General principles for modeling of thermal prebiotic synthesis and protocell self-organization in planetary environment simulators: from non-equilibrium thermodynamics to engineering thermophysics

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Abstract: This paper considers the problem of achieving plausible and effective (leading to the formation of structures similar to biological ones) conditions for modeling thermally induced prebiotic processes from the perspective of thermodynamics, thermal physics, and thermal engineering. The article's presentation is based on the principle of transition from thermal physics and thermodynamics to thermal engineering for constructing planetary environment simulators with controlled environmental conditions. Based on the physical premises from the first parts of this comprehensive review, a conclusion is made regarding the need to consider an additional set of controlled physical parameters or additional factors influencing the models of prebiotic synthesis and formation of precellular/protocell structures implemented in planetary environment simulators and hydrothermal synthesis reactors. Non-thermal heating sources are also considered, such as radiofrequency and microwave irradiation for dielectric heating, as well as radioisotope heating in the early Earth/protoplanet conditions. The coexistence of physical and chemical pathways for heating the prebiotic environment and the feasibility of modeling this separation in planetary environment simulators and controllable climate chamber facilities are highlighted. Exothermic reactions during hydrothermal serpentinization are considered as an example of chemical heating in prebiotic environments. This can lead to the abiotic synthesis of organic matter (which correlates well with the existing hypotheses of the origin of life in alkaline hydrothermal vents, with the mineral genesis of protocells and membrane potential generation on inorganic catalytic protomembranes). Thermal proteinoids and thermal proteinoid microspheres that form on their basis are considered an example of purely organic prebiotic structures obtained via hydrothermal heating. It is demonstrated that the application of thermophysical and thermal engineering approaches to modeling prebiotic systems enables the simulation of many key cellular functions by varying the precursor medium composition and the conditions in thermal experimental setups. Protobiocatalysis and protometabolism, surface (or membrane) potential oscillations, excitability, and physical heredity (thermal fission) are observed in such structures. After addition of the genetic components, the machinery for transcription and translation of the expressed genetic code can also operate within them. The possibility of implementing such models as "hypercycle in protocells" and other proto-metabolic and protogenetic networks capable of oscillation is indicated in prebiotic system models obtained in thermally cycling experimental setups. Kompanichenko's thermodynamic theory, which also applies to hydrothermal and volcanic conditions that can be simulated in planetary environment simulators, is considered a theoretical justification for the possibility of assembling prebiological systems under such oscillatory conditions. Thus, it becomes possible to move from formal thermodynamics for describing the origin of life to engineering thermodynamics and thermal physics, which allows for the development of experimental setups and simulation chambers for validating various models of prebiological synthesis and the formation of protobiological structures, based on thermodynamic and thermochemical criteria.

Keywords: non-equilibrium thermodynamics; thermal prebiotic synthesis; geothermal conditions; hydrothermal conditions; planetary environment simulator; hydrothermal synthesis reactor; thermocycling; serpentinization; thermodynamic inversion; thermal proteinoids; thermal proteinoid microspheres; thermal systems engineering

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1. Introduction: Thermodynamic and thermophysical approaches to the origin of life

A fundamental issue in all origin of life concepts is the energy supply for the processes of abiogenesis and chemical evolution—from prebiotic synthesis of organic compounds to bioenergetic mechanisms in finely compartmentalized prebiological and protobiological systems [1–5]. The problem of energy conversion for the origin of life has been posed since the classical works of the 1970s (see, for example, the paper by pioneers of the origin of life studies—Joan Oro, Stanley Miller and Harold Urey, published in 1977 [6]), although thermodynamic considerations for the Oparin's theory of the origin of life have already been published since the mid-1950s [7], and the first NASA reports on "thermodynamic mechanisms for the production of complex compounds essential for the origin of life" date back to the mid-1960s [8]. The solution of a number of fundamental problems (sources of heated debate in the field of the origin of life) is possible only from the standpoint of thermodynamics, since any protobiological system and any path of prebiotic synthesis/chemical evolution in the absence of a sufficient energy supply could not exist as a "far from equilibrium self-maintaining chemical system"/"living system" [9]. Recently, a thermodynamic approach has become widespread, which states that energy determines, directs, and increases the probability of certain events in the origin of life and evolution of self-organizing prebiological structures—the so-called "energy-directed probabilistic self-assembly" [10,11].

Addressing the origin of life problems from the standpoint of thermodynamics within the context of the real geophysical conditions on the early Earth began in the 1970s, and the highest level of its development is the concept of Sidney Walter Fox, described in volume 4 of "Studies in the Natural Sciences," dedicated to Lars Onsager (Norwegian and American physical chemist/theoretical physicist and pioneer of irreversible thermodynamics), "Quantum Statistical Mechanics in the Natural Sciences." According to this complex concept [12], "in relating thermodynamic concepts to the understanding of the origin of life, we shall examine the recently enlarged experimental laboratory model for macromolecular and cellular origins. The experimental model now extends from organic matter in the Solar System through amino acids, protoprotein, and a reproducing, heterotrophic protocell to systems capable of making their own internucleotide and peptide bonds and relates to the origin of the genetic code." Moreover, the approach developed by Sidney Walter Fox is not speculative, but has deep experimental (and not just theoretical and thermodynamic) foundations, and, as it is specifically emphasized, "the experiments have been performed under geologically relevant conditions." It is quite obvious that these experiments were conducted on proteinoids/proteinoid microspheres proposed by Sidney Walter Fox as model prebiological structures and obtained since the 1950s by thermal copolymerization of amino acids [13–18] and thermally synthesized polynucleotides [19]. Therefore, the first protocol using heating to obtain model prebiological structures corresponding to the thermodynamic and geological conditions of the early Earth relates specifically to the proteinoid microstructures proposed by Sidney Walter Fox.

However, it was not by chance mentioned above that the first publication of Sidney Walter Fox's thermodynamic concept of abiogenesis was in a collection dedicated to the pioneer of irreversible thermodynamics, Lars Onsager. It is quite evident that self-assembly and self-organization of stable prebiological structures are within the scope of irreversible thermodynamics rather than equilibrium

thermodynamics. In the same 1970s, the Third International Biophysics Conference "Irreversible Thermodynamics and the Origin of Life" was held at MIT [20]. It fit well with the trend towards nonequilibrium thermodynamics within the discourse established by Ilya Prigogine. It is noteworthy that his dissertation in 1947 was published as "Étude thermodynamique des phénomènes irreversibles", and already in 1949, a commentary-review by Ludwig von Bertalanffy (an Austrian biologist known as one of the founders of general systems theory) was published in the journal "Nature," within the framework of which irreversible thermodynamics found a connection between the physical chemistry of open systems (which undoubtedly include prebiological systems or reaction networks of prebiotic synthesis of organic compounds during chemical evolution) and the formation of organisms, maintaining themselves in a continuous exchange [21]: "Since 1934, the present reviewer has advanced the conception of the organism as an 'open system'. So far, physical chemistry has been concerned almost exclusively with reactions and equilibria in closed systems, while living organisms are open systems, maintaining themselves in a continuous exchange of materials with the environment. We have stressed the need for an extension of physical chemistry, stated kinetic principles, and demonstrated that the theory of open systems leads to the derivation of fundamental biological characteristics as well as to quantitative laws of biological phenomena. It has also been emphasized that "according to definition, the second law of thermodynamics applies only to closed systems; it does not define the steady state." Therefore, even before Ilya Prigogine himself recognized the biological aspects of the applicability of irreversible thermodynamics (see, for example, [22]), since the 1950s, works began to appear examining the biological aspects of irreversible thermodynamics and new physical criteria for the evolution of metabolic pathways based on the thermodynamic theory of irreversible processes [23,24]. So, extrapolation of the above ideas to the study of prebiological systems seemed quite logical. However, many researchers were unable to "bridge the gap" between conventional thermodynamics they had known since their university days and irreversible thermodynamics/nonequilibrium thermodynamics. For this reason many researchers have attempted to "reproduce protolife" under equilibrium conditions without a continuous energy input or in closed systems, which have obviously failed. The greatest number of fruitless debates were conducted around the applicability of the second law of thermodynamics in biology and prebiological systems, with a significant number of absurd objections being of an idealistic nature (including in the literature published by creationists) [25–29]. And if for the early works of the 1940s this was justified, then after the dissemination of the concepts of general systems theory developed by Ludwig von Bertalanffy, the disregard for his warnings (according to the cited review of L. von Bertalanffy on "Étude thermodynamique des phénomènes irréversibles", "the second law of thermodynamics applies only to closed systems, it does not define the steady state") could only be explained by heuristic inertia.

