-Miller extensions [31]). After these initial

excitements, unfortunately, the efforts in this field have advanced little to the resolution of the original question, beyond speculation and redundancy [32–41].

What if we just search for the parts of the clock that produce its characteristic “tic-tac”? Abiogenesis is often conceptualised as a lucky generation of first replicators. We generally acknowledge that the first replicator was probably a RNA autocatalyst, maybe similar to a ribozyme [42]. In a nutshell, the hypothesis is that a ferric impactor led to a reduced environment in which RNA could be formed on a proper geological time [43]. We indeed achieved RNA oligomerization catalysed by olivine in reduced, alkalyne environments [44], but self-reproduction was never achieved without human engineering [45]. However, we know that replicators of other nature are possible [46], although the ability to storage substantial information on them is absent (Prigogine’s *historical element* [18]), so that selection is contingent on competitive kinetics [47], as aperiodic crystals growing. All efforts to arrange a sequential chemical evolution leading to the emergence of life have failed.

Now a brief note on synthetic biologists, that would rather be proper watchmakers, or better said, engineers who dissect and try to recreate the clock’s “tic-tac” by understanding the relationship among the elements of the most sophisticated rolex, or modern-day life. That the construction of a synthetic life can ultimately lead to a natural answer is debatable [48], but at least it might, in theory, generate new knowledge about the necessary steps in the chemical evolution, without assuming certain prebiotic conditions. Maybe, if we understand a cell better, we could improve our definition of life to search for its emergence [49]. Unfortunately, the obtained knowledge is more related to maintain the stability of modern-day cells [50]. The questions rapidly derived on “how many functions we can alter or delete from this modern cell without compromising its long term viability?”. So we ended with models like the minimum cell [51–53], way too much complex to be accounted for the question of abiogenesis [54].

Whether this is a consequence of poor praxis (eg. urge to maintain publishing outcome of a decaying field) or moral blindness (eg. abiogenesis is idealised as an adaptive, sequential progression), both approaches have progressed little into solving the question. The field is arguably lacking creativity because a lot of research output depend on circling over partially-solved chemical pathways. I here provide what I believe a novel view towards the resolution of this problem. As I am certain that, at least, it is still to be experimentally contested, I wanted to elaborate on some principia towards the design of future experiments.

Evolvability of the trait-fitness covariates

Part of the difficulty in answering this question may be that we have not formalised very well what we are looking for. The watchmaker’s view on abiogenesis requires selection in the first steps of living “purpose” (rupture of symmetries, like enrichment of L-molecules in the amino acid pool), to surpass the imposed threshold of chance. That is usually the argument since selection is the only distinctive feature of living matter that we know of that can govern over such an unfeasible thermodynamic fate, which regime of possibility is determined by a Boltzmann distribution that includes both state functions, energy and entropy [18, 26, 55].

An interpretation of the latter is that the amount of selection should be fairly high and constant at any time during biological evolution, including first gradualist reactions – as depicted, for example, in the third chapter of Dawkins’ *Selfish Gene* [56]. But, how selection itself has evolved? Does it make sense to think in those terms in the advent of biological evolution itself? To help our thinking, we could make use of the Price equation to establish a new model in which selection is 0 before the emergence of life [57]. The Price equation [58] is often expressed as

$$\Delta\bar{z} = \text{Cov}(w, z) + \mathbb{E}(w\Delta z') \quad (1)$$

Where $\Delta\bar{z}$ is the change in the average value of the trait z across generations and can be approximated with the sum of two terms. The first term, $\text{Cov}(w, z)$, is just the covariance between fitness w , and the trait value z , representing the effect of natural selection (memory of traits that worked better). The second, $\mathbb{E}(w\Delta z')$, is the expected value of the within-group changes in the trait z , and it is weighted by fitness w to impact the number of descendants on the next generation. This reflect neutral variation. Although eq. (1) is commonly used to assess selection among conflicting organizational levels [59], it provides a simple mathematical description of any adaptive population, and is therefore most suitable to help a hypothesis on the origins of natural selection. However, these equations are just correlative (not causal). A more proper way to causally isolate the selection would be to remove the influence of fitness w from the second term [57],

$$\Delta\bar{z} = \text{Cov}\left(\frac{w}{\bar{w}}, z'\right) + \bar{\delta} \quad (2)$$

Where the first term is now the covariance between the relative fitness and a given trait, and $\bar{\delta}$ is the average transmission bias. Thus, we can trace the infinitesimal appearance of the selection, that is, the inheritability of the trait's value fitness,

$$\lim_{t \rightarrow t_1^+} \text{Cov}\left(\frac{w}{\bar{w}}, z'\right) > 0, \quad \text{where } t_1 \text{ is the first occurrence of inheritability} \quad (3)$$

