The Principles of Life

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Abstract

The questions of what life is and how it first started have for a long-time daunted science. Our rather small understanding of what living systems are is demonstrated by the inexistence of a widely accepted chemical definition of them. This work intends to solve this long-lasting problem by laying such a definition as well as the principles that have governed living systems since their inception up to their extant forms. Here I show that living entities are productive chemical systems that bias their own formation. It will be shown that these two aspects inevitably lead to a selection by the highest replicative metabolic flux, explaining all the characteristics of extant living systems, where the strength of the biasing effect can be considered the main difference between life now, and at its origin. By building a narrative on how such a journey may have taken place, this work intends to provide the theoretical framework and experimental inspiration for a complete understanding of evolution, simultaneously creating new avenues to the search for extra-terrestrial life forms and opening the doors to the development of living technologies.

Main Text

Life has for a long time been a mysterious state of matter that lured curious minds into trying to discern it (1). Nonetheless, opinions exist that for the last 60-70 years, successes in this field existed only on its own researchers' terms, and consequently the problem still remains largely unsolved (2). Nowadays the problem is torn apart into many sub-problems (3) whose researchers are to a great extent "stuck" (4). This work aims at finally exposing the ultimate principles of life and how it began, hoping to provide the theoretical context long needed in the field so the right "puzzles" can finally be solved (2). For that, a narrative will be built in order to explain how inanimate matter may have turned into the first living systems, followed by a definition of what they are and a discussion on how that relates to some characteristics we usually associate with living systems, namely self-replication, compartmentalization, function and information. Lastly, a proposal will be made on what could have been the free energy source that fuelled the first living systems and how it led to other free energy convertors used nowadays.

Before we proceed some concepts need to be recalled.

I hereby consider a productive chemical system one that transforms feedstock into (complex) chemical products, necessarily fuelled by a thermodynamic gradient existent in the environment (5). In order to do so, the importance of free energy converting engines cannot be overstated as they are key to any living system successively increase its free energy content at the expense of the environment's, and thus be able to keep itself in a steady state far from equilibrium (5).

To the set of metabolites that may, at a given moment, be generated by a productive chemical system I shall name accessible chemical space.

Besides, as feedstock enters living systems and products leave, their gross composition does not change significantly over time. They are at a dynamic steady state, in which reactants are being generated at the rate their products are consumed. The rate of such flow of metabolites in each reaction, and ultimately pathway and network, is called metabolic flux. It is controlled at the scale of individual reactions both kinetically and thermodynamically in the following way (6): if a reaction is irreversible, there will be a kinetic control in which the main products will be those with smaller activation energies to

them. On the other hand, reversible reactions tend to be close to equilibrium, and so the rates of the reverse and forward reactions are similar. In this case, thermodynamics will control which products will have the highest net formation rates. If one of the products is consumed, the system will tend to compensate that interference. Thus, the products with the highest net formation rates will be the ones interacting and/or reacting the most with other metabolites or the environment. These are the two extremes. Reality mostly comes somewhere in between.

To the process where a molecule, or a set of molecules, increases its own net formation rate relative to alternative products, through kinetic or thermodynamic effects, we shall call self-bias. Cross-bias will be used to refer to the kinetic or thermodynamic biasing effect entities can have on one another.

Finally, when regarding a metabolic flow through a molecule, or a set of them, capable of self-bias, I shall consider that to be a replicative metabolic flow.

The stage is now set for the next section, in which it will be shown how one productive chemical system serendipitously may have developed into the extant living systems.

A Story of Perseverance

Phase A - Inconsistent Production

In order for life to start, at some point in space and time, complex chemicals must have been routinely generated with the help of a free energy converting engine. Such engine (ultimately an environmental heterogeneity) would use a given fuel (frustrated free energy) to produce chemicals from feedstock. As previously introduced, such apparatus would constitute a productive chemical system. Quite importantly, there is no restriction that such engine was present only at feedstock uptake. Rather, whatever engine was used at life's origin, it must have been capable of pumping free energy into the system at many stages/reactions other than the starting fixation.

One important question is what the accessible chemical space after the metabolite's activation was. The answer to that would necessarily lie in the interactions available to them. Both the environment and previously produced molecules would interactively orient the accessible chemical space for each reaction. Every time a new product was created, by kinetic or thermodynamic means, new possibilities became accessible to the subsequent ones.