2. Non-equilibrium thermodynamics and the origin of life

Currently, almost all origin of life concepts are based on non-equilibrium thermodynamics (and a pioneer in this direction is the author of thermal proteinoids, Sidney Walter Fox, cited above, who back in 1972 [30] set himself a goal "to bring together the basic concepts of non-equilibrium thermodynamics and biochemical energetics, in order to sharply define the problem of the origin of life"). Various energy sources can provide a nonequilibrium character of the conditions of chemical evolution (for example, photons in the thermodynamic

dissipation theory for the origin of life [31,32] or plasma/coronal gas discharge in the Miller-Urey experiments [33–37]), as well as the formation of cell precursors with physicochemical gradients (from non-equilibrium conditions inside the rock pores [38] to the thermodynamically nonequilibrium ocean/atmosphere interface, at which protocells can emerge [39]). This does not contradict the laws of thermodynamics. Thus, in the work "Life as a manifestation of the second law of thermodynamics" [40], the authors studied "thermodynamic evolution of various evolving systems, from primitive physical systems to complex living systems, and conclude that they involve similar processes which are phenomenological manifestations of the second law of thermodynamics." The authors take "the reformed second law of thermodynamics … and extend it to nonequilibrium regions, where nonequilibrium is described in terms of gradients maintaining systems at some distance away from equilibrium. The reformed second law suggests that as systems are moved away from equilibrium, they will take advantage of all available means to resist externally applied gradients" [40].

Thus, a fundamental task during modeling the origin of life is to create nonequilibrium conditions for the constant influx of matter and energy into an open system during the formation of prebiological structures/systems. A recognized expert in the field of protocells and inorganic cells (with chemical gradients), S. Mann, in his widely cited article devoted to the emergence of life from nonliving matter [41], writes: "life can be considered as a system property that is internally maintained and regenerated under nonequilibrium conditions by flows of energy, matter, and information." Therefore, it is fundamentally important to create such geologically relevant and chemically functional sources of nonequilibrium that will be similar to those providing the functioning of biological and the formation of prebiological systems. A co-author of a Nobel Prize laureate J.W. Szostak, Irene Chen, in her works on creating protocells (based on fatty acid vesicles) capable of membrane structure development and transmembrane pH gradient generation [42–44], in an editorial article [45] rigorously addresses this issue: "A third major issue for research on the origin of life is a question that is often the elephant in the room: how would early life escape equilibrium? To maintain life, the system must be open, accepting energetic input constantly or periodically, to be driven away from chemical equilibrium." She also states that "current understanding of this critical issue is quite poor." Later, this issue has been comprehensively addressed in the papers by Wolfgang Nitschke, Simon Duval, and Michael J. Russell [46,47]. According to their joint concept, life is considered as a dissipative structure supported by the environmental redox disequilibrium as a permanent free energy source for sustainable non-equilibrium maintenance in the living systems. Electrochemical disequilibrium providing endergonic chemical reactions has been available from the very beginning, even at the first stages of the origin of life, with serpentinization of the early ocean's crust being a permanent geochemical free energy source [48]. Thus, since its emergence, the biophysical mechanism of life includes converting free energy of the environmental electrochemical gradients into a reduction in entropy, i.e., driving compartmentalized redox reactions providing energy metabolism [49].

3. The possible sources of energy supply for prebiological processes and the transition to a nonequilibrium state supported by the biological structure

Let us consider the possible energy sources for prebiological processes and the transition to a nonequilibrium state supported by biological structures. A distinction should be made between the energy

sources that ensured prebiotic synthesis of organic compounds (which may subsequently exist in an equilibrium state before being incorporated into the metabolic networks of protolife), the energy sources that maintained a nonequilibrium state of the first compartmentalized prebiological structures as open systems, and bioenergetics or protobioenergetics that ensured the functioning of the physiology of protocells—protophysiology (a rare but apt term in the literature [50,51]). Even at the end of the 20th century, it was clear that the energetics of the origin of life should be divided into several areas, according to which the first and earliest (non-reproducible by the organism) energy sources could be physical, while the later energy conversion systems associated with the metabolism of protobionts must have been chemical in nature [52] (albeit variable in chemical composition and not necessarily identical to the modern bioenergetics of evolutionarily higher biological forms). In the work [53], this idea is formulated quite successfully:

Among the many still open questions about the energetics of the origin of life are:

1) was the source of energy for the origin of life photic or chemical or both, and were there other significant energy sources, such as electrical discharges etc.?;

2) were the first energy-rich chemical compounds of late chemical or early biological evolution inorganic or organic or of both kinds?;

and

3) were there several systems for energy conversion at the prenucleotide level, such as, for example, those which have been suggested to be based on inorganic pyrophosphate ("PPi world"), organic thioesters ("thioester world") and iron-sulphur compounds ("iron-sulphur world"), and were there close chemical links between such "worlds"?

To resolve such questions about the origin of life, one should proceed from the biosimilarity or biological "prototypalism" of its conditions of emergence in relation to the primary forms of its implementation. One can accept as an aphorism the phrase "Life is a guide to its own origins", considering life as a process conditioned by a multitude of mechanisms, and not as a separate structure or form in which they are manifested (the classic "Life is a verb, not a noun"—the idea of M.J. Russell) [54,55]. In this case, it turns out to be easy to separate arbitrary energy sources for the synthesis of prebiotic organics (which, after synthesis, can be deposited and sedimented in an abiogenic environment and, without being included into metabolic networks, operate outside the framework of open systems of protolife, without requiring a nonequilibrium state) and energy sources for protometabolism, which is by definition a nonequilibrium process (protometabolism as out-of-equilibrium chemistry [56]). Moreover, the energy source that supports proto-metabolism must be regular (as opposed to an inductor or trigger of phase transitions during the formation of elementary prebiological structures) and maintain flows and stationary concentration profiles in a prebiological open system. The unity of resource flows and their own stationary concentration profiles/distributions in the microstructure of protobionts is an ontological condition for their existence as open systems. As early as in the 1950s, the annotation to the book "The Origin of Life on the Earth" by the brilliant Alexander Ivanovich Oparin [57] stated: "The simplest

abiogenic system which could have served as a starting point for the evolution of life must have been an open system, the separate reactions forming a network of interdependent chemical transformations coordinated in time."

But how was the transition from an energy inductor to a self-sustaining system made? "The major bottleneck then seems to be the organization of those building blocks into systems (i.e., non-reducible combinations of molecules and transformation processes) that sustain themselves in non-equilibrium conditions," write the authors of the review [58], attempting to answer this question. "How recursively changing conditions could help them engage in self-organized and dissipative networks/assemblies (i.e., systems that consume chemical or physical energy from their environment to maintain their internal organization in a dynamic steady state out of equilibrium)" this is how they pose a fundamentally important question, the answer to which is identical to the answer to Irene Chen's question: "How would early life escape equilibrium?"

A remarkable example of this implementation in laboratory comditions is the work "Energy propagation through a protometabolism leading to the local emergence of singular stationary concentration profiles" [59], in which "the spontaneous onset of an energy-transfer chain notably drives the local generation of singular dissipative chemical structures; continuous matter fluxes are dynamically maintained at boundaries between spatially and chemically segregated zones." In this experimental work, "by using energy patterning and a diffusing hub reactant," the authors essentially achieve propagation of a sustained energy fluxes through a cascade of reaction cycles, which is equivalent to the transfer of energy through an abiotic protometabolism. In such systems, bioenergetic processes are feasible, which are characteristic of some photosynthetic processes (since the above-mentioned behavior in an open system is maintained by patterned illumination, and it resulted in the local onset of a proton pump). Turing morphogenesis can also potentially occur is such systems as a reaction-diffusion process, since the local onset of a proton pump triggers an extended reaction-diffusion cycle in the system that involves pH-sensitive reactants (interpreted in the redox chemistry of morphogenesis in terms of activators and inhibitors, including in gels that model the cytoplasm [60,61], similar to models of (redox-)microphysiometry of cellular structures [62]). Thus, the formation of a (proto)biological structure is associated with the establishment of (proto)metabolism; and only those energy flows that are integrated into the energy-transfer chain driving the local generation of singular dissipative chemical structures of the protocell benefit from selection, since they are physically inherited, reproducing within the stationary concentration profiles of these dissipative chemical structures. Note that, by definition, a dissipative structure is a dissipative system that has a dynamic regime that is in a reproducible steady state (this definition is generally accepted both by the International Society for the Systems Sciences, founded in 1954 with the direct participation of the creator of open systems theory, Ludwig von Bertalanffy [63,64], and among researchers in the field of origins of life and mathematical biophysicists [65–67]). All flows operating before and beyond this "physical reproducibility"/"physical heredity" of energy-transfer chains do not relate to life and proto-metabolism, but can be reproduced in laboratory conditions (regardless of the similarity of the final product to life/protocells with proto-metabolism).