However, spontaneous rupture of chemical symmetries could fulfill the condition of eq. (3) [46, 60]. As fixing a threshold for “life” seems subjective, and this is a problem when defining the origins of it, we first need to extract a quantitative property which is unique to life – common from the first to the last consensual living being. It is found that this shared property is not the inheritability alone of a fitter trait, but the *control* over this information-enrichment process, so that living systems keep optimizing the amount of selection until equilibrium. Thus total accumulated change in the covariance between fitness w and a trait z remains finite over time

$$\int_{t_1}^{\infty} \left| \frac{d}{dt} \text{Cov}\left(\frac{w}{\bar{w}}, z'\right) \right| dt < \infty$$

This implies that the rate of change of covariance decays as time approaches infinite, where the trait will be –theoretically– perfectly fitted to an invariant context. We do not need to assume any function for the evolution of selection, so we can introduce the limit with an equilibrium value W such that

$$\int_{t_1}^{\infty} \left| \frac{d}{dt} \text{Cov}\left(\frac{w}{\bar{w}}, z'\right) \right| dt < \infty, \quad \text{with} \quad \lim_{t \rightarrow \infty} \text{Cov}\left(\frac{w}{\bar{w}}, z'\right) = W, \quad W > 0 \quad (4)$$

Where W represents the maximum optimal value for the covariance between a given trait and its associated fitness for an invariant context. However, such equilibrium remains unattainable in practice, as the context to which they must adapt is in perpetual change. We can imagine, as an example, a catastrophic perturbation, where the continuity of selection is impossible (ie. life's extinction due to meteorite impact). One may interpret the trait's value extinction ($\Delta\bar{z}$) as an infinite decrease in fitness (w). Thus, W is a perturbable theoretical fitness goal, and this perturbation is extricated from the variability on transmission bias ($\bar{\delta}$)

$$\frac{dW}{dt} = f(t) + \xi(t), \quad \text{where } W \text{ may approach } 0 \text{ under large perturbations}$$

Conceptually this is a clear epistemic rule to search for: a point in time at which eq. (4) first holds but continues to hold for all subsequent moments in any given chemical system, provided the integrity of the living system is maintained. In Table 1, a simple syllogism with these premises is proposed to account for the emergence and evolvability of natural selection.

	logical value
premise 1	$\text{Cov}\left(\frac{w}{\bar{w}}, z'\right)$ is ≈ 0 and uncontrolled in abiotic systems
premise 2	$\text{Cov}\left(\frac{w}{\bar{w}}, z'\right)$ in current organisms tends to equilibrium (W)
conclusion	$\text{Cov}\left(\frac{w}{\bar{w}}, z'\right)$ changed from ≈ 0 (abiogenesis) to W

Table 1: Syllogism of null selection. The syllogism may be reversed for the transmission bias ($\bar{\delta}$), which interpretation is that trait inheritability had a maximum noise value at the origins of life.

The problem of unprecedented complexity

A problem with the above is, how the emergence of life-grade complexity can be attained in absence of selection? Could teleonomic principles be acquired by chance? [61]. The history of this issue is indeed tortuous [62]. Instead, I invite the reader to think of that characteristic annoying tangle of wires and cords occurring with any vintage computer hardware. This process, surely, occurs due to the great probabilities for the disordered state to exist, without precluding any adaptive advantage or increase in fitness. This is a common representation for the so-called Constructive Neutral Evolution [63]. This is a concept in which, at any level (genetic or not) complexity can be attained without an adaptive response [64]. There are some evidence that these processes are common in biological systems, specifically, regarding the over-complicated kinetoplastid regulation of a protist and gene scrambling, among others [63, 65]. It was formulated for biological systems with “excess capacities”; we here invoke it as a way to understand arbitrary (nonadaptive) coalescence under conditions of free energy excess. Furthermore, molecules of high complexity can be attained abiotically [66]. This concept is therefore of much help to allow a syllogism for unprecedented complexity (Table 2).

	logical value
premise 1	unprecedented complexity is attainable nonadaptatively
premise 2	abiogenesis has an unprecedented complexity value
conclusion	abiogenesis-level complexity is attainable nonadaptatively

Table 2: Syllogism of complexity.

This interpretation is in line with the Prigogine’s *Theory of Dissipative Structures*, in which the “order through fluctuations” is a mechanism (not reducible to the equilibrium principle) leading to “inhomogeneous spontaneities” [67].

A nonadaptive, nonsequential model of abiogenesis

The combination of previous syllogisms’ conclusions grants a novel nonselective view of abiogenesis, in which life-grade complexity is attainable nonadaptatively, but where nonadaptativeness’ rupture is forced in abiogenesis. This allow for broader views of life’s emergence, where the sequential evolution of the “clock’s parts” may be violated.

