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Prebiotic chemical refugia:

multifaceted scenario for the formation of biomolecules in primitive Earth

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Abstract

The origin of life was a cosmic event happened on primitive Earth. A critical problem to better understand the origins of life in Earth is to glimpse in which chemical scenarios the basic building blocks of biological molecules could be produced. Classic works in pre-biotic chemistry frequently considered early Earth as a homogeneous atmosphere constituted by chemical elements such as methane (CH_4), ammonia (NH_3), water (H_2O), hydrogen (H_2) and hydrogen sulfide (H_2S). Under that scenario, Stanley Miller was capable to produce amino acids and solved the question about the origin of proteins. Conversely, the origin of nucleic acids has tricked scientists for decades as nucleotides are complex though necessary molecules to allow the existence of life. Here we review possible chemical scenarios that allowed not only the formation of nucleotides but also other significant biomolecules. We aim to provide a theoretical solution for the origin of biomolecules at specific sites named "Prebiotic Chemical Refugia". A prebiotic chemical refugium should therefore be understood as a geographic site in prebiotic Earth on which certain chemical elements were accumulated in higher proportion than expected, facilitating the production of basic biomolecules. Plus, this higher proportion should not be understood as static, but dynamic; once the physicochemical conditions of our planet changed periodically. This different concentration of elements, together with geochemical and astronomical changes along days, synodic months and years provided somewhat periodic changes in temperature, pressure, electromagnetic fields, and conditions of humidity; among other features. Recent and classic works suggesting most likely prebiotic refugia on which the main building blocks of biological molecules might be accumulated are reviewed and discussed.

1. Introduction

The most classic experiment in pre-biotic chemistry was conducted in 1953 by a 23 years-old American chemist named Stanley Miller (Miller, 1953). Published on Science Magazine in May, the 15th, and signed by Miller alone, this keystone manuscript was inspired by the theory of the primordial soup, described by the Russian researcher Alexander Oparin in his 1924's book entitled "The Origin of Life" (translated to English in 1938; Oparin, 1938). Also, the British-Indian researcher JBS Haldane described explicitly about a "hot diluted soup" in his 1929's book also entitled "The Origin of Life" to refer to the accumulation of organic material in primitive Earth (Haldane, 1929). Even Charles Darwin, in a letter to JD Hooker (1871), had suggested that life should have been originated in "*some warm little pond with all sort of ammonia and phosphoric salts*" (Peretó, Bada and Lazcano, 2009).

Miller's article cites no more than three works in his two-pages publication, suggesting that the most important point on his experimental proposition was the changing of old assumptions about the chemical constitution of early Earth. Miller suggested that, instead of being composed of carbon dioxide (CO_2), nitrogen (N_2), oxygen (O_2), and water (H_2O), the most likely composition of early Earth atmosphere was methane (CH_4), ammonia (NH_3), water (H_2O), and hydrogen (H_2). According to him, this fact had been suggested by Oparin, in 1924, followed by both the Irish scientist John Desmond Bernal (Bernal, 1949) and, in the year just before, by his PhD advisor Harold C. Urey (Urey, 1952). Although Urey is not an author of this work, Miller thanks him explicitly for "*many helpful suggestions and guidance in the course of this investigation*". Historically, however, the experiment has often been assigned as the Urey-Miller experiment.

The title of Miller's work was "*A production of amino acids under possible primitive Earth conditions*" and certainly the most striking result achieved by Miller was the finding that amino acids could be produced by mixing simple compounds putatively present in early Earth's atmosphere, together with electric discharges. Miller confirmed the presence of glycine, alpha-alanine and beta-alanine, possibly the simplest amino acids, together with other unknown amino acids and traces of aspartic acid and alpha-amino-n-butyric acid. About 55 years later, Miller's students reanalyzed his original samples using modern techniques and found the presence of 22 amino acids (Johnson et al., 2008).