4. A conceptual basis for constructing laboratory setups, chambers and facilities for modeling the origin of life in open thermodynamic systems

In this article, we will focus on the above-mentioned laboratory-reproducible energy flows. We will proceed from the following assumptions in analyzing the potential contribution of various energy sources in abiogenesis:

1. Solving the problems of the origin of life from the standpoint of thermodynamics within the context of real geophysical (and, more broadly, planetary) conditions of life emergence. The answer to the question "what was the inducer of abiogenesis" or "what was the source of energy during the prebiotic synthesis of organic compounds" (even with full compliance of all proposed scenario with thermodynamics) cannot be achieved outside the framework of real conditions for a specific geological period and a specific hypothetical landscape of these processes (or outside the framework of the answer to the question "what planetary environment conditions does the experiment simulate"). To define these conditions, David Deamer coined the apt term "urability". According to the definition [68], "the meaning of urability does not reflect an exact set of conditions, but rather the broader concept that there exists a set of conditions, which, in combination, create a window of opportunity for life to emerge." The presence of one of the environmental properties in the absence of others cannot be sufficient for "urability". In the above cited work, the urability graph is a combination of three factors, such as water temperature ("optimal liquid state between boiling and freezing"—pure thermal physics), illumination ("optimal range of light energy"—thermodynamics, as in Michaelian's non-equilibrium thermodynamic foundations of the origin of life cited above [31,32]), and wet-dry factor/cycles between hydrated and dehydrated conditions [69]. ("Wet-dry cycling is one of the simplest sources of chemical energy that can drive ester and peptide bond synthesis to form biologically relevant polymers"; formally, this relates to the thermodynamics and kinetics of prebiotic polymer synthesis, but without taking into account real geological and/or hydrological conditions, it does not make sense). Hence, from the objective reality of the complex geophysical conditions in which prebiotic organic synthesis and assembly of the simplest membraneous structures took place, the following point follows.

2. A multiphysical nature of the natural manifestations of the aforementioned energy sources. Unlike single-factor, pure laboratory experiments (for identifying individual mechanisms and patterns in isolated systems), in geophysical systems of the origin of life period it is impractical to ignore the coexistence of multiple energy sources in real conditions. And what appears to be the effect of one "obvious" energy source on prebiological organic matter (but for some reason, experiments fail to bring this system to a sufficiently biosimilar state to qualify it as a protobiont model) actually turns out to be a synergistic product of a number of physical mechanisms/energy sources. For example, in the "obvious" thermal model of the volcanic origin of life (since the 1970s reduced to the models of prebiotic organic synthesis/high-temperature synthesis/formation of heteroaromatic and polymeric structures during volcanic eruptions [70–75]), as information about the "geological machinery" of volcanism accumulates, additional factors appear, such as volcanic lightning (as in Miller's spark discharge experiments [76–80]), and hence, accompanying physical effects emerge, such as electrification of the atmosphere, surfaces, microparticles and dispersed systems [81,82], pressure-induced

waves and piezoelectric effects in minerals in volcanic eruptions [83] with possible ultrasound signal generation (including piezoeffect-based generation) [84], electromagnetic pulses and oscillations including radio frequency pulses in the ULF, ELF and VLF ranges (ultra low frequency, extremely low frequency and very low frequency bands) [85–89], volcanic lightning-induced local variations of the planetary magnetic fields, inducing electric currents—magnetotelluric currents [90,91]. All these phenomena and mechanisms can influence the course of chemical processes in an open system, leading to the new pathways and chains of chemical reactions, generation and transfer of new reactive intermediates and implementation of spin chemistry processes (in induced geomagnetic/geoelectromagnetic fields and in lightning radio-frequency fields many biochemical processes can proceed qualitatively differently than in intact biochemical systems, including those with inducing enantiomeric excess by spin-polarized electrons [92–94], which is ensured by spin chemistry mechanisms [95–99]). Therefore, strictly speaking, even within the simple thermochemical approaches to the study of the volcanic and hydrothermal origin of life, one should also take into account the real geophysical conditions of prebiotic synthesis, leading to consideration of not only thermal factors, but also thermoelectrochemistry, magnetothermochemistry, radiofrequency electrochemistry, microwave electrochemistry, microwave photochemistry/microwave photoelectrochemistry, etc.

3. Going beyond the assumed limitations of the environment/geological localization by using an expanded physical background. Typically, when modeling the process of abiogenic synthesis of a certain substance in the laboratory, the geological or cosmic localization of the model is predetermined, thereby preventing the search for heuristic approaches to finding similar mechanisms in other locations. In all such cases, there is a "methodological attribution error" and an unintentional confusion between existential quantification (existentialization) and uniqueness quantification (or unique existential quantification). In fact, based on physics, one can assume the probability of such processes or declare their inevitability in a variety of prototerrestrial or cosmic objects, and only then can one claim that there are prerequisites for interpreting the modeled process as prebiotic synthesis. This approach significantly changes the results of analysis and prediction. For example, instead of pre-annotating a single-factor experiment as a model reproduction of Hadean volcanic origin-of-life conditions (e.g., synthesis of α-hydroxy and α-amino acids at temperatures of 145–280 °C with catalytic Ni^{2+} or by carbon fixation at 80–120 °C with catalytic Ni^{2+} or Fe-Ni precipitates with carbonyl, cyano or methylthio ligands as C sources [100,101]), one can proceed from the above physics to understanding possible multifactorial synthesis scenarios with volcanic activity as the main energy source. And then it will turn out that these scenarios can be implemented beyond Earth, including on extraterrestrial planets [102] (without reference to a specific dating, as in the studies of similar processes on Earth [103]), and physically they will be as multifactorial as their terrestrial analogs (or their special cases). For example, prebiotic/abiogenic organic synthesis by lightning in Martian volcanic activity is known [104,105]. It is also known that radio-frequency phenomena accompanying lightning discharges are detected on Mars, and the Martian ionopause or ionosphere even favors the formation of whistlers and chorus waves [106–109], as in geophysical conditions [110,111]. About 10 years ago, the first observations of "volcanic whistlers" [112] (whistlers in volcanic lightning) were made and the new term "whistling volcanoes" [113] was introduced, while the relations between lightning discharges and whistlers have been well known since the 1950s [114,115]. Therefore, taking into account lightning and volcanic activities on Venus (known since the 1980s [116–124]

with the Venus lightning detection carried out by detecting whistler signals [125,126] or very low frequency signals [127,128]), it is possible to extend multiphysical models of volcanic-assisted and lightning-assisted prebiological processes to Venus as well. It is noteworthy that the occurrence of pre-biological organic synthesis is not identical to the presence of protolife on Venus or of its earlier existence [129], since the abiogenic synthesis of organic compounds becomes "prebiological" only *post factum*, after registration of life phenomena on its direct products. The presence on Venus of lightning-generating clouds containing sulfuric acid and various sulfur compounds, formed due to volcanic activity (favorable for certain synthesis processes within the framework of the above-mentioned multiphysics approach), which has been a source of speculation since the 1960s [130–135], does not actually prove the presence of volcanic-assisted and lightning-assisted prebiological processes on it. However, this fact expands the horizon of the search for physical analogies of "terrestrial" (i.e., initially discovered on Earth and, for psychological reasons, declared as purely "terrestrial") processes associated with volcanic-assisted and lightning-assisted prebiological syntheses. Thus, a smooth transition occurs from a geophysical discourse to an exoplanetary one, where only the physical feasibility of clouds and hazes in exoplanetary atmospheres [136–140] and lightning phenomena on other planets [141–144] is considered (including within the scope of the origin of life problem). Moreover, the data on analogs of such processes on Earth (and, more broadly, in the solar system [145]) are presented mostly in the context of comparative planetology or in the context of defining exoplanets (Earth-like exoplanets [146,147]), as well as the data on tectonics of the planets of the solar system is considered in the course of substantiating the possibilities of volcanism and magmatism on them and identifying the differences between them [148–153]. Planetary and ionospheric phenomena accompanying volcanic eruptions and volcanic lightning, reflected high in the ionosphere and ionopause or magnetosphere in other planets (where one exists—Venus and Mars do not have a global magnetic field, which led to the loss of a significant part of the atmosphere by Mars) can be considered in a similar way: through the existence of whistlers and related wave phenomena on other planetary bodies, not only on Mars, but also on Venus [154,155]. An expanded physical approach, removing the "blinders of illusions" in the analysis and modeling of prebiotic synthesis processes in the geophysical and planetary (or astrophysical) aspect, allows one to move from speculation to model reproduction of prebiological processes in multiphysical/multifactor physicochemical experiments in laboratory conditions with the possibility of varying or eliminating individual factors and parameters (for example, the lightning parameters [156–158]), moving in a single series of experiments from modeling for the early Earth conditions to modeling for other planets and vice versa (in accordance with the limitations of the physical mechanisms involved [159]).