This view rejects the intuition that, gradually, chemical systems achieve life-grade complexity in a slow sequential fashion, and that this process is adaptive and necessary, i.e.: the conditions, the parts, and their change over time were the ones meant to be to achieve abiogenesis, and no others. In such model, gradual evolution and assembly of parts is paradoxical (Fig. 1). Acquisition of parts are – by definition – not slow gradual events, but major transitions towards complexity. The features of coalescent structures are achieved contingently, so evolution would eventually purify any of the nonadaptive traits that may be required to achieve abiogenesis, since – again, by definition – they were acquired before life begun and they may carry a great cost on fitness. In addition, gradualism does not account for dramatic global changes (eg precipitation of the oceans), in which sudden increase on complexity may have been favoured. A recent experiment strongly support this narrative [68]. A variety of semihollow structures (with different morphologies and thickness) were achieved spontaneously in a Miller-Urey experiment. The latter consist of silicon-enriched HCN polymers, a kind of compartment not present in modern-day biology. Altogether, these reasons would be a sufficient explanation of why we are failing so far: we may be exploring a very narrow spectrum of the chemical possibilities [62].

Other recent study has also pointed out the fundamental historical limitations of sequential models, particularly in the context of the RNA-world hypotheses [69]. While this perspective presented a compelling view of the field, it adheres to a concept similar to the Jacob’s “molecular bricolage” [70]. Here, the coalescence of molecular components remains excessively constrained by biochemical architectures akin to extant life (eg. the need of a protein coding system). In addition, they invoke selection to facilitate the assembly of parts, whose chemistry is necessarily similar to that of modern life. A truly generalist model for abiogenesis must not rely on strict biochemical continuity with known life. This may, nonetheless, be a legitimate model for abiogenesis on Earth. Here I propose a different one, in which conditions for coalescence of the parts are most varied when selection is null (possible interactions are maximal because they are uncontrolled by selection in prebiotic conditions), and that this list of conditions must be not limited to Earth’s prebiotic environment. Possible interactions between parts on the successful populations would be rapidly constrained by selection, explaining for example the *post-hoc* generality of the genetic code. But, importantly, in the nonsequential–nonadaptive model achievement of a rudimentary code is not necessarily time-placed at the very same occurrence of abiogenesis, as there could be other ways to control inheritability of fitness and fulfil eq. (4) [71]. I provide a succinct comparative for these three models of abiogenesis (Table 3).

But how could these models be tested?

Abiogenesis can be abstracted as a rare, mineral, spontaneous (favorable), and complexifying reaction, and, when it occurs, the abiogenic products can store information from the environment in order to permeate it more efficiently. Should our efforts be directed in pondering how to reach such coalescence-prone conditions, in any system? In this line, R. Hazen argued that mineral evolution and its reactions are inherently governed by a regime of chance [62]. He proposed a semi-quantitative estimate of the feasible prebiotic reactions leading to the origins of life on Earth-like planets, calculated with time and surface areas for mineral reactions. His result, 2×10^{53} abiogenesis experiments, is way beyond of any human laboratory setting. However, reaching abiogenesis could be inevitable over planetary timescales in Earth-sized natural laboratories [62]. Despite being a simplistic demonstration, we may consider it a good proxy for the upper limit of uncontrolled reactions needed to achieve abiogenesis (in Earth-like planets). The

Feature	Nonadaptive-Nonsequential	Molecular Bricolage (Seelig & Chen, 2025)	Sequential (Oparin-Haldane)
Abiogenesis definition	$\lim_{t \rightarrow t_1^+} \text{Cov} \left(\frac{w}{W}, z' \right) > 0$, tending to W	Not defined in the coalescence of modular parts	Gradual chemical evolution leading to self-replication
Selection timestamp	When fitness-trait covariance begins to be controlled (abiogenesis)	Selection follows from modular assembly, but no defined onset	Proto-selection in chemical reactions, evolvability of selection not defined
Formalism	Derived from the Price’s equation	Absent	Absent
Generality	It relies on premises, but can be tested (and be wrong) in any chemical or computational system	Assumes necessity of code and modern-day parts	Assumes necessity of Earth-like conditions (reducing atmosphere, etc.) modern-day parts, and sequential evolution
Experimental Feasibility	Testable experimentally and computationally, as long as we can measure the complexity and the fitness-trait covariate of the systems over time	Experimentally testable for limited conditions on chemical systems	Relies on historical plausibility rather than experimental validation, testability is narrow

Table 3: Comparison of three abiogenesis models.

more interesting question is whether we can use the nonsequential–nonadaptive model to delimit further the regimen of chance; ie. to investigate only the compounds–conditions–reactions where chemical systems increase their trait–fitness covariates spontaneously, and control them over time.