One defining characteristic of this phase is that, excluding environmental effects, this production process would have no temporal consistency whatsoever. At this phase, there were no self-perpetuating characteristics on the produced metabolites – and quite likely neither on the environment. The accessible chemical space consisted of molecules that would in no way bias their own formation.

Nevertheless, it could be expected that the longest chemical pathways – the ones whose atoms had been through the most reactions since their uptake – would be those whose metabolites were able to interact with the engine, fuelling (activating) them into further stretches (reactions) away from the initial fixation. Even so, it would make little sense to speak about metabolic flow, as the free energy, always coupled to the metabolites, would go from the engine to almost random relaxation pathways which would easily appear and disappear and so there simply wasn't a dynamic steady state.

And without something else, never would life begin, and this scenario – a productive chemical system – would be everything to it.

Phase B - Selection of Recurrent Pathways

What made the trick were self-biasing effects. Molecules, or a set of them, that would be capable of biasing (even if only slightly) themselves. These would be molecules that increased their net formation rate compared to, and probably at the expense of, the side-products'.

Although it may not seem much, it started the whole process of life.

A direct consequence of these self-biasing effects was that, besides the environment, the produced metabolites were bringing about some (however small) time consistent bias - towards themselves - of the accessible chemical space. Such consistent bias is an inevitable consequence of an engine periodically pumping free energy and matter into a system capable of inducing itself.

This bias of production (free energy, and matter and energy) towards specific metabolites and correspondent reaction products, would allow for more complex molecules to be formed. As a consequence of that, new interactions would be serendipitously found, increasing the probabilities for the biasing effects to encompass a larger and richer set of molecules. And this effect would feed on itself: metabolites capable of self-bias, or cross-bias with the existing pool of molecules, the fastest, would have their net formation rate increased the most. More precursors for those metabolites would be consumed, and that increased consumption effect would trace back to the sources of free energy and matter.

Ultimately, those (rather unspecific) pathways leading to self- or cross-biasing intermediates would create the highest negative pressures at the sources, pulling towards themselves higher fuel and feedstock fluxes, progressively neglecting the rate of formation of other pathways with smaller metabolic fluxes or weaker interacting capacities. In other words, higher metabolic fluxes would go into progressively less pathways. They were being selected.

Even though cross-biasing effects were likely ruling the interactions between the compounds, and thus their selection, there was at least one clear advantage for self-biasing molecules or small sets of them: they would not depend on the presence of other metabolites to bias their own formation. A consequence of that was a higher resilience to, for instance, dilutions to extinction. Over time, this would favour themselves, their pathways and ultimately the metabolites with which they interacted. Consequently, if those self-biasing molecules, or small sets of them, did appear, they would tend to become dominant and have the metabolism built around them. We may call them proto-genes.

Although this may have evolved in successive sub-stages where different types of proto-genes would predominate, looking from the end result, we can now understand why purine-pyrimidine-based interactions became the ultimate self-biasing set of molecules and such central figures in the extant metabolisms. Irrespective of what came before, once such a complementary base pairing came within reach, a strong thermodynamic cross-biasing effect took place from the beginning. This then led to the selection of the proto-nucleotides' chemical sub-spaces, and shortly after the second complementary base pairing must have been discovered, further favouring these sub-spaces. These interactions would last up to extant metabolisms, all thanks to their selective cross-biasing effect – or pairwise self-bias.

In the same way, those proto-genes that would be able to react with one another, arguably with some help from the free energy engine, would be selected out of self-bias, and we may thus have gotten to strands of them.

This hypothesis to be correct, the metabolites that interacted with such time-resilient type of molecules would equally go on to last. Fortunately, staggering evidence exists that the genetic code – both its amino acids and correspondent interactions - was established on the basis of stereo-chemical affinities between the amino acids and the corresponding codons or anti-codons, before any process of translation appeared⁶. In other words, the selection of the amino acids used as of today was, to a high extension, based on their interactions with the proto-genes that ultimately came to dominate. This genetic code would then become a proxy for the majority of the interactions between the proto-genes and the remaining metabolism.