4. A complex and heterogeneous/heterophase nature of the abiogenesis chemistry (messy chemistry [160–165]). By modeling the phases of chemical evolution and abiogenic synthesis (and replication) of organic compounds without taking into account the environment, a multiphase and chemically (including sterically, electrochemically, and thermochemically) heterogeneous environment, it is impossible to achieve similarity between the model and its real prebiological prototype. This condition is emergent, and the nature of the products depends on its fulfillment (it is well known that in colloidal and supramolecular chemistry the nature of the products is dictated by the chemical environment, the sequence of the synthesis stages, and the physicochemical conditions for the product synthesis) and therefore is controlled by the external factors of the "messy media," which for a long time were not taken into account in the simplified monofactorial versions of

experiments in the field of prebiotic synthesis of organic compounds and the origin of life studies. For example, with a simplified thermochemical approach, volcanic models of abiogenesis have generally failed to reproduce such features important for prebiological processes as reduced phosphorus species (which may have been critical, energy-rich precursors to modern ATP-based systems) and the prebiological nitrogen fixation mechanism (because usually nitrogen fixation is a highly energy-intensive process where diazotrophs reduce atmospheric nitrogen to ammonia using the nitrogenase enzyme complex that requires massive inputs of ATP—at least 16 ATP per molecule—and low-potential electrons, often provided by photosynthesis or respiration [166–175]. At the same time, modeling of volcanic lightning phenomena allows one to reproduce nitrogen fixation by volcanic lightning in the early Earth [176,177]. Lightning-induced reduction of the phosphorus oxidation state by high-energy lightning events can also be reproduced [178,179]. In the last cited work, the authors state: "phosphate can be reduced to phosphides during high-energy events, such as lightning and impacts." Thus, the increasing levels of physical fidelity and multiphysical complexity of modeling lead to the emergence of intermediates and products in the model system simulating prebiological conditions that qualitatively change the direction of processes and are capable of transferring chemical reactions from one prebiological scenario to another. The addition of lightning-induced electrochemistry into the set of studied and modeled factors further increases the messy chemistry grade or complexity level of redox-chemical processes in the (early) planet-mimicking media. Thus, a recent paper [180] "demonstrates how cloud-to-ground lightning storms could have driven radical and electrochemical reactions across interfaces that connect gas (i.e., the atmosphere), liquid (i.e., oceans, lakes, and ponds), and solid (i.e., sediments, rocks, and land) phases on the early Earth." This paper shows that protogeological "interfaces enable reactants (e.g., minerals) that may have been on land, in lakes, and in oceans to participate in radical and redox reactions, leading to higher yields compared to gas-phase-only reactions." At the same time, during lightning in the atmosphere of a comet or lightning in the rare gas-grain medium, the set of products is qualitatively different from the heterophase analog of bulk matter lightning electrochemistry or photoelectrochemistry [181–183]. Thus, differences in the set of registered chemical products and the corresponding processes of abiogenic synthesis in various messy chemistry media (and with different geological or geomimetic catalytic and electrochemical participants in these processes) can serve as a plausibility indicator for various hypotheses on prebiological processes, which can be used for their validation. Where similarity to biochemical products cannot be achieved in a simplified experiment with the production of a specific substance of interest, when working in multifactorial messy chemical systems and multiphysical systems (in which, due to the multiplicity of physical energy sources and synthesis stimulators, a larger set of compounds is produced) it is possible to synthesize messy chemical libraries of all prebiotically relevant compounds sufficient for the validation of any hypotheses.

The above principles should underlie the design of devices and installations for simulating the origin of life in space and terrestrial (including hydrothermal) conditions. What does this mean in terms of implementing these principles in hardware?

1. They must reproduce the entirety of geophysical or planetary (or cosmophysical) factors that explicitly or implicitly accompanied all prebiological processes in a given landscape, and ensure their correspondence/correlation with each other. For example, heating in photochemical modeling schemes should

be produced by light radiation simultaneously with modeling of insolation at a specific time of day, and not by a separate thermal device on a separate control link; or the cycles of reversible dehydration in thermal modeling schemes should be achieved by simulating the actually existing conditions of geothermodynamics, and not, for example, by freeze-drying. Modeling of prebiological terrestrial conditions must take into account the presence of solar-terrestrial relations, expressed not only in the optical, but also in other electromagnetic ranges (from radio-frequency atmospherics to the cosmic ray particles).

2. Chambers and setups for modeling the physics of the origin of life must be multiphysical. Specifically, a chamber for modeling hydrothermal processes in the origin of life should not be an improved version of an environmental chamber/climate chamber or laboratory incubator, just as a chamber for modeling prebiological synthesis of organic compounds in Miller's spark discharge experiments should not be simply a plasma-chemical synthesis reactor.

3. Simulation chambers must be designed with a wider range of parameters than required for a specific model of prebiological synthesis and chemical evolution being tested. It should provide the possibility of transition from one "model discourse" to another under the same conditions and experimental volumes to maintain the correctness and reproducibility of the models.

4. Experiments in chambers should not be limited to the usual single-phase/wet chemistry, but should also consider interphase interactions modeling the relationships in the ocean-atmosphere system, weathering and serpentinization processes at the liquid-solid interface, enrichment of prebiological fluid with ions from geological rocks and subsequent variations in the ionic strength of the medium, which influence self-assembly or conservative self-organization processes. The dialectics of interaction between the dispersed phase and dispersion medium within the framework of model analysis should not ignore their mutual influences (feedbacks), recognizing one of them as almost active and the other one as almost passive. When an unexpected additional product (not "target" for the model tested) appears in the medium during abiogenic synthesis, it must be taken into account as a participant in further phase interactions and chemical reactions instead of ignoring it as a chemical or physical (phase) artifact. This means that already at the setup design stage it is necessary to provide an expanded range of detectors and detection principles (spectral, electrical, thermal, and others) in order to avoid false negative experimental results, which often arise due to ignoring individual unrecorded chemical constituents, phases, or states of matter during the experiment.

5. Examples of thermal chambers and facilities for studying prebiological processes

It has been shown that the design of experiments and the construction of planet simulators/simulation chambers and associated embedded devices (microfluidic chips, sensor arrays, DAQs, etc.) must meet the above-mentioned multiparametric requirements and ensure not only multiparametric multisensor measurements in a chamber with a single energy source, but also with multiple energy sources for initiating prebiological phenomena and complex modeling of planetary habitability conditions.

Chambers of this type have been known since the last third of the 20th century and are still actively developed. Examples include some of the LSAIP (Laboratory for Simulation of Ambient Interest and Planetary Evolution) facilities [184]:

- Planetary Atmospheres and Surfaces Chamber (PASC) [185,186], where studies were conducted under conditions simulating the atmospheric compositions, pressures, and UV fluxes of early planetary environments for astrobiological experiments in prebiotically active mineral environments/catalytically active geomineralogical conditions. According to the work [184], "silicates, oxides, and sulphides were probably present on the early Earth in several environments," which led to the study of "the interaction of amino acids [187–189], small peptides [190,191], and nucleic bases [192] on several mineral surfaces." The authors of the above cited paper limit the objectives of their work to studies of photostability, desorption, and partial dissociation of organic molecules (for example, adenine on mineral surfaces under UV radiation, triglycine on the pyrite surface irradiated with UV light, and the protective role of clays in relation to prebiological organics under UV irradiation simulating modern Martian conditions). However, given the photoelectrochemical, photosemiconductor, and photocorrosion properties of pyrite and other similar protobiocatalytic minerals (in the above cited paper [184] it is indicated that photocatalytic efficiency of pyrite leads to the formation of oxide-containing minerals and iron sulfates under Martian conditions with the reference to unpublished papers and conference proceedings [193]), this active photoelectrochemical system with catalyzed weathering under irradiation conditions and desorption with photochemical ion exchange on the surface can be considered within the semiconductor world model [194], while the setup for its study can be considered as a UV photocatalytic weatherometer [195–197]. Such setups for studying photostability and photocatalytic activity can reveal the possible mechanisms of prebiotic nitrogen and carbon fixation, the mechanisms of protophotosynthesis and formation of "geosphere-protobioorganic matter" relations, including those mediated by coordination/supramolecular interactions [198,199]. The latter can be facilitated by the introduction of new compact spectral sensors into the systems engineering of such installations, for example, the introduction of a Raman spectrometer in the Planetary Atmosphere and Surfaces Chamber (PASC) for identifying the mechanisms of protobiomolecular processing in simulated Martian conditions [200,201].

- InterStellar Astrochemistry Chamber (ISAC) for modeling the interstellar medium and cold cosmic astrophysical environments with simulated cosmic rays and UV irradiation in ultra-high vacuum conditions to observe the chemical evolution of interstellar dust or ice analogs [202–207]. According to [184], ISAC is used jointly with the group of E. Dartois at the Institut d'Astrophysique Spatiale and the Institut des Sciences Moléculaires d'Orsay (France) to study in detail "the processes that occur in interplanetary dust particles and… interstellar carbon grains [208–219]". If our multimodal approach is correct, then multiphysical/nonthermal mechanisms should be involved in modeling chemical evolution processes using ISAC. According to [184], a new type of desorption is observed—"photochemical desorption," ensuring a constant desorption rate of photoproducts formed on the ice surface and desorbed due to the excess energy of the reaction [220]. It has been proven that not only photons but also excitons formed under UV irradiation are involved in this process [221,222]. Although the experiments at ISAC were conducted using a hydrogen lamp without the need for a synchrotron light source, almost all of the results were subsequently confirmed at soft X-ray synchrotron

sources, including the National Synchrotron of Taiwan (NSRRC) as a soft X-ray source [223–228]. All these results are directly related to the chemical evolution and production of prebiotic organic matter [229–231] and illustrate the multiphysical (and "multichemical" in terms of reaction pathways not limited to the single thermal or photochemical mechanisms) nature of its generation.

- High-Pressure Planetary Environment Chambers (HPPECs). Both the parameters of this setup and the data obtained from it are remarkable, but not relevant to the conditions of prebiological synthesis [232–235], so they are not discussed further.