Indeed, if we consider all the physicochemical combinatorics needed, it is a daunting task. That is why our experiments just explored the well known, modern-day based biochemistry. Instead, we could search for chemical compounds and conditions that fulfil eq. (4). First, we already acknowledged that start to storage and to control chemical traits is definitory of life (syllogism of null selection). Therefore, we should extract a value corresponding to the number of compounds and conditions not able to generate such reactions, n . $2 \times 10^{53-n}$ is therefore a substantially smaller subset of the chemical possibilities. Second, abiogenesis only requires reactions that increase the complexity of the system (syllogism of complexity). We can extract again a theoretical value for all the conditions leading to compound-simplification reactions, c . We now have that only $2 \times 10^{53-(n+c)}$ abiogenesis experiments are needed to assess for Earth-like conditions, which, although unknown, should be an insignificant proportion of reactions to test (Fig. 2). But determining n and c is a pending task; how can we estimate the magnitude and nature of these parameters?

To empirically ask nature if this model accurately accounts for the origins of life —on Earth or elsewhere— we must first establish the subset of this multidimensional matrix of compounds-conditions-reactions that enable abiotic complexification, and predict those that may spontaneously control inheritability of acquired traits. Once we have extracted these lists, we can start thinking how to test each of these chemical problems. Only through such an approach can we capture the breadth of nonadaptive interactions that could play fundamental roles in spontaneous abiogenic processes during any mineral evolution. Traditional models, constrained by an implicit assumption of adaptive sequential progression (with modern-day biochemistry), risk overlooking the true spectrum of chemical possibilities for abiogenesis to occur. This same idea has been extensively reviewed recently by Barlett *et al.* [72]. They propose to examine the increase in information processing over time, using the internal complexity of the system as an indicator. In fact, this effect could be best captured by quantifying $\text{Cov}(\frac{w}{w}, z')$ over time, as this provides a quantitative proxy to assess whether selection has emerged and inheritability is controlled —thus serving as a falsification criterion for any abiogenesis model. In relation to this, some authors investigated how to search for group selection on chemical systems [60, 73]. One recent attempt to do this is promising [74], but this still remains a theoretical and logistical challenge.

In the end, the quest is still to figure out the material rules of this elusive *generatio aequivoca* to occur —the very phenomenon long deemed impossible by the most grivous materialists.

What an irony!

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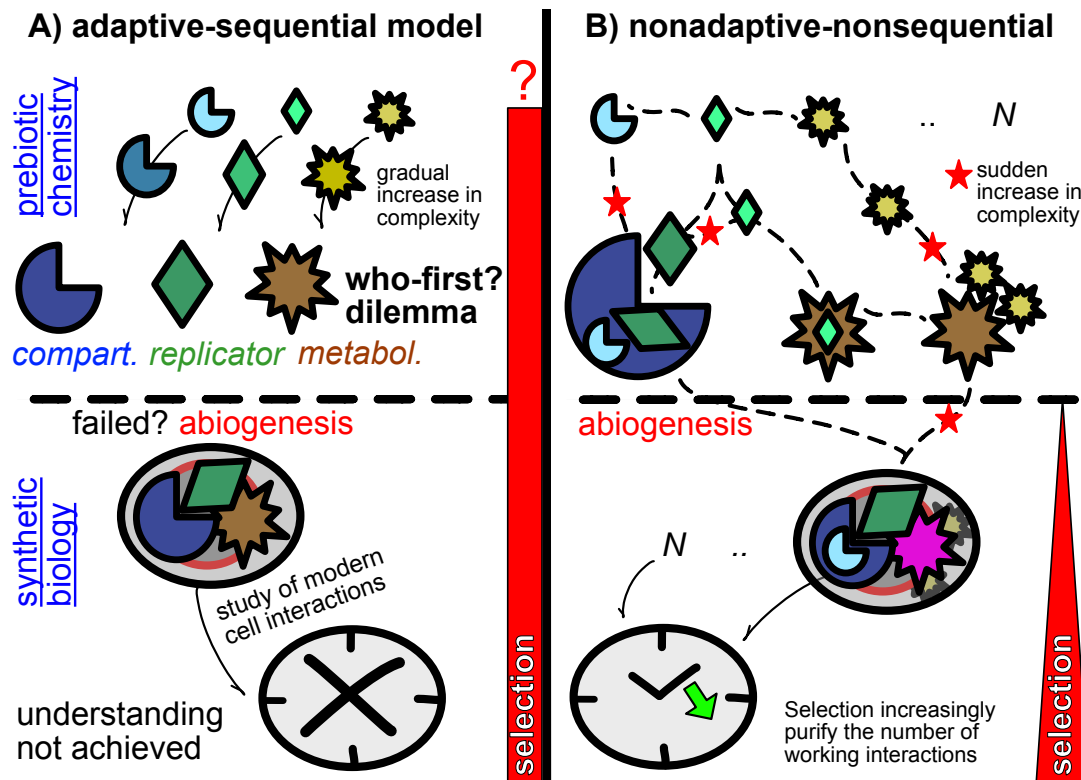