Since 1953, therefore, it has been a consensus on scientific approaches to the origins of life the fact that amino acids could be produced in early Earth under relative abundance. Based on that information, many researchers have proposed the origins of life as based in peptides and proteins alone. Following that line of reasoning, researchers have proven that whole metabolic pathways such as glycolysis, pentose phosphate pathway and others biochemical cycles could be reproduced without any form of encoding, operating under special conditions by physico-chemical forces alone (Keller et al., 2016; Keller, Piedrafita and Ralser, 2015). Also, the Nobel laureated German researcher Manfred Eigen suggested that life started due to the presence of protein hypercycles (Eigen, 1971). These hypercycles would be produced by a closed cycle containing few interconnected molecules on which one would produce another spontaneously (given certain conditions), until a last molecule in the cycle would produce the first, restarting the cycle and allowing its maintenance. However, even Eigen recognized that informational molecules such as nucleic acids would be better choices for storing chemical information and avoid the dissolution of the entire system (Eigen and Schuster, 1979). In any case, nucleic acids also needed to overcome a critical mutation rate to allow their information to endure along generations. Otherwise, as Eigen noticed, they would disappear when conditions became unfavorable.

The question whether nucleic acids or proteins would make the first informational molecules is historical and frequently referred as the chicken-and-egg dilemma related to the origin of life (Davis, 2001; Cleaves, 2011; Giri and Jain, 2012). Although complete nucleotides still could not be produced in experimental simulations about the origin of life, some of their building blocks were shown to be produced under specific prebiotic conditions (Powner et al., 2010; Sponer et al., 2012; 2016; Lamour et al., 2019). In any case, nucleotides must have been present since very early in order to allow the emergence of biological systems because there is a consensus that life have emerged over the formation of the ribosome and the genetic code (Agmon, 2009; Fox, 2010; Root-Bernstein and Root-Bernstein, 2015; Prosdocimi et al., 2019).

2. The RNA-World

Outside the research program of pre-biotic chemistry, other influential approaches have been developed to explain the origin of life. Undoubtedly, the most significant of these approaches is the RNA-world theory, that is grounded on two important notions: the fact that RNAs are capable to (i) self-replicate, and (ii) perform catalysis. The development of this theory could only be made after RNA catalysis has been discovered (Guerrier-Takada et al., 1983). Thus, the RNA-world theory was originally published in a classical work by the American biochemist Walter Gilbert, in 1986 (Gilbert, 1986). Published in a 20th of February in Nature and cited more than 2500 times, it was proposed by a 53 years-old Nobel laureated. Gilbert had won his Nobel prize in Chemistry a few years earlier (1980), together with Frederick Sanger and Paul Berg. On that single-page first proposition of an RNA-World, Gilbert argued that the recent finding of new catalytic properties by RNAs suggested that "*if there are activities among these RNA enzymes, or ribozymes, that can catalyse the synthesis of a new RNA molecule from precursors and an RNA template, then there is no need for protein enzymes at the beginning of evolution.*" He continues arguing that, under an RNA-world, RNA molecules should "*assemble themselves from a nucleotidic soup*" and also suggested that the evolution of the translation apparatus should have happened very early. Another important arguments raised were: (i) self-splicing RNAs recently discovered by the group of the American chemist Thomas Cech (Kruger et al., 1982; Cech, 1985; Zaug and Cech, 1986); and (ii) other forms of catalytic RNA identified by the group of the Canadian-American biochemist Sidney Altman (Guerrier-Takada et al., 1983) would be important to allow recombination and the creation of new genes (being possibly responsible to produce the exon-intron structure observed nowadays in eukaryotic genes). Although never mentioning prebiotic conditions in early Earth, the ideas proposed by Gilbert and his followers implicitly considered the existence of a nucleotidic soup from which RNA molecules could be assembled and replicated. But where should these nucleotides come from?

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3. Prebiotic Synthesis of Nucleotides: state of the art

Due to the influential entrance of RNA-World scenarios into the origin of life research field, scientific works trying to produce RNA nucleotides started to appear (Usher and Needels, 1986; Ferris and Ertem, 1993; Orgel, 2004). Nevertheless, the task of proposing putative routes to produce RNA oligomers from prebiotic scenarios has shown to be full of challenges (Stribling and Miller, 1991; Unrau and Bartel, 1998). As complex molecules, nucleotides contain at least three different parts that seemed necessary to be built separately: the ribose, the nucleotidic bases (nucleobases) and the phosphate group.