In other countries, similar facilities are being developed and installed for the same purpose of modeling prebiotic chemical evolution (usually with an emphasis on organic matter). For example, in the Netherlands (Earth Sciences Department, Utrecht University, Utrecht, the Netherlands), the PALLAS ("Planetary Analogues Laboratory for Light, Atmosphere, and Surface Simulations") system has been developed. The PALLAS system is designed for experimentally studying organic compounds under simulated planetary surface and subsurface conditions on rocky bodies in our solar system [236]. According to the above-cited paper, the emphasis is on "planetary conditions that can be simulated in this facility and that are known to affect organic compounds," including radiation, atmospheric composition, temperature, and surface composition. Accordingly, the general trend of such developments fits into the approach of a multiphysical and multichannel (with multiplexing in the nomenclature of registered or detectable physical descriptors) technical methodology considered in this paper.

6. The main problems of technical feasibility and safety in modeling prebiological processes within chambers: how to avoid reducing ab initio modeling to ad hoc modeling?

It has already been noted that objective modeling of the heat sources for abiogenesis requires considering all representative energy sources, not just those that are easily reproduced within the technical conditions available to the authors during constructing the instalations (i.e., looking for the problem solution where it can be optimally solved rather than "looking for the keys under a street lamp because it's easier to see there than where you have lost them"). Often such chamber or facility systems engineering is based on the engineering solutions that are feasible and safe for personnel, rather than on those corresponding to the complex physical conditions inherent to prebiological processes under simulation. So, in most works, as a rule, the following energy sources are not used:

1. Radioactive heating sources, although they are naturally found not only in terrestrial geological conditions [237–247], but also in planetary cores/exoplanetary cores [248–250], on planetary satellites, including the Moon [251], in comet nuclei [252–254] (where they promote thermal evolution of cometary nuclei by radioactive heating and possible formation of organic chemicals [255], which physically corresponds to the role of radioactive heating in astrobiology [256]), and even in outer space as a source [257]. For example, in the note [258], the entire formulation of the idea based on which the corresponding setup can be built, is described in one sentence: "This heretical idea also offers a head start on the formation of prebiotic molecules necessary for the origin of life, as well as a natural explanation for thermally processing primitive materials (chondrules and

refractory inclusions) found in meteorites, large-scale radial transport of refractories and ices, mixing and homogenization of initially heterogeneous short-lived radioactivities, and transport of stable oxygen isotopes inward from the outer disk surface, as required by cosmochemical constraints on the formation of the Solar System." The introduction of radioisotope sources into the setups for modeling various synthetic processes under hydrothermal conditions is also relevant for such works as [259], where, in addition to the easily modeled temperature of hydrothermal synthesis at high-pressure and high temperature of the supercritical state of water, as well as prebiotic synthesis of biological molecules in Miller's experiments, it is also indicated that "the excitation process could come from gamma rays simulating the terrestrial radioactivity or from the products of water radiolysis by gamma rays, such as hydrated electron, H^+, H_2O_2 or O_2." However, the problem of modeling prebiological processes using radioisotopes and gamma sources in the laboratory is not often discussed, as there are safety regulations that, in most cases, do not allow the construction of the appropriate infrastructure without specific permissions and huge investments affordable only for the nuclear industry or specialized radioisotope laboratories.

2. High-frequency and microwave heating power sources, especially those with tunable frequencies. As a rule, modeling in these ranges does not go beyond the standard frequencies of microwave ovens and ultra-high-frequency physiotherapy systems, since they are rather accessible and permitted for use. Most radio and microwave bands are inaccessible to civilian researchers due to the fact that they are used by communications systems, including military and intelligence services. However, even for realistic modeling of the role of lightning sparks, taking into account radio heating in Miller-Urey experiments, not the individual wavelengths of a magnetron are required, but all the microwave and radio frequency spectral bands that are generated by thunderstorms or volcanic eruptions with lightning in the atmosphere under natural conditions, which lead to the lightning heating effects [260–264]. It is also true for ball-lightning ejection by volcanoes [265–267] (also known as "ball lightning plasma and plasma arc formation during the microwave heating" [268]). Therefore, strictly speaking, a chamber for modeling of prebiotic thermal synthesis in discharges can also be considered as a microwave plasmatron [269–275], also capable of operating as a microwave reactor for plasma chemistry [276–279] and a heat source [280] for spatiotemporal integrated microwave plasma-enhanced and microwave-heated chemical reactions [281–286] (as well as a microwave-pumped ultraviolet radiation source, which promotes photoelectrochemical processes in the prebiotic synthesis system [287–292]). A similar statement is true for high-frequency lightning discharges modeled by plasmatron-based setups [293]. Thus, the high-frequency thermal effect of lightning is known to every geophysicist or aerophysicist in the form of stratospheric Joule heating by lightning [294] and lightning-induced heating of the ionosphere [295–299] (especially lightning-induced heating and ionization of the D region [300–302] or in the lower ionosphere). The effect of high-frequency heating of materials during a lightning strike is also known both for native minerals—dielectrics (melting in rocks by lightning-induced electrical heating [303]), and for metals (wires, aircraft and airship bodies [304–306], with the first observations of heating of a balloon wire by lightning dating back to the first decade of the 20th century [307]). Ultrahigh-frequency radiation from lightning has been well studied since the 1960s–1970s, and at the same time, intensive studies (including pyrometric or spectropyrometric ones) of channel heating in return-stroke lightning were performed [308,309]. Therefore, high-frequency and microwave measurements in model Miller-Urey-type systems should be combined with thermophysical methods and

thermovisiography, micropyrometry, or thermomicroscopy (and, possibly, microwave chemotronic chemometric and catalymetric techniques [310]) in the structure generation zone.

7. Complexity of thermal energy sources in the systems for prebiotic modeling

We have mentioned above the most obvious non-conventional heating sources (radioisotopic and microwave or radiofrequency ones), although the diversity of additional heating sources in the prebiological times was substantially greater, we do not aim to list all of them. They might have been either chemical (for example, exothermic reactions) or physical (for example, ultrasonic heating) in nature.

Yet it is quite evident that models of multiphase and multiparametric / multiphysical processes employing natural heat sources of any origin cannot be sufficiently accurate unless they account for the remaining energy-emission characteristics of the process by which the heat is generated. Conversely, the effect of the concomitant physical factors often cannot be energetically sufficient without consideration of the primary contribution of thermal heating. On the other hand, the simultaneous application of all the factors likewise lacks geophysical or astrophysical relevance for a model of prebiological synthesis or self-organization of protobiological systems. This approach is well described at the level of evolutionary cybernetics, but it demands considerable mathematics to characterize the factors and operative forces, some of which function as extensive variables whilst others function as intensive variables (physical or thermodynamic quantities whose value is independent of size or mass). Accordingly, we provide here merely an intuitive account of the distinction between factors and the possibility of non-destructive decomposition (or transition to sequential phases from the parallel action) of regimes in the corresponding apparatus—simulators for modeling prebiological processes.

Although the colocalization of natural thermal and radioisotopic energy sources has been widely discussed in protobiochemistry since the 1960s [311], their roles and targeted processes of abiogenic synthesis of protobiochemicals in hydrothermal model systems under the influence of ionizing radiation differed qualitatively, and the results of protobiochemical synthesis under conditions of pure hydrothermal and pure radiational exposure were not reproduced under combined exposure. This testified to the emergent and distinctive role of these factors. An analogous thesis holds for non-ionizing electromagnetic radiation sources. We have discussed radiofrequency heating/dielectric heating above; however, radiofrequency exposure per se exerts an effect upon the reaction medium (at minimum, in a considerable number of cases fundamental to biochemistry, according to the criteria of chemical radiophysics [312–316]), though only selectively within certain frequency bands. Purely electromagnetic energy sources, disregarding heating effects (ranging down to ELF, extremely low frequencies in the frequency band from 3 Hz to 30 Hz or up to 300 Hz in the context of electrical power grids and magnetospheric science), were discussed as inducers of prebiotic synthesis and Archaean prebiological chemical evolution as early as in the 1970s–1990s [317,318]. However, the formation of precellular and cytomorphic structures under the action of low-energy electromagnetic radiation alone is impossible (although their dynamics, in the form of combinations of electrokinetic phenomena, particularly dielectrophoresis, may be induced by an electric field, prove substantially nonlinear, and generate behaviour more complex than that of microstructures outside the field [319]). Therefore, all ranges of the electromagnetic spectrum surrounding contemporary life are assigned distinct roles in its emergence and development, whilst

their synchronous application may function only as a source of chaotic dynamics or destruction of the ensemble of biological (or prebiological) phenomena through disruption of the stability achieved as a result of selective application of the particular inducers of individual processes.

As stated in the keynote article "The origin of life: what we know, what we can know and what we will never know," [320] when speaking of completeness and stability in the aspect of the origin of life, we refer not to the attainment of a stationary state, but to something more complex: "The stability kind referred to, however, is dynamic kinetic stability, and quite distinct from the traditional thermodynamic stability which conventionally dominates physical and chemical thinking. Significantly, that stability kind is generally found to be enhanced by increasing complexification." It is precisely through this dynamic kinetic stability that "…an explanation for the emergence of life's extraordinary complexity" may be realized. This may be summarized and extrapolated from the perspectives of cosmic thermobiology and thermal constraints on the origin or evolution of life not only on Earth, but also under different exoplanetary and cosmic conditions [321].