Figure 1: Trying to replicate abiogenesis with a sequential evolution has been failing for one-and-a-half centuries (A). Prebiotic chemistry and synthetic biology remain decoupled, as the link between them correspond to the unresolved question. Origin of selection has been a matter of debate in the sequential (classical) model, but is intuitively time-bounded to the competition of molecules that slowly generate complexity within a primeval broth, as narrated in the third chapter of Dawkins' *Selfish Gene* [56]. We can imagine an alternative model where nonadaptive traits drive contingent emergences of complexity (B). Global changes, like condensation reactions, could be important in producing spontaneous changes in complexity (red stars). Several different ways may be equivalent to generate abiogenesis. Importantly, in this model modern-day cells may have lost some nonadaptive traits that could be key to achieve a particular abiogenesis, as modern-day cellular life has a suboptimal fitness and their genomes have been increasingly been pruned by purifying selection. The number of allowed interactions between the primeval parts also decay over time, as they begin to be controlled by abiogenesis' products to perpetuate the "tic-tac" of the clocks – but not before!

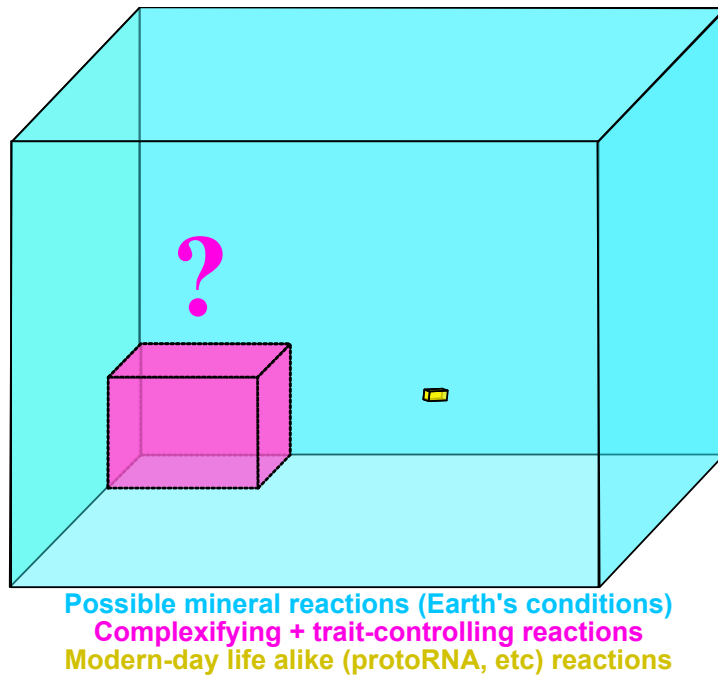


Figure 2: Schematic view of a mineral (abiotic) reaction space. In blue, we have the upper limit of reactions for Earth-like historical conditions 2×10^{53} [62]. In yellow, a representation of the narrow space of reactions explored by prebiotic chemistry experiments so far, which by definition are outside the boundaries of abiogenic conditions (we did not achieve abiogenesis). In pink, the abiogenic reactions are represented. The size of this space ($2 \times 10^{53-(n+c)}$), however, remains to be elucidated experimentally and/or computationally. The dimensions are just for visualisation, as real magnitude differences could not be directly compared in a linear scale.