Once again, those pathways with which the engine would interact the most frequently and seamlessly, would channel the most free energy and matter into their products and intermediates, ultimately increasing their metabolic flux, further extending their selective advantage. In order to do so, somewhere in time, what we now interpret as energy currencies and other types of carriers may have been selected by their very strong cross-biasing interactions with the respective sources and some of the metabolites. Whatever cross-biasing interaction that had proto-genes involved would be prone to survive the test of time, and that may be the reason ATP (as the nucleotide-based “energy currency”) is so central and common to

the biological metabolisms (6). Similar cross-biases with nucleotides would develop into what we now interpret as enzyme cofactors and chemical messengers (6).

Summarizing the ideas thus far, we understand that those groups of metabolites/pathways capable of biasing themselves with the highest metabolic fluxes would be selected by outcompeting the others in the processing of matter and free energy. Generically, evolution led towards solutions that biased themselves faster than the alternatives. A consequence of that was the selection of metabolites that would form rich interactomes and of interactions that would orient the production towards such metabolites.

By now it starts to become clear that living systems did not evolve out of functional considerations nor the capability of holding information per se, but rather by a process of continuous selection by replicative metabolic flux: constantly fed by a free energy engine and accompanied by the discovery of self-biasing properties – the only two needed conditions for living systems to develop from inanimate matter.

Phase C – Selection of Interactomes

Evolution would thus favour metabolites and pathways that were interaction rich. This led to an interconnectedness among themselves with little sense to it but that overall would channel the metabolic flow towards interesting products with multiple interactions (regulations) on the way. This was the origin of metabolic networks and metabolism as we know it.

Once again knowing the final solution, somewhere in time, a specific chemical sub-space must have been selected: amphiphilic molecules. At the first stage, this chemical sub-space would be unbiased and so different types of such molecules would be formed. But given enough of them, they would aggregate by hydrophobic effects, constantly shifting the production towards themselves, consequently pulling more and more metabolic flux towards this sub-space.

Not only was this selection a landmark but also were its consequences. The newly available confinement kinetic effect probably allowed a whole new magnitude of metabolic fluxes, and once a functioning network was sampled inside one of these compartments there was never a look back. Rudimentary cellular replication would eventually start, and, in retrospective, the initially unbiased exploration of this chemical sub-space may have been crucial to the stability of the compartments (7).

At this point, we not only have a unique network whose pathways would be evolving, but rather a population of them being selected by competition for the same fuel and feedstock. By now, the environment must have been dissolved and made portable, including the all too important engine. The agents of dissolution probably were proto-siderophores whose selection must have been favoured by self-biasing interactions with the environment.

As to ensure a higher percentage of functional/complete daughter-cells, the evolutive pressure towards proto-genes – by now central figures of the metabolism - capable of condensing into fewer packages (strands and eventually chromosomes), hence facilitating the replication process, would be very significant. The better this was done, the more of those characteristics would last through generations. The ultimate result of this evolutive pressure may have been DNA and all the intricate structure of chromosomes (6).

As always, the metabolic flow at the sources would go towards solutions that maximized it. So, the same way pathways were under evolutive pressure to increase the replicative metabolic flux through themselves, so were the individual self-biasing networks. Either in phase B or C, the results of it must have been an uniformization on the production of the metabolites, progressively leading to homochirality in α -amino acids and sugars, ribose as the common sugar to all nucleotides and a restricted set of amino acids, lipidic molecules, among others.

In due course, complex structures, such as tRNA and other ribozymes, would accelerate and add selectivity to previously acquired metabolic processes, ultimately improving the whole metabolic flux. Alternatively, they could channel it into all new interesting chemical sub-spaces. For instance, tRNA may have been modularly selected and eventually combined to

increase the metabolic flux of a network by bringing about heritable increased reaction rates and selectivity. This would come in hand with the also favoured homogenization of the genetic code.

Relevant to mention that all these catalytic interactions were serendipitous discoveries and not necessarily selected for they “catalytic” intentions. Rather, the catalytic properties were a consequence of cross-biasing interactions that combined more than two chemical sub-spaces. Peptides “catalysing” reactions between sugars and nitrogenous bases, did not simply put two different metabolic pathways together, but rather three. Extending the reasoning, we understand the existence of numerous co-factors and co-enzymes in the extant metabolisms. Although it may look like only the sugar-nucleobase interaction is being catalysed, as this may be the only covalent bond being established, in fact all the involved pathways were cross-biasing themselves before a catalytic reaction came into being.