The completeness of a model lies not in its maximal saturation with factors, but in the precise sequence and purposefulness of their application for modeling well-investigated processes and mechanisms leading to the specific products of organization, which fit well into the emergent picture of the formation of the living cell as a whole. The structural macrokinetics of physical stimulation of chemical processes may be regarded as an algorithmic sequence of stages of its self-organization. A good example (though not necessarily reliable, as experimental verification requires the construction of complex apparatus for longitudinal experiments) of a comprehensive model is Trevors's concept [322], which accounts for high-energy electrical discharges, infrared radiation (IR), thermosynthesis and possibly pre-photosynthesis, yet assigns to each factor/each spectral range of the electromagnetic spectrum its own role and its own timing of activation for chemical evolution:

- "High-energy electrical discharges generated some simple organic molecules available for the origin of life.
- Infrared radiation, both incoming to the Earth and generated on the cooling Earth with day/night and warming/cooling cycles, is a component of heat engine thermosynthesis before enzymes and the genetic code were present.
- Eventually, a primitive forerunner of photosynthesis and the capability to capture visible light emerged."

Moreover, even the wavelengths of the optical and infrared ranges have distinct functions in the development of prebiological processes, which may be predicted using computational simulation. Thus, according to [323], "the thermodynamic potential of physical sources of energy capable of feeding the emergence of this capacity can be inferred, which leads to the identification of photochemistry at the wavelength of visible light or processes capable of generating activated species by heating a chemical environment transiently."

Such a distinction between thermal and photochemical factors may be useful not only for describing the formation of supramolecular and phase-separated structures at the late stages of chemical evolution, but also for the early stages of generating the molecular basis of the future selection processes. Thus, in the paper [324]

examining various energy resources for abiotic synthesis of the substances ensuring the formation of prebiological structures, thermal volcanic activity and photochemical action of solar UV radiation are considered as the most possible energy sources. It is demonstrated that one-carbon compounds, including formaldehyde and hydrogen cyanide, could have served as the synthesis precursors, while various amino acids, lipids, carbohydrates, and nucleotides were synthesized as a result of reactions between the initial substances with further photoreduction of their products in a sulphur-containing medium. It is quite evident that even at this early stage, decomposition with elimination of either a thermal or a photochemical component alone would have led merely to the complete absence of the declared synthesis products (in one case something would not be synthesized, while in the other it would not be photoreduced). From the perspective of nonlinear physics and thermodynamics of irreversible processes, this conclusion is obvious and trivial. However, for many specialists in abiogenic synthesis it appears revelatory, owing to the absence of a systematic emergent approach to the experimental design (and the construction of the corresponding apparatus and facilities, which have been indicated and partially considered above according to the optimality criteria).

8. Discussions about optimal nonequilibrium thermodynamic models of prebiological processes

A fundamental problem is determination of the proximity degree of the results of non-equilibrium processes in the above-described multiparametric chambers and chips to the real prebiological systems (as phenomena) and processes considered by the authors of such systems as biological prototypes requiring reproduction under non-equilibrium conditions (as noumena of life). This corresponds to the conceptions regarding the important role of interpretation and understanding of what constitutes a 'minimal interpreting entity' of life in origin-of-life research [325], according to which a system must acquire substantially increased selective advantage by evolving the properties of autocatalysis and the capacity to perform a thermodynamic work-cycle. That is, in order to be an autonomous system, protolife must begin to function not within the thermodynamic cycles of the machinery/machine for its generation, but as an independent and thermodynamically active self-sustaining and self-regulating system. The chambers in which we attempt to model the origin of life, generating artificial systems without reproducing the completeness of the emergent prebiotic processes, do not reproduce the thermophysics and bioenergetics of the protocell, which could have arisen only through a complete utilization of all the phenomena imprinted in its organization and cytophysiological set of functions, which we know to this day. This problem is well captured in the aphorism of Homunculus from Faust, written by Johann Wolfgang Goethe: "It's in the very nature of the thing: For the natural the world has barely space: What's artificial commands a narrow place" [326,327]. (It is noteworthy that in the original work the reference is precisely to obtaining life in laboratory conditions using laboratory glass: "Komm, drücke mich recht zärtlich an dein Herz! Doch nicht zu fest, damit das Glas nicht springe. Das ist die Eigenschaft der Dinge: Natürlichem genügt das Weltall kaum, Was künstlich ist, verlangt geschloss'nen Raum").

The transition from thermodynamics governing the formation of prebiological compounds and systems to the thermodynamics of properly biological systems is well evident in numerous works by V.N. Kompanichenko and in his thermodynamic inversion theory of the origin of living systems (emergence of biological organization through thermodynamic inversion with multiple stages of transition from precellular organic microsystems to primary prokaryotic communities) [328–339]. However, he investigated the processes of organic matter accumulation in hydrothermal systems and did not consider many other energy sources applicable for such purposes. According to Kompanichenko [340], "the transition of prebiotic microsystems into simplest living units might occur only under oscillating thermodynamic and physico-chemical parameters… It seems that organic matter of any origin had a chance to be transformed into a living unit under oscillating hydrothermal conditions through three successive stages:

(1) an organic microsystem becomes unstable at the critical point of the bifurcate transition under conditions far from equilibrium;

(2) relative stabilization of the microsystem due to the balanced oscillations around the critical point (appearance of the paradoxical state 'stabilized instability');

(3) inversion of the energetic balance, free energy contribution begins to prevail over entropy contribution."

Thus, exogenous thermodynamic self-oscillations and autocatalytic cycles were internalized by the emerging system, which manifests the inseparable connection between thermodynamics and kinetics in the origin of life [341]. This corresponds well to the recent work [342] examining kinetic requirements for compensating the entropic costs of self-organization and natural selection, postulating that "The evolutionary process requires a reproduction cycle involving out-of-equilibrium intermediates and kinetic barriers that prevent the reproductive cycle from proceeding in reverse." In the aspect of entropy, the aforementioned approach correlates well with Kompanichenko's model, as this paper asserts that "self-organization, evolution and dissipation processes need to be metabolically coupled and fueled by low-entropy energy harvested from the environment" (this also corresponds well to another work [343] by the authors). This approach is directly related to the emergence of natural selection, but we do not pursue such far-reaching biological analogies further in this article, as we limit ourselves to the reductionist thermophysical and thermodynamic aspects of prebiological evolution.

Almost contemporaneous with Kompanichenko's model is the model [344] based on the dynamics of surface binding of metabolites on iron sulphide minerals. It is also compatible with hydrothermal scenarios readily reproducible in the thermophysical chambers discussed above. In this model, "processes in a microporous hydrothermal mineral environment can provide both solution autocatalytic chemistry and a backdrop of homeostasis," since "the dynamic solvation processes are compatible with selective accumulation of biochemically significant species in the supernatant." From the perspective of thermodynamics, this approach is entirely logical, as it is well compatible with the interpretation "of the emergence of metabolism as a property of autocatalytic processes that dissipate a thermochemical gradient and which are localized within microporous compartments." As stated in this propositional work, "Inheritable reproduction and variation of such discrete autocatalytic processes, with selection for more efficient catalysis and enhanced reaction dynamics, provides the basis for Darwinian selection to arise at a molecular level thus seeding the emergence of a protometabolic foundation for life."

From the foregoing examples it follows that the reliability of the models of prebiological systems (and their proximity to the models of biological systems) increases with the transition from pure thermophysical models to the systems integrating non-equilibrium thermodynamics and kinetics, particularly autocatalytic, cyclic, and oscillatory kinetics (in several models synchronized by thermodynamic cycles). This corresponds to both thermodynamic (disequilibrium) and geological and evolutionary conceptions of the prerequisites of life and mechanisms of emergence of prebiological systems [345], and therefore permits the posing of questions not only regarding the modeling of geological history, but also the evolutionary future of the model systems. It is quite evident that as a consequence of self-organization of non-equilibrium reaction networks, the emergence of protometabolism [346] may occur (moreover, on the basis of kinetic and thermodynamic criteria, such energy-dissipating protometabolism may be based on nonenzymatic metabolic reactions [347] and even be carbon-free or inorganic). On the same basis, one may propose different types of reactivity, up to those preserved and developed in the contemporary biosystems. Therefore, the next criterion for the correspondence of the models

(synthesized in the optimal thermochambers-simulators and thermoreactors imitating prebiological conditions) to the protobionts and biological prototypes is reproduction of the higher forms of behaviour (more complex than simple chemical reactions under regular heating), dependent upon self-sustaining, by virtue of non-equilibrium thermodynamics, biomimetic processes, rather than upon the regimes determined by the operating modes of the hydrothermal reactor or thermochamber of a planetary simulator. However, for this purpose, a technical system must operate not as a substitute for the functions and cyclic kinetic regimes of the modeled system, but rather as an initiator or trigger that induces them. (Metaphorically speaking, the origin's simulator should function not as a heart-lung machine/cardiopulmonary bypass or an artificial heart device, but as an artificial cardiac pacemaker or an external defibrillator). Thus, abiotic oscillations in hydrothermal, volcanic, tidal/littoral or other conditions, accompanied by the oscillations of temperatures, pressures, phase transitions, concentrations and hydration parameters [348], must lead to the emergence of biological cycles at the corresponding levels of organization of protobionts [349]. The correct periodic regime of the processes in geomimetic apparatus-simulators (similar to the indicated diurnal, tidal, and other geophysical processes) should initiate in the system periodic kinetic oscillations (similar to the regimes of a thermocycler).