References

- [1] Aleksandr Ivanovich Oparin. The origin of life on the earth. 1957.
- [2] H Charlton Bastian. Spontaneous generation. *Nature*, 9(234):482–483, 1874.
- [3] ML Pasteur. On the origin of ferments. new experiments relative to so-termed spontaneous generation. *Journal of Cell Science*, 1(32):255–259, 1860.
- [4] WT Thiselton Dyer. On spontaneous generation and evolution. *Journal of Cell Science*, 2(40):333–354, 1870.
- [5] H Charlton Bastian. Spontaneous generation: A reply. *The Nineteenth century and after: a monthly review*, 3(12):261–277, 1878.
- [6] Percy Frankland. The work of pasteur and what it has led to. *Journal of the Federated Institutes of Brewing*, 2(1):19–36, 1896.
- [7] Rudolf Virchow. *Cellular pathology: As based upon physiological and pathological histology. Twenty lectures delivered in the Pathological institute of Berlin during the months of February, March and April, 1858.* RM De Witt, 1860.
- [8] Thomas Henry Huxley. *On the physical basis of life.* Number 1. Van Nostrand, 1871.
- [9] Chas E Townsend. Protoplasm and extra philosophy. *The Phrenological Journal and Science of Health (1870-1911)*, 55(5):352, 1872.
- [10] J Bell Pettigrew. Dr. bell pettigrew on vitality. *The Lancet*, 102(2624):855–856, 1873.
- [11] Lionel Smith Beale. *Protoplasm: Or Life, Force, and Matter.* 1870.
- [12] H Charlton Bastian. The evolution hypothesis, and the origin of life. *The Contemporary review, 1866-1900*, 23:703–720, 1873.
- [13] H L. Smith. Archebiosis and heterogenesis. *Journal of Cell Science*, 2(52):357–366, 1873.
- [14] AI Oparin. The origin of life and the origin of enzymes. *Advances in enzymology and related areas of molecular biology*, 27:347–380, 1965.
- [15] Juli Peretó, Jeffrey L Bada, and Antonio Lazcano. Charles darwin and the origin of life. *Origins of life and evolution of biospheres*, 39:395–406, 2009.
- [16] Stéphane Tirard. Origin of life and definition of life, from buffon to oparin. *Origins of life and evolution of biospheres*, 40:215–220, 2010.
- [17] John Scott Haldane. Life and mechanism. *Mind*, 9(33):27–47, 1884.
- [18] Ilya Prigogine and Gregoire Nicolis. Biological order, structure and instabilities1. *Quarterly reviews of biophysics*, 4(2-3):107–148, 1971.
- [19] Tonći Kokić. The oparin hypothesis is a falling star. *Athens Journal of Philosophy*, 2(1):39–52, 2023.

- [20] Alexander I Oparin. Původ života (origin of life). *Dover Publications, New York*, 1953:196, 1936.
- [21] Raffaele Saladino, Giorgia Botta, Samanta Pino, Giovanna Costanzo, and Ernesto Di Mauro. Genetics first or metabolism first? the formamide clue. *Chemical Society Reviews*, 41(16):5526–5565, 2012.
- [22] Vera Vasas, Eörs Szathmáry, and Mauro Santos. Lack of evolvability in self-sustaining autocatalytic networks constraints metabolism-first scenarios for the origin of life. *Proceedings of the National Academy of Sciences*, 107(4):1470–1475, 2010.
- [23] BS Palmer. A review on the spontaneous formation of the building blocks of life and the generation of a set of hypotheses governing universal abiogenesis. *International Journal of Astrobiology*, 12(1):39–44, 2013.
- [24] David Deamer. Membranes and the origin of life: a century of conjecture. *Journal of molecular evolution*, 83(5):159–168, 2016.
- [25] Addy Pross. Causation and the origin of life. metabolism or replication first? *Origins of Life and Evolution of the Biosphere*, 34:307–321, 2004.
- [26] Erkki J Brändas. Abiogenesis and the second law of thermodynamics. In *Advances in Quantum Systems in Chemistry, Physics, and Biology: Selected Proceedings of QSCP-XXIII (Kruger Park, South Africa, September 2018) 23*, pages 393–436. Springer, 2020.
- [27] Stanley L Miller and Harold C Urey. Organic compound synthesis on the primitive earth: Several questions about the origin of life have been answered, but much remains to be studied. *Science*, 130(3370):245–251, 1959.
- [28] Martin Ferus, Fabio Pietrucci, Antonino Marco Saitta, Antonín Knížek, Petr Kubelík, Ondřej Ivanek, Violetta Shestivska, and Svatopluk Civiš. Formation of nucleobases in a miller–urey reducing atmosphere. *Proceedings of the National Academy of Sciences*, 114(17):4306–4311, 2017.
- [29] Joaquín Criado-Reyes, Bruno M Bizzarri, Juan Manuel García-Ruiz, Raffaele Saladino, and Ernesto Di Mauro. The role of borosilicate glass in miller–urey experiment. *Scientific reports*, 11(1):21009, 2021.
- [30] Joan Oró and Aubrey P Kimball. Synthesis of purines under possible primitive earth conditions: II. purine intermediates from hydrogen cyanide. *Archives of biochemistry and biophysics*, 96(2):293–313, 1962.
- [31] Cyril Ponnampereuma, Richard M Lemmon, Ruth Mariner, and Melvin Calvin. Formation of adenine by electron irradiation of methane, ammonia, and water. *Proceedings of the National Academy of Sciences*, 49(5):737–740, 1963.
- [32] Matthew W Powner, Béatrice Gerland, and John D Sutherland. Synthesis of activated pyrimidine ribonucleotides in prebiotically plausible conditions. *Nature*, 459(7244):239–242, 2009.
- [33] Matthew W Powner and John D Sutherland. Prebiotic chemistry: a new modus operandi. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 366(1580):2870–2877, 2011.