Regarding the formation of nucleobases, research groups in Japan started to wonder in which chemical conditions these molecules could be formed. In that sense, Hashizume and colleagues (2019) recuperated classic works from the British chemist Leslie Orgel showing that (i) Adenine might have been formed by a pentamer of hydrogen cyanide (HCN) (Sanchez, Ferris and Orgel, 1966a); and (ii) Guanine might be formed by the addition of cyanogen (dicyan; C_2N_2) and water (H_2O) into a 4-aminoimidazole-5-carboxamid compound (Sanchez, Ferris and Orgel, 1966b). Besides, another Japanese group had reported the abiotic synthesis of guanine under a gas mixture of 90% N_2 and 10% of CO-H_2O under high temperature conditions (Miyakawa et al., 2000). Considered more challenging, a prebiotic scenario favorable to pyrimidine formation has been envisioned by Stanley Miller himself and Michael Robertson (1995). These researchers have been capable to produce Cytosine from cyanoacetylene (C_3HN) and cyanate (OCN^-), even if the reaction required a high concentration of cyanate (Robertson and Miller, 1995). Studying environments presenting acetylene (C_2H_2) in anoxic conditions, the Spanish researchers César Menor-Salván and Margarita Marín-Yaseli (2013) were capable to produce guanine, cytosine, uracil and other products with the presence of ultraviolet irradiation and urea/water systems in cold environments. Therefore, it has been proved that nucleobases could actually be formed in prebiotic environments, even if these environments required special conditions, such as the ones we will propose for the chemical refugia.

A further challenge was trying to glimpse a putative scenario for the formation of the sugar part of the nucleotides: the riboses. A series of reactions based on formaldehyde (CH_2O) were known since the XIX^th^ century to produce sugars according to the works of the Russian chemist Alexander Bluterow, that discovered the “formose reaction”. More recently, Hashizume and collaborators (2019) proposed that ribulose and ribose could be formed by the following path: (i) the condensation of formaldehyde producing glycolaldehyde ($HOCH_2$-CHO); (ii) the reaction of glycolaldehyde with another formaldehyde to produce glyceraldehyde ($C_3H_6O_3$); (iii) the isomerization of glyceraldehyde to produce dihydroxyacetone ($C_3H_6O_3$); the reaction of dihydroxyacetone with glyceraldehyde producing ribulose ($C_5H_{10}O_5$); and, finally, the isomerization of ribulose to produce ribose ($C_5H_{10}O_5$). According to Ricardo and collaborators (2004), ribose and sister pentoses could be made under alkaline conditions from formaldehyde and glycolaldehyde, molecules that are known in interstellar space (Hollis et al., 2000). The presence of glycolaldehyde in the giant cloud of gas *Sagittarius B2* was reported by Hollis and collaborators (2000) and opened the possibility that these molecules could be either formed in early Earth or brought here by a meteorite. Additionally, there has been found evidence that both ribose and other related sugars could be formed in substantial quantities from photo-processed interstellar ice (mainly composed of H_2O, CH_3OH, and NH_3) even at room temperature (Meinert et al., 2016).

If researchers have difficulties to simulate conditions to produce nucleobases and riboses separately, it has been a greater challenge to propose physicochemical scenarios on which these molecules could bind together to form nucleosides (Orgel, 2004) and then react to phosphoric substances to produce nucleotides. According to Powner, Gerland and Sutherland (2009): “*Ribose is difficult to form selectively, and the addition of nucleobases to ribose is inefficient in the case of purines and does not occur at all in the case of the canonical pyrimidines*”. Additionally, Hud and Fialho (2019) suggested that the main problem under prebiotic approaches should be the production of the glycosidic bond that links the RNA nucleotidic bases to the phosphate-ribose backbone. In 2014, Chen and collaborators demonstrated the possibility of producing a prebiotic reaction between a putative ancestral pyrimidine nucleobase (2,4,6-triaminopyrimidine, TAP) and ribose. They also demonstrated the possibility that supramolecular assemblies could be formed in water by mixing cyanuric acid (a putative ancestral nucleoside) and a β-ribofuranoside (Chen et al., 2014). A plausible though complex scenario for the formation of nucleosides has been recently proposed by Becker and collaborators (2019). Starting from simple molecules and simulating a geochemistry based in wet-dry cycles, these researchers proposed a scenario on which molecules of NO_2^-, HSO_3^-, and urea could be delivered by rain to form the intermediates necessary to the one-pot synthesis of purine and pyrimidine nucleosides. In their proposal, the solvent 3-aminoisoxazole ($C_3H_4N_2O$) would form nitrosopyrimidines after a dry period. Then, in a further wet season, these compounds would react with zinc to form different formamidopyrimidines (FaPy). FaPy would then need to get dry and wet again until they meet ribose to finally produce nucleosides (Becker et al., 2019). Other possibilities have been proposed by Saladino and collaborators (2017), suggesting the formation of nucleosides by the proton irradiation of adenine and ribose (or deoxyribose) in the presence of a carbonaceous chondrite meteorite.