9. From the correct geomimetic chemistry and thermochemistry to the functional kinetic models of prebiological systems

Many specialists' questions about the role of various planetary factors in habitability are generally grounded in terrestrial analogs [350–352], since the early evolution of Earth and its role in the origin of life are well studied [353], as are the physical conditions on the early Earth [354–367]. Even the setups for hydrothermal simulation experiments, used to study the origin of life on other terrestrial planets, are constructed by analogy with the oceans or other components of the hydrosphere (for example, the outstanding results from geochemical modeling research papers on alternative sites for the origin of life, such as alkaline off-ridge springs, which have "conditions conducive to the formation of early cellular membranes" [358] on the early Earth [359,360]). However, this is due to the fact that "we only have one example of life in the Universe thus far, and it is still hotly debated which chemical reactions, and underlying conditions, led to the origin of Earth's biosphere" [361]. According to the above-cited work [361], "for evidence of life on other worlds, it becomes increasingly important to understand the broad types of planetary conditions that can lead to the emergence of life, so that we can recognize them elsewhere in the solar system. Particularly, it is important not to make assumptions about the specific conditions (able to be simulated in the laboratory) that a type of environment does or does not contain, or what list of environments may have a particular desired condition, since there is great unexpected variety in geological and planetary systems both at the macro and micro scale." A similar thesis has been proposed in the present review, concerning the necessity of expanding the conditions modeled in various thermochambers and planetary simulators, with the aim of overcoming the limitations of Earth's physics. It is evident that the thermophysical and thermochemical characteristics of the media and open systems in which the origin of life might have occurred, should it arise on other planets, differ qualitatively from terrestrial ones. For example, the survival of certain membrane systems of terrestrial life would be impossible under the cationic balance conditions of Mars, and the selection of chemical systems would proceed according to different criteria and within different temperature intervals of stability [362]. The authors of the above-cited

breakthrough work write: “We suggest it would be strategic to focus on searches for origin-of-life environments in and beyond the solar system that facilitate combinatorial chemical selection and complexity generation.” Accordingly, one should move from attempts to fit the conditions of the origin of life to terrestrial life toward an ab initio definition and search for the required conditions for the origin of life in the Universe on the basis of thermodynamics and complex kinetics, as indicated above, and toward the implementation of this approach in laboratory modeling of prebiological processes and systems.

Thus, Vladimir Kompanichenko, who has developed one of the above cited models, writes [363]: “A prebiotic organic microsystem can reach the intermediate state between non-life and life only under high-frequency and multilevel oscillations of physico-chemical parameters in hydrothermal environments.” The trigger mechanism of the origin of life “in nonequilibrium prebiotic microsystems (being at the intermediate state)” was “continuous response (counteraction) of prebiotic microsystems to incessant physico-chemical oscillations.” Therefore, in laboratory simulations we should achieve the optimal conditions for reproducing such oscillations: “The next step of laboratory simulations on the origin of life directed to the exploration of the microsystems’ response to high-frequency oscillations ($>10^{-10}$ s–<30 min)”; although this statement lacks more precise physical limitation of different oscillations with different frequencies, leading to different types of response in prebiological and protobiological systems).

Sergey D. Varfolomeev and colleagues, developing various kinetic models of prebiological evolution of macromolecules, demonstrated through mathematical kinetics and experimentally that thermal cycling may be regarded as a condition for synthesis and combinatorial selection, as well as a cyclic mechanism for generating evolutionary combinatorics in the formation and evolution of protobiopolymers [364–368] (see also the paper [369]). Within the discourse transforming formerly “unsolvable” problems of biophysics (to which many problems of the origin of life belonged) into “solvable” ones (in the terminology of L.A. Blumenfeld), Sergey D. Varfolomeev wrote: “Evolutionary combinatorics and the possibility of ‘multiplication’ of macromolecules in the processes of polycondensation of monomers are provided by a thermal cycle that overcomes the phase transition point of water (‘synthesis–hydrolysis’ a process with adsorption of the monomer on the matrix of the primary polymer) [370].” It is noteworthy that the problem of phase transition is of substantial significance for any biopolymers, as it is a prerequisite or obstacle for their further integration into the structures of protoplasm or cytoplasm. Only by involving phase transitions, especially non-equilibrium ones, can the origin of life under thermal conditions be reconstructed and modeled, integrating structural and functional aspects of prebiological systems. For example, in the well-known thermosynthesis model for the origin of life (which is almost “thermophysical”, because according to the author of this concept—Anthonie W. J. Muller—“life (can be) explained by heat engines,” and their “biological progenitors” can be driven “by convection in volcanic hot springs or by oscillation in the thermal gradient above submarine hydrothermal vents” [371]), Thus, thermocycling during circulation of prebiotic molecules through the hot and cold zones, for instance in convective hydrothermal systems, may have promoted reversible phase transitions, whereby these molecules underwent expansion-compression cycles and conformational changes [372,373]. In protobiomembranes, thermosynthesis is coupled with thermotropic phase transitions in asymmetric membranes [374]. During this process, changes in the membrane dipole potential during thermoinduced transition/transition to a thermotropic

state (a transition from a gel state to a liquid crystalline state) lead to the changes in the electrochemical potential across the protocell membrane, which maintains membrane bioenergetics in the absence of contemporary rotary ATP synthases (their protobiophysical analogue could have been any thermosynthetic/thermal engine adapted for membrane gradient formation before the evolution of chemiosmotic gradient machinery). As one would expect from such a membrane-mimetic system, its bioenergetic and proto-electrophysiological functionality is regulated according to the principles of ionic gradients: the thermosynthesis model links the origin of life and the emergence of regulation by Ca^{2+} [375]. (This conclusion is consistent with the conclusions from the article of the collective supervised by D.W. Deamer and B.F. Damer on the possible biogenesis of membrane structures on Earth and on Mars, limited by cations, particularly calcium [362]). Bioenergetic models of this kind do not contradict their development under the conditions of protophotosynthesis, since both heating and convection [376] (of flows of protobiomacromolecules or protocells) could have occurred under solar irradiation and convection under the action of solar heating in the photic zone (as shown in the first illustration on page 140 in the paper [377]). Incidentally, thermal radiation of the Sun (or exosuns, if one speaks about the possible analogous processes on exoplanets) could have participated in the self-organization of dissipative structures in protoplasm, simultaneously generating a potential gradient on the protomembrane, as in a similar model [378], where gel-like pre-cytoplasm exposed to radiant energy, especially in the infrared spectrum resulted in the production of zones with a charge differential (between −100 and −200 mV) and boundary that may have been a possible location for the later organization of the cytoplasmic membrane.

The energetic capabilities of the thermosynthesis origin of life model are sufficient not only for supporting the elementary membrane processes, but also for linking amino acids during the simple protein formation, and for the maintenance of an RNA world (most likely in a membrane-compartmentalized format) [379]. Although the above model is not complete, and many details require refinement, it does not contradict not only thermodynamics and terrestrial geothermal or heliothermal conditions, but also cosmic exoplanetary conditions for the search for life and the possible pathways of its origin [380,381]. Moreover (as may be seen from the references provided in this paragraph), satisfying all the “bottom-up” criteria we have established, it provides sufficiently complete reproduction of the biological phenomena which go beyond the bounds of physical regulation of any setup and being an emergent consequence of the biological machinery: from the possibility of maintaining heredity (RNA world) to bioenergetics and membrane ionics underlying physiological reactivity and signaling of all biosystems with the higher levels of complexity (up to the brain neural structure and exteroceptors providing connection of the brain with the external world).

Thus, any experimentally validatable model of a prebiological system, for which a necessary and sufficient number of the reductionist points of physical similarity are satisfied during its emergence, may achieve a superadditive emergent similarity to the modeled system (prototype) according to the anti-reductionist or holistic criteria. In essence, an isomorphism of the formation conditions of the model and its prototype (characterized in mathematics and set theory by the coincidence of the necessary and sufficient conditions of existence) leads to the isomorphism of the model product and its prototype, or to the similarity of their functions. However, the similarity gradation is generally not complete, owing to the ontological reasons: since a

complete isomorphism of a system, by definition, is an automorphism, and only another life/living cell possesses an automorphism for life or for a living cell, while the obtaining of life or a cell by a substantially different way under artificial conditions has not yet led to the creation of a complete and fully functional equivalent of a cell “from a zero point” / “bottom up”. Although a complete simulation of all the conditions of abiogenesis and spatial separation / compartmentalization (“protocellularization”) of prebiotic biochemical cycles/kinetic networks is impossible, at minimum, by epistemological criteria analogous to the Gödel’s incompleteness theorem [382–387] (or, to be more precise in formulation, as a consequence of the “butterfly effect” in the emergence of life from prebiological systems), by including into the emergent conditions of modeling a known nomenclature of causes operating during self-organization of the prototype, one may obtain a sufficiently complete set of the consequences of their realization in the model. Together they may demonstrate biosimilarity and biomimetic behavior (from the structural similarity and bioenergetics to the reactivity of the system to the external signals and its active response to them).