- [34] Margarita R Marín-Yaseli, Cristina Mompeán, and Marta Ruiz-Bermejo. A prebiotic synthesis of pterins. *Chemistry—A European Journal*, 21(39):13531–13534, 2015.
- [35] Sunil Pulletikurti, Mahipal Yadav, Greg Springsteen, and Ramanarayanan Krishnamurthy. Prebiotic synthesis of α -amino acids and orotate from α -ketoacids potentiates transition to extant metabolic pathways. *Nature Chemistry*, 14(10):1142–1150, 2022.
- [36] Michele Fiore, Carolina Chieffo, Augustin Lopez, Dimitri Fayolle, Johal Ruiz, Laurent Soullère, Philippe Oger, Emiliano Altamura, Florence Popowycz, and René Buchet. Synthesis of phospholipids under plausible prebiotic conditions and analogies with phospholipid biochemistry for origin of life studies. *Astrobiology*, 22(5):598–627, 2022.
- [37] César Menor-Salván, Dra Marta Ruiz-Bermejo, Marcelo I Guzmán, Susana Osuna-Esteban, and Sabino Veintemillas-Verdaguer. Synthesis of pyrimidines and triazines in ice: implications for the prebiotic chemistry of nucleobases. *Chemistry—A European Journal*, 15(17):4411–4418, 2009.
- [38] RA Sanchez, JP Ferris, and LE Orgel. Cyanoacetylene in prebiotic synthesis. *Science*, 154(3750):784–785, 1966.
- [39] Michael P Robertson and Stanley L Miller. An efficient prebiotic synthesis of cytosine and uracil. *Nature*, 375(6534):772–774, 1995.
- [40] Josep M Ribó, Celia Blanco, Joaquim Crusats, Zoubir El-Hachemi, David Hochberg, and Albert Moyano. Absolute asymmetric synthesis in enantioselective autocatalytic reaction networks: Theoretical games, speculations on chemical evolution and perhaps a synthetic option. *Chemistry—A European Journal*, 20(52):17250–17271, 2014.
- [41] Saúl A Villafañe-Barajas, Marta Ruiz-Bermejo, Pedro Rayo-Pizarroso, Santos Gálvez-Martínez, Eva Mateo-Martí, and María Colín-García. A lizardite–hcn interaction leading the increasing of molecular complexity in an alkaline hydrothermal scenario: implications for origin of life studies. *Life*, 11(7):661, 2021.
- [42] Thomas A Steitz and Peter B Moore. Rna, the first macromolecular catalyst: the ribosome is a ribozyme. *Trends in biochemical sciences*, 28(8):411–418, 2003.
- [43] Steven A Benner, Elizabeth A Bell, Elisa Biondi, Ramon Brassler, Thomas Carell, Hyo-Joong Kim, Stephen J Mojzsis, Arthur Omran, Matthew A Pasek, and Dustin Trail. When did life likely emerge on earth in an rna-first process? *ChemSystemsChem*, 2(2):e1900035, 2020.
- [44] Bradley T Burcar, Laura M Barge, Dustin Trail, E Bruce Watson, Michael J Russell, and Linda B McGown. Rna oligomerization in laboratory analogues of alkaline hydrothermal vent systems. *Astrobiology*, 15(7):509–522, 2015.
- [45] Ryo Mizuuchi, Taro Furubayashi, and Norikazu Ichihashi. Evolutionary transition from a single rna replicator to a multiple replicator network. *Nature Communications*, 13(1):1460, 2022.
- [46] T Tjivikua, Pablo Ballester, and Julius Rebek Jr. Self-replicating system. *Journal of the American Chemical Society*, 112(3):1249–1250, 1990.
- [47] Laurence D Hurst and Richard Dawkins. Life in a test tube. *Nature*, 357(6375), 1992.