The ultimate challenge should be the production of the entire nucleotidic molecule bound to the triphosphate radical. Leslie Orgel (2004) suggested that inorganic or polyphosphates should be the most likely phosphate sources for prebiotic synthesis even if the phosphorous present nowadays in Earth (and probably in early Earth too) is almost entirely formed by insoluble calcium phosphates. Also, Stanley Miller pointed out that geochemical processes for the abiotic production of polyphosphates in early Earth had not been discovered (Keefe and Miller, 1995). Orgel pointed to the possibility that ammonium phosphates (NaH_2PO_4) could be produced by Vulcan activities in high temperatures (Orgel, 2004). Thinking about the geochemistry of phosphorous in early Earth, the American geologist Matthew Pasek suggested that phosphorous was probably originated by extraterrestrial materials that could be found soluble in the form of phosphites (HPO_3^{2-}) (Pasek, 2008). He also suggested the existence of microenvironments with high concentrations of activated phosphoric compounds caused by the impact of iron meteorites (Pasek and Lauretta, 2008). Finally, Orgel (2004) suggested that it would be more plausible that ribose would be phosphorylated previously to the addition of the nucleobases, such as proposed more recently by Kim and Kim (2019).

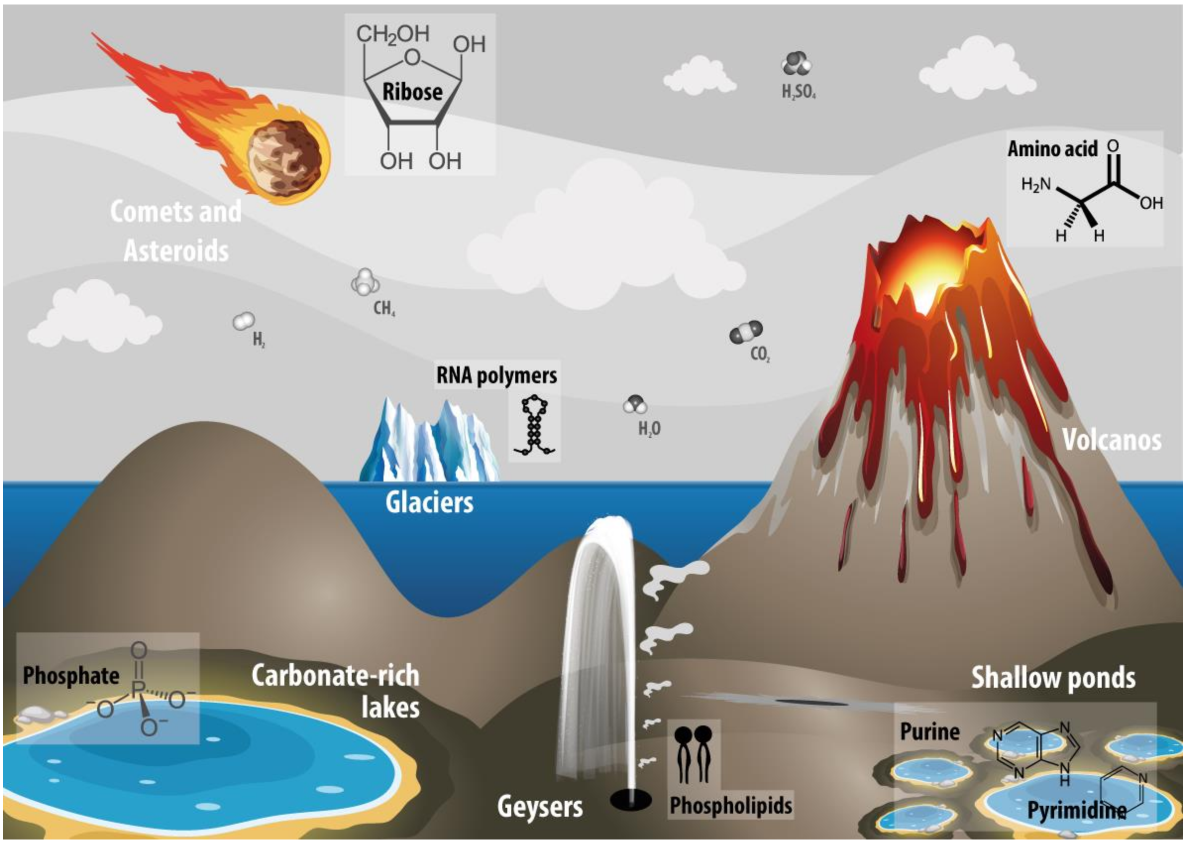
4. Prebiotic Refugia

> "*We must now try to determine how the various starting materials could have accumulated in a relatively pure and concentrated form in local environments on early Earth*." Jack W. Szostak (2009)

In the last section we have confirmed that it is possible to propose that nucleotides could be made in prebiotic Earth. However, a credible narrative about their spontaneous formation and availability needs to be built avoiding simplistic, Miller-like chemical scenarios. Besides important exceptions, many current and historical researches tend to consider that early Earth's surface and atmosphere was homogeneous, and the primitive soup was mainly composed of H_2, CO_2, CH_4, H_2S and NH_3 molecules. It is clear that simulations that do not start with any phosphoric compound will not be able to produce nucleotides as outputs. The problem on those accounts resides in the reductionist view that the primitive soup has been chemically homogenous all over the globe. This is not what we find today, and, bearing in mind the considerable extension of Earth as a planet, it was certainly not the case that happened in the starting days of our planet's physico-chemistry. The deposition of atoms and molecules on Earth has always been extremely heterogeneous (Sun and Nesbitt, 1977; Arndt et al., 1986) and cannot be claimed to be composed merely by those basic molecules of Urey-Miller's experiment.