The tendency for proto-genes to play a central role in the metabolism never disappeared and chances are that for whatever exploration of the chemical space that lasted in time, proto-genes would be mediating it. For instance, hand-in-hand with the process of homogenization of the metabolites, (proto-)genes encoding for enzymes with extraordinary substrate-selectivity were selected by simple cross-bias with those metabolites. This was a cross-bias necessarily mediated by the proteins.

At some point, some living networks would be able to convert free energy that had been pre-packaged and delivered into the environment by living systems. They would be capable of surviving on a thermodynamic gradient other than the one available in the environment. And so was heterotrophy born.

Ultimately, this is the phase life still stands at. Darwin’s theory of evolution is an interpretation of this selection by metabolic flux: in a population of whatever self-biasing networks, being them either these rudimentary metabolisms or Darwin’s finches, evolution will select the one with the highest replicative metabolic flux. This would be the fittest, in the sense that given a set of conditions, it would be the fastest one turning the available fuel and feedstock into more of itself, potentially starving the others to extinction. A selection by replicative metabolic flux ultimately explains the evolution towards slimmer self-biasing structures through progressively stronger biases on the accessible chemical space, leading to a clean-up of the metabolism and eventually the loss of dispensable genes (8).

I am sure that there are a lot of more precise explanations that could be given and many others that were entirely overlooked. But the purpose of this section was not to state as the whole process went as truthfully as possible, and much less in the correct temporal order. Rather, the objective was to lay down a conceptual scaffold to work with, and I hope that any wrong suggestion that may have been given does not invalidate the principles that are about to be discussed.

The Principles of a Living System

By now, we are ready for a formal definition of what productive chemical systems and living systems are.

Productive chemical system: A system where an environmental thermodynamic gradient is periodically converted into chemical free energy.

Living system: A productive chemical system (or a set of) whose accessible chemical space biases itself.

Although at the first stages of life, the bias was quite small, it was the enough to spark the progressive improvement towards such a bias that living systems became predictive – and books were written on how they consistently operate. Necessarily, the less biased a system is, the more prone it is to explore previously inaccessible chemical space and more apt it is to significant improvement.

An interesting note is that viruses are not considered living systems - as they are not productive chemical systems. Besides, this classification does not mention any of the complex characteristics of modern living beings, and herein is advocated that for those characteristics to appear - or the capacity to make productive use from them - living systems would be needed. A clear example is self-replication, which is a mere consequence of chemical production going through a self-biasing metabolism in which the bias is strong enough to neglect the appearance of alternative products.

Furthermore, there is no reason to limit living systems to physically compartmentalized specimens under the argument that otherwise populations would not evolve. Evolution needs entities to select from, and entities require individualization. But it would be too narrowing to consider solely physical individualization or compartmentalization. Examples were present in phase B - considered the stage at which life began - where the entities under an evolutive process (the chemical pathways) shared the physical space but were nonetheless individualized in their own accessible chemical sub-spaces.

Albeit technologically useful, a function-based interpretation of living systems may be conceptually misleading. By analysing the interactions a gene has with the remaining metabolism, we can perhaps assert it one or more functions. But maybe the reason that gene exists does not fit into any of the productive roles we would normally expect. Perhaps a gene may just be there because it is a residue of a proto-gene that was so central to the proto-metabolism that, for some still unknown type of interaction, it just binds the whole metabolism together nowadays. As hinted by the functional redundancy of extant metabolisms, there never was an explicit selection by function per se; rather by which implications a given metabolite's interactions had in the whole system's replicative metabolic flux.

The role of information in life has long been a hot topic (1). I would argue that there is information being stored in living systems, and that is what makes them such interesting entropic devices. What may have been less explicit up to now is how it is stored and transferred. Although it may be tempting to conclude that genes hold the information, that would not be correct. The best scrutiny is that the only information a living system carries through generations – its accessible chemical space - is being held by the metabolism as a whole. Besides, the more restricted the accessible chemical space is, the more information it holds. And the accumulation and replication of that information is entirely powered by the free energy (or thermodynamic gradients) in the environment. I would hence argue against an explicit information sub-system in life, namely because (proto-)genes were not required at all. As was mentioned before, they became central to the metabolism thanks to their resilience, due to their selective self-biasing capabilities, and eventually the metabolism built itself around them. But would life have never discovered such a particular self-biasing pairing, and had instead evolved into a more distributed form, it would not be less alive because of that.

Finally, I would like to emphasize that living systems were defined as *chemically* productive. Emulation of these principles, for instance in the realm of information, should be considered to produce life-like systems.