- [48] Christophe Malaterre. Can synthetic biology shed light on the origins of life? *Biological Theory*, 4:357–367, 2009.
- [49] Gong Cheng and Juan Pérez-Mercader. Polymerization-induced self-assembly for artificial biology: Opportunities and challenges. *Macromolecular Rapid Communications*, 40(2):1800513, 2019.
- [50] Lynn J Rothschild, Nils JH Aversch, Elizabeth A Strychalski, Felix Moser, John I Glass, Rolando Cruz Perez, Ibrahim O Yekinni, Brooke Rothschild-Mancinelli, Garrett A Roberts Kingman, Feilun Wu, et al. Building synthetic cells from the technology infrastructure to cellular entities. *ACS Synthetic Biology*, 13(4):974–997, 2024.
- [51] Anthony C Forster and George M Church. Towards synthesis of a minimal cell. *Molecular systems biology*, 2(1):45, 2006.
- [52] James F Pelletier, Lijie Sun, Kim S Wise, Nacyra Assad-Garcia, Bogumil J Karas, Thomas J Deerinck, Mark H Ellisman, Andreas Mershin, Neil Gershenfeld, Ray-Yuan Chuang, et al. Genetic requirements for cell division in a genomically minimal cell. *Cell*, 184(9):2430–2440, 2021.
- [53] Clyde A Hutchison III, Ray-Yuan Chuang, Vladimir N Noskov, Nacyra Assad-Garcia, Thomas J Deerinck, Mark H Ellisman, John Gill, Krishna Kannan, Bogumil J Karas, Li Ma, et al. Design and synthesis of a minimal bacterial genome. *Science*, 351(6280):aad6253, 2016.
- [54] Olen R Brown and David A Hullender. Biological evolution is dead in the water of darwin’s warm little pond. *Progress in Biophysics and Molecular Biology*, 2024.
- [55] Laurel O Sillerud. Abiogenesis.
- [56] Richard Dawkins. *The extended selfish gene*. Oxford University Press, 2016.
- [57] Samir Okasha and Jun Otsuka. The price equation and the causal analysis of evolutionary change. *Philosophical Transactions of the Royal Society B*, 375(1797):20190365, 2020.
- [58] George R Price. Selection and covariance. 1970.
- [59] Samir Okasha. *Evolution and the levels of selection*. Clarendon Press, 2006.
- [60] Kuniyiko Kaneko. Kinetic origin of heredity in a replicating system with a catalytic network. *Journal of Biological Physics*, 28:781–792, 2002.
- [61] Jacques Monod. *On chance and necessity*. Springer, 1974.
- [62] Robert M Hazen. Chance, necessity and the origins of life: a physical sciences perspective. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*, 375(2109):20160353, 2017.
- [63] Sergio A Muñoz-Gómez, Gaurav Bilollikar, Jeremy G Wideman, and Kerry Geiler-Samerotte. Constructive neutral evolution 20 years later. *Journal of molecular evolution*, 89:172–182, 2021.
- [64] Arlin Stoltzfus. On the possibility of constructive neutral evolution. *Journal of molecular evolution*, 49:169–181, 1999.

- [65] Jaroslav Flegr. Constructive neutral evolution. In *Encyclopedia of Sexual Psychology and Behavior*, pages 1–4. Springer, 2023.
- [66] Robert M Hazen, Peter C Burns, H James Cleaves, Robert T Downs, Sergey V Krivovichev, and Michael L Wong. Molecular assembly indices of mineral heteropolyanions: some abiotic molecules are as complex as large biomolecules. *Journal of the Royal Society Interface*, 21(211):20230632, 2024.
- [67] Ilya Prigogine and René Lefever. Theory of dissipative structures. *Synergetics: Cooperative phenomena in multi-component systems*, pages 124–135, 1973.
- [68] Christian Jenewein, Aurora Maíz-Sicilia, Fernando Rull, Lorena González-Souto, and Juan Manuel García-Ruiz. Concomitant formation of protocells and prebiotic compounds under a plausible early earth atmosphere. *Proceedings of the National Academy of Sciences*, 122(2):e2413816122, 2025.
- [69] Burckhard Seelig and Irene A Chen. Intellectual frameworks to understand complex biochemical systems at the origin of life. *Nature Chemistry*, 17(1):11–19, 2025.
- [70] François Jacob. *Of flies, mice, and men*. Harvard University Press, 1998.
- [71] Sean R Eddy. Non-coding rna genes and the modern rna world. *Nature Reviews Genetics*, 2(12):919–929, 2001.
- [72] Stuart Bartlett, Andrew W Eckford, Matthew Egbert, Manasvi Lingam, Artemy Kolchinsky, Adam Frank, and Gourab Ghoshal. The physics of life: Exploring information as a distinctive feature of living systems. *arXiv preprint arXiv:2501.08683*, 2025.
- [73] Omer Markovitch, Olaf Witkowski, and Nathaniel Virgo. Chemical heredity as group selection at the molecular level. *arXiv preprint arXiv:1802.08024*, 2018.
- [74] Tymofii Sokolskyi, Bruno Cuevas Zuviria, Sydney Gargulak, Esau Allen, and David Baum. From messy chemistry to ecology: autocatalysis and heritability in prebiotically plausible chemical systems. *bioRxiv*, pages 2024–08, 2024.