Finally, let us illustrate the latter thesis with two examples, one of which possesses a minimal (mineral) level of complexification of the model prebiological functions and concerns hydrothermal synthesis and serpentinization, while the second one demonstrates a maximal cytomimetic level of complexity and is represented by the reactive models of protocells such as thermal proteinoid microspheres. It is noteworthy that at such different levels, the criteria of complexity and emergence of the systems generating prebiological structures function with equal correctness, and in the course of creating their models one can observe both morphisms of similarity (limited by the criteria capable of being reproduced in the model) and autonomous active behaviour, superadditive (going beyond the behaviour of the constituents), are observed (similar to the metabolic networks in prebiological processes associated with serpentinization, irreducible to the synthesis of the individual protobiochemical constituents in the same mineral or geothermal system).

10. Serpentinization as an exothermic process and an energy source at the origin of life

Michael Russell and William Martin proposed the serpentinization process as a source of energy for the origin of life (typically at the alkaline hydrothermal vents [388–393]). This concept was experimentally verified in hydrothermal reactors for origin-of-life experiments [394,395]. Gases formed during serpentinization (such as hydrogen, hydrogen sulfide, and methane) are used as energy sources by deep-sea chemo(auto)trophic organisms or extremophiles [396–399]. At the same time, serpentinization as an exothermic process is associated with heat generation, both under Earth conditions [400–402] and in space on celestial bodies (such as planets/exopanets, planetesimals, moons/exomoons, comets) [403–406], for example, on Mars [407–410]. Such an expanded approach, not limited to the conditions of the early Earth, satisfies the above-mentioned universality criteria and is heuristically valuable in terms of predicting the possible sites of abiotic synthesis and protolife formation "by planetological analogy" (since, according to Müntener's ideas, serpentine and serpentinization are the links between planet formation and life [411]). Thus, hydrothermal fields such as the Lost City, characterized by serpentinization and corresponding geothermogenesis, may be spectroscopic and astrobiological analogues for the possible prebiotic exothermic energy sources on other planets, such as Nili Fossae on Mars [412].

In the course of rigorous hydrothermal modeling of prebiological system generation, not only single biochemical protocell constituents, but also biomimetic structures should emerge, whose origin is determined by the same thermal factors as the synthesis of the biochemical substances from which they are formed. Since hydrothermal simulation experiments and apparatus have been known for several decades [413,414], and the contemporary reviews [415] slightly differ in the details (the synthesis products or attributions of the observed effects to the specific conditions of the early Earth and Ocean [416]) from the general lines established by the "founders" [417–420] (and the hydrothermal approach to the origin of life and the search for extraterrestrial life is already included in the reference books and handbooks for astrobiologists [421,422]), validation of the above thesis should be feasible under any suitable conditions. At the same time, positive experimental results will allow validating the conditions for complex thermally induced self-organization of prebiological colloidal structures [423,424]. Almost all biochemical constituents—prerequisites for this process can be synthesized under hydrothermal conditions, in particular:

1. Pre-RNA world constituents and noncanonical nucleobases for alternatives to genetic structures of classical RNA world models [425–428]. Accumulation of nucleotides in hydrothermal pores [429] (enhancing the production efficacy of the protogenetic code variants and their catalytic reproduction, since "processes in a microporous hydrothermal mineral environment can provide both solution autocatalytic chemistry and a backdrop of homeostasis").

2. Thermal synthesis of amino acids [430,431].

3. Formation and elongation of oligopeptides [432,433] (a classical problem since the 1960s–1970s [434,435]), without which the emergence of the contemporary amino acid-based and protein-based living cells would be impossible [436].

4. Prebiotic interplay between fatty acids and amino acids, without which the membranization/compartmentalization of protocells from the synthesized organic matter could not have occurred [437].

5. Construction of protobioenergetic systems, for example, nucleotide phosphorylation and ATP hydrolysis [438,439], including under microwave-heated hydrothermal conditions [440,441].

However, as noted in the literature [442], “abiotic organic compounds are not biomarkers per se because they do not originate from biosynthesis. Thus, they should be regarded as a distinctly separate group, termed prebiotic or synthetic organic compounds, in explorations for evidence of life.” Moreover, even the evolution of individual biomolecules in hydrothermal environments, without their synergistic integration into supramolecular and phase-separated systems or protocells [443], is insufficient for the emergence of contemporary biology, in which the cell is “a unit of life” (albeit with a minimal set of functions [444–451] realized by a complex of different biomolecules).

The logical self-consistency and non-contradiction of currently developed conceptions regarding the role of serpentinization in the origin of life permit the integration, within a unified system, of geochemistry, ancient metabolism, and hydrogenation [452,453], particularly (and this is especially important for the integration of functions in the emergence of prebiological systems):

1. Synthesis of abiogenic organic compounds [454]

2. Serpentinization-associated mineral catalysis of the protometabolic processes and the emergence of guided metabolism [48,455].

3. Geochemical bioenergetics [456], since serpentinization is a possible source of energy, electrons, organics, catalysts, nutrients, and pH gradients for the origin of life [457].

4. Initially inorganic semipermeable membranes (according to M.J. Russell and A.J. Hall [458]” “FeS membrane, laced with nickel, acted as a semipermeable catalytic boundary between the two fluids, encouraging synthesis of organic anions by hydrogenation and carboxylation of hydrothermal organic primers” and “redox potential (delta Eh) across the membrane, with the energy to drive synthesis, would have approximated to 300 millivolts”).

Such a scheme, where semipermeable inorganic structures initially function as protomembranes and subsequently are replaced by organic structures, integrates well with the thermochemistry of hydrothermal systems, since the composition of microspheres and other cytomorphic structures generated under thermal conditions may vary considerably. For instance, hydrothermally associated organic microspheres are well known since the 1970s [459], whilst the work of Nobel prize laureate J. Szostak and colleagues demonstrated the formation of protocell-like organic vesicles in thermal diffusion columns modeling hydrothermal conditions [460]. Simultaneously, dozens of publications describe the hydrothermal synthesis of inorganic microspheres, including those realized under microwave heating conditions [461–469]. Consequently, on the one hand, one

may develop various (both organic and inorganic) chemical scenarios for protocell formation in hydrothermal systems; and, on the other hand, certain scenarios may be extrapolated to the terrestrial volcanic conditions accompanied by lightning, which generates microwave and radiofrequency effects capable of dielectric heating of the medium during eruptions. It should be noted that under Archaean volcanic conditions, a wide diversity of organic compounds was synthesized—from simple organics to metalloporphyrins and molecular complexes of amino acids with porphyrins [470,471], so the building material for the protocells accumulated in sufficient quantity and nomenclature of constituents necessary for the subsequent evolution of protometabolism.

The known geochemical and hydrochemical constraints for the origin of abiogenic organic compounds in hydrothermal systems [472] are, in essence, not compositional/chemical but rather thermodynamic and protobiokinetic in nature. In the aforementioned work, it is “proposed that abiotic synthesis of organic compounds occurs in metastable states. These states are permitted by kinetic barriers which inhibit the approach to stable equilibrium.” Nevertheless, in this model a proper correlation is realized between thermodynamics and kinetic constraints with the actual geochemical and hydrochemical conditions of the environment, which was postulated at the beginning of this review. The following quotation reads: “Evidence for metastable equilibrium among organic compounds in sedimentary basins is reviewed... This analysis shows that at hydrothermal conditions, organic compounds are formed or destroyed primarily through oxidation/reduction reactions, and that the role of temperature is to lower the kinetic barriers to these reactions.” Evidently, such redox conditions at least partially intersect with the conditions of energetics and thermodynamics of the chemical interactions necessary for realizing the mechanisms of chemical evolution at varying pH in hydrothermal systems (“Such non-equilibrium conditions are conducive to the kind of complex chemical interactions that may have been involved in the processes of the earliest life” [473]).

Consequently, hydrothermal synthesis and formation of the microstructures—protocell precursors—from a thermodynamic perspective should be considered in the light of the fundamental work “Energy sources, self-organization, and the origin of life,” [1] which posits that potential energy sources should be “considered for their propensity to induce self-organization within the scope of the chemical approach to the origin of life” and proposes “a direct connection between the free energy content of intermediates of early pathways and the quanta of energy delivered by available sources of energy.” According to this work, there is an energy matching the needs of early biochemical pathways or the reproduction of self-replicating entities. Thus, the energy accumulated under geothermal conditions must be sufficient not only for sustaining metabolic cycles within the protocells but also for enabling their reproduction. However, this applies to the protocells already possessing the necessary molecular machinery for such processes. In the following section, we’ll consider purely organic thermal microspheres derived from proteinoids.

11. Thermal proteinoid microspheres as models of multifunctional reactive protocells

One cannot limit the role of thermal factors in the origin of life to thermoinduced synthesis of organic compounds and hydrothermal protobioenergetics/protometabolism. It is necessary to account for the fact that early protocellular structures could also have been formed under the action of thermal factors, and their formation was (and should have been, in light of continuity principles in chemical evolution) a direct consequence and product of prebiotic synthesis and phase separation of prebiotic (proto)biopolymers