Since all biological systems present a controlled translation system between nucleic acid information and peptides, we must consider that pre-biotic environments did present reasonable amounts of nucleotides. Therefore, we propose the idea of *prebiotic chemical refugia* that aims to clearly consider the existence of chemical microenvironments in primitive Earth that presented complex mixtures of certain molecules flowing under cyclic environmental conditions. It was the existence of chemical refugia that made possible the formation of the main building blocks of biomolecules in separate sites. This idea has been inspired by the Pleistocene refugia theory originally proposed by the German ornithologist Jürgen Haffer to explain how species of birds have survived under severe periods of glaciation during Pleistocene Era (Haffer, 1969; Waltari et al., 2007). This idea inherits downwards, *i. e.*, from biology to chemistry, the idea of endemism and could be understood as a "chemical endemism". The prebiotic chemical refugia theory reinforces the idea that the surface and atmosphere of early Earth has never been homogenous. In that sense, one can imagine the presence of countless microenvironments on which the number of chemical molecules available had been considerable different. This fact happened due to multiple factors, such as: (i) the statistical variation on the concentration of atoms and molecules; (ii) the fall of comets, asteroids or other bodies in specific sites; (iii) the presence of different amounts of electrical discharges, volcano eruptions, hydrothermal pools, glaciers and other environmental features, such as temperature and/or pressure; and other geochemical variations (**Figure 1**). As big as Earth is, it is clear that it presented multiple microenvironments with different richness of molecules. Under that scenario, it stands to reason to propose the existence of specific microenvironments on which nucleotides might have been produced in higher yields. In that sense, Cafferty and collaborators (2016) have proposed putative prebiotic heterocycles that could produce nucleosides and nucleotides in reasonable amounts. According to the Japanese researchers Kitadai and Maruyama (2018), the chemical evolution that happened in prebiotic earth required at least eight different chemical conditions, including "*(1) reductive gas phase, (2) alkaline pH, (3) freezing temperature, (4) fresh water, (5) dry/dry-wet cycle, (6) coupling with high energy reactions, (7) heating-cooling cycle inwater, and (8) extraterrestrial input of life's building blocks and reactive nutrients*" (Kitadai and Maruyama, 2018). Besides, most of our liquid water is now known to have reached Earth from outside and deposited in specific sites forming lagoons, seas and oceans (Morbidelli et al., 2000; Daly and Schultz, 2018).