[A note on the free energy conversion engine](#)

In order to bring this home, it is important to try to connect the concepts discussed thus far with a specific free energy convertor. Not only that but also to propose a narrative on how two other extant engines – photosynthesis and chemiosmosis – came into being. Those are the purposes of this final section.

Up to now, we can assert that the engine that started the specific productive system that led to life as we know it should be: portable, somewhat unspecific to substrates, simple (as much as such a mechanistic process (5) can be), not a rare and unreproducible event, able to withstand the countless conversions that were needed without degrading – hence whose properties wouldn't tend to change upon usage -, and, for consistence-sake, not a complex organic structure.

From these considerations, only one mechanism seems plausible at the moment: electron bifurcation, whose presence in the early stages of life has been previously proposed (9,10). Namely, it has been shown that molybdenum complexes are capable of producing such an effect in extant biology, being thus possible candidates for the first engines (5,10). One pleasant

characteristic of this mechanism is that relatively simple organic molecules, for instance flavins (9) (commonly associated with two nucleotides to form flavin adenine dinucleotide (6)) and quinones (10) (which even today are used under this role in the Q-cycle (11)), could, and did, take over the job and there is no reason why it couldn't have happened relatively soon in the whole process, probably in an environment rich in iron-sulphur clusters, key components of extant electron-bifurcating hydrogenases in acetogenesis (9), which would very well connect with the hypothesis that ferredoxins (iron-sulphur proteins) are ancestral energy currencies (9). A lot more of detail could be given here but nothing can be further added to the existent literature (9).

The question now is how could the chemiosmotic solution appear? What came first: the ability to build the proton gradient or the ability to use it? It would be my guess that it was the latter; and that the proton gradient first appeared as a by-product of the environmental fuel for whatever electron bifurcation process: H_2 . Once the cellularization phase got started, selection could have favoured the existence of a proto-Q cycle in the membranes - it would allow for oxidation of the fuel on the outside and activation of the metabolism on the inside. On the course of H_2 oxidation, just like in the extant versions (11), protons would inevitably accumulate on the outer surface. The thermodynamic gradient would start to decrease, and the motive force of the whole system would progressively weaken, perhaps even threatening the metabolites' activation by the process of electron confurcation (9). Although the membrane would have some degree of proton permeability, there probably was an enormous selective pressure to increase the thermodynamic gradient. The solution must have come in a rudimentary form of the extant ion channels. Eventually a new evolutionary pressure may have existed towards gating the proton-flux, and this may have been the basis for the intricacy of ATPases and H^+ -pyrophosphatases. A new type of free energy converting engine would then appear, and a whole new chemical sub-space became available, whose ultimate solution was phosphate chemistry (12).

The better this ancestral version of the electron transport chain was, the higher the maximum allowed metabolic flux would be, so selection pushed towards its enhancement, where photosynthesis was a clear milestone. And the rest is history.

This engine hypothesis to be correct, it would point towards the hydrothermal vents as life's hatchery given its abundance on the previously mentioned constituents, namely H_2 (13,14).

Final comments

Although the experimental reproduction of these principles is quite feasible, the effect of the environment, both regarding its constitution and respective concentrations, may make the exact reproduction of the original process a lasting endeavour. Besides other environmental variables, temperature alone provides a specific balance between the thermodynamic and kinetic controls that were at play in the initial phases, and ripples may have lasted up to now. The purpose of this work was not to identify exactly which reactions did or did not take place. Rather, the purpose was to lay the foundations for a complete understanding of what living systems are, how to find them and eventually make them.

On interesting question is how optimized biology is. Given even more time, would another massive discovery in the chemical space ever appear, perhaps selected by some specific environment? To which extent were the extant solutions limited by the initial hatchery? Could any other initial environment lead to a much different solution in the long term? Could a single change in temperature make the metabolic flow select entirely new sub-spaces? Or is this a confluence point given the conditions on Earth?

Regarding the search for extra-terrestrial lifeforms, it will be interesting to know if any other thermodynamic gradient can bring about a productive chemical system in conditions where some of the products could bias themselves. At first sight, the combination of a geological electrochemical system with the abundance of the perfect type of fuel, does seem hard to emulate. Besides, the identification of a living system based on complexity alone isn't necessarily the best approach. Although high complexity most surely points to the existence of a productive chemical system, it may be a phase A type of

system where the environment is intricate enough to generate highly complex products. Although complexity measures give us a very good hint, ultimately, we shall look for chemical bias being produced.