Besides the fact that the concentration of chemicals had been different in microenvironments, the current proposal must consider cyclic environmental modifications that provided complex though periodically ordered stimuli of temperature, water availability, electromagnetic fields, gravity, pressure, x-ray, ozone, salinity, and pH to the molecules in the refugia. These somewhat periodic cycles would make chemical refugia dynamic and complex; providing molecular possibilities of binding and release, aggregating and separating over time. In line with the current propositions, works from Sidney Becker and Thomas Carell from the chemistry department of Munich University and their collaborators have come to consider such complex scenarios for the emergence of life in prebiotic Earth (Becker et al., 2016; 2018; 2019; Okamura et al., 2019). These researches focus in the unstable nature of early Earth when considering mainly the wet-dry cycles, but also day-night and winter-summer cycles that operated in early Earth and provided the physico-chemical basis for the assembly of molecules. Also, Stüeken and collaborators suggested that plausible models for the origin of life need to take into account the geological complexity and chemical diversity of the early Earth, suggesting the idea of a global chemical reactor (Stüeken et al., 2013).



Legend to Figure 1. Examples of prebiotic chemical refugia. Each of the most important compounds necessary to build biological molecules agglomerate at specific chemical environments in prebiotic Earth, such as: ribose, coming from comets and found in their craters (Meinert et al., 2016; Lazcano and Bada, 2003); glyceraldehyde, coming from comets, became ribose under alkaline conditions by the formose reaction (Hollis et al., 2000); nucleobases could also come from meteorites (Burton et al., 2012) or they could be formed in solutions of water, ice and urea under ultraviolet irradiation of acetylene in anoxia (Menor-Salván and Marín-Yaseli, 2013); but also in wet-dry cycles around shallow ponds (Becker et al., 2019). Phosphates could be produced in carbonate-rich lakes (Toner and Catling, 2019). Amino acids could be produced simply precipitating from atmosphere (Miller, 1953), in volcanos (Johnson et al., 2008) or in meteorites (Burton et al., 2012). Phospholipids are supposed to be formed in hydrothermal pools like geysers (Lopez and Fiore, 2019; Damer and Deamer, 2015), volcanos (Orgel, 2004) or craters or iron meteorites (Pasek and Lauretta, 2008). Glaciers may have allowed the production of nucleotides, amino acids (Levy et al., 2000) and the replication of small RNA polymers (Price, 2007).

5. Discussion

Finally, it would be interesting to come into some epistemological aspects regarding the notion of prebiotic refugia. We should therefore consider how scientists behave when their theories do not fit into reality. The history of science has plenty of examples about theories that could not be proved at some point or, alternatively, refuted theories that are still in use. For example, the Newtonian physics has been refuted since the Theory of Relativity was proposed by Albert Einstein, yet civil and mechanic engineers keeps using inasmuch it provides good approximations and easy calculations for what they need. In that sense, science and technology can be understood under a pragmatist approach: if they work well, it does not matter whether the theories have been refuted or not (Laudan, 1996).

Regarding the origins of life, the fact that RNA nucleotides have not been produced yet under experiments on prebiotic Earth could be seen as a refutation of the RNA-world theory; and, also, of other RNP-world ones. Even nowadays, researchers cannot clearly and mechanistically explain how RNA nucleosides and nucleotides should have been produced by the ancient atmosphere that chemists suggest being present in the Hadean or Eoarchean Earth (from 4.5 billion to 3.6 billion years ago, at the time we suppose that life has originated). This observation makes some researchers to avoid RNA-world theories, opening the field to metabolism-first theories (Smith and Morowitz, 2004; Shapiro, 2006; Schiller, 2016; Virgo et al., 2016; Lancet et al., 2018). Worse than that, metabolism-first theories often fail to explain how nucleic acids came into game so that they could store the hereditary information that earthling living organisms require nowadays to exist.

Classic epistemological questions come to one's mind when considering this dilemma. The question about the orbit of Uranus is a classic example. Although the planet Uranus has been observed by the Greek astronomer Hipparchus de Nicea even before Christ (128 BC), the planet is often considered to be discovered in 1781 by the German-born British astronomer Friedrich Wilhelm Herschel (1738-1822). The orbit of Uranus was first calculated in 1783 by the French scholar Pierre-Simon Laplace. After further studies, astronomers started to doubt Laplace's calculations as the predicted and observed orbits did not match. According to some science historians, these differences might indicate that Newtonian physics was flawed and should be refuted. But why should someone refute an entire and solid corpus of theory without any other epistemic alternative on hand to substitute it? Thus, when science cannot answer certain questions or provide efficient solutions for some observations, scientists may still maintain their theories based on a sort of "belief" that they are right and the anomalous observation will be understood later, when other discoveries could be made to clarify the phenomenon. This was precisely what happened when, in 1841, the British astronomer John Couch Adams proposed the hypothesis that the orbit of Uranus did not respect the Newtonian laws because some other stellar corpse could be modifying its trajectory, such as an unseen planet.

In the study of epistemology, it is known that scientists are used to propose what is named as *ad-hoc hypotheses* to save their dear theories from refutation. *Ad-hoc* hypotheses are therefore employed to overcome known anomalies in theories and add exceptions considered to operate under special cases. Some philosophers suggest that no theories could be verified completely and without any exceptions because nature refuses to operate under the strict logical reasonings present in humans' minds. However, *ad-hoc* hypotheses clearly weaken scientific theories once a theory with many exceptions has no use and cannot predict regularities in the real world. When confirmed, such as happened in the case of Uranus' orbit, that has been shown to fit Newtonian calculations after the discovery of Neptune by the German astronomer Johann Gottfried Galle (in 1846), the ad-hoc hypothesis is often restated as an auxiliary hypothesis. This means that the hypothesis that another planet (Neptune) existed and changed the predicted orbit of Uranus was first seen as an ad-hoc hypothesis and further confirmed as an auxiliary hypothesis that helped and guided researchers to search for something else that might have been shifting Uranus' predicted orbit.

In that sense, the prebiotic chemical refugia hypothesis described here is certainly an *ad-hoc* hypothesis at this momentum, and it aims to provide a provisory explanation about how nucleotides and other biomolecules could be formed in specific locations in the primitive Earth. In order to become an auxiliary hypothesis, the proposed theory will need to be confirmed by evidences that may confirm the existence of these refugia in the old past. Although unlikely that these refugia could be preserved nowadays, the theory can be verified by finding specific sites on which old stellar corpses had been fallen, together with predictions of chemical composition of these refugia using radioactive decay calculations, for example. The most relevant issue however is to understand the complexity of early Earth environment and to acknowledge the existence of different and multiple chemical microenvironments on which nucleotides could be formed in high amounts. Also, it is important to take into account the periodic nature of Earth cycles that provided intermittent changes of hot/cold, dry/humid and other physical stimuli that brought together and apart atoms and molecules, allowing "unpredictable" reactions to occur when one considers stable and homogeneous environments. Both Hadean and Eoarchaen Earth were composed by extremely complex environments, with multiple geographic sites showing extreme differences in the concentration of atoms and molecules. What keeps still missing is the finding of the appropriate conditions on which nucleotides could actually be made under significant amounts. It has recently been found how nucleobases and nucleosides could be formed under dry/humid cycles (Becker et al., 2019), but it is still missing issues regarding the formation of riboses and the phosphorylation of nucleosides to form nucleotides. We expect that specific though complex chemical microenvironments on which these reactions can happen spontaneously will be proposed shortly. Although we have focused in the current problem of building nucleotides, a well-known anomaly of RNA-world theory, it is possible to think about chemical refugia suitable for making all sorts of biomolecules and their building blocks.

6. Disclosure declaration

The authors declare no competing interests.

7. Acknowledgements

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