It is my expectation that the understanding of the principles underlying living systems will now open the doors to the development of living technologies. Everything that one can see was most probably, directly or indirectly, produced by a living system or at least deeply influenced by it. A great power is about to be given to us and the need to make it right is alarming. The urge to bring about ethical considerations, rules to develop such technologies, and even legislation will start to become unavoidable.

To enumerate possible applications to such a key enabling technology would be biasing them to the author's imagination, namely when we are discussing a technology capable of colonising worlds and of creating all the wonders in this planet. If I dare to take a small peak at what is to come, I would emphasise that this kind of technology cannot be programmed. It cannot be too much rationalised. It needs to be bootstrapped and rightfully evolved. And this, I believe, is going to be the art of this technology: to know how to evolve it and set the right frame to guide it towards the chemical sub-space we want it to explore. It may all turn out to be wrong but mind-blowing excitement and anxiety is the least we can say about what is bound to be a beautiful technology capable of reaching all corners of our human life.

References

1. Schrödinger E. What is Life?: With Mind and Matter and Autobiographical Sketches [Internet]. Canto. Cambridge: Cambridge University Press; 1992. Available from: <https://www.cambridge.org/core/books/what-is-life/A876185F2DB06FF5C2CC67C9A60DAD7F>
2. Benner SA. Paradoxes in the Origin of Life. *Orig Life Evol Biosph* [Internet]. 2014;44(4):339–43. Available from: <https://doi.org/10.1007/s11084-014-9379-0>
3. Preiner M, Asche S, Becker S, Betts HC, Boniface A, Camprubi E, et al. The Future of Origin of Life Research: Bridging Decades-Old Divisions. *Life* [Internet]. 2020 Feb 26 [cited 2020 Jun 8];10(3):20. Available from: <https://www.mdpi.com/2075-1729/10/3/20>
4. Kun Á, Radványi Á. The evolution of the genetic code: Impasses and challenges. *Biosystems*. 2018 Feb;164:217–25.
5. Branscomb E, Russell MJ. Turnstiles and bifurcators: the disequilibrium converting engines that put metabolism on the road. *Biochim Biophys Acta*. 2013 Feb;1827(2):62–78.
6. Nelson DL, Lehninger AL, Cox MM. *Lehninger Principles of Biochemistry* [Internet]. W. H. Freeman; 2008. (Lehninger Principles of Biochemistry). Available from: <https://books.google.pt/books?id=5Ek9J4p3NfkC>
7. Deamer D. The Role of Lipid Membranes in Life's Origin. *Life (Basel, Switzerland)* [Internet]. 2017 Jan 17;7(1):5. Available from: <https://pubmed.ncbi.nlm.nih.gov/28106741>
8. Albalat R, Cañestro C. Evolution by gene loss. *Nat Rev Genet* [Internet]. 2016;17(7):379–91. Available from: <https://doi.org/10.1038/nrg.2016.39>
9. Müller V, Chowdhury NP, Basen M. Electron Bifurcation: A Long-Hidden Energy-Coupling Mechanism. *Annu Rev Microbiol*. 2018 Sep;72:331–53.
10. Nitschke W, Russell MJ. Redox bifurcations: Mechanisms and importance to life now, and at its origin. *BioEssays* [Internet]. 2012;34(2):106–9. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/bies.201100134>
11. Crofts AR, Meinhardt SW, Jones KR, Snozzi M. The role of the quinone pool in the cyclic electron-transfer chain of

- Rhodopseudomonas sphaeroides A modified Q-cycle mechanism. Biochim Biophys Acta - Bioenerg [Internet]. 1983;723(2):202–18. Available from: <http://www.sciencedirect.com/science/article/pii/0005272883901202>
12. Westheimer FH. Why nature chose phosphates. Science. 1987 Mar;235(4793):1173–8.
 13. Martin W, Baross J, Kelley D, Russell M. Hydrothermal vents and the origin of life. Nat Rev Microbiol. 2008 Jan 1;29:1–10.
 14. McDermott JM, Seewald JS, German CR, Sylva SP. Pathways for abiotic organic synthesis at submarine hydrothermal fields. Proc Natl Acad Sci [Internet]. 2015;112(25):7668–72. Available from: <https://www.pnas.org/content/112/25/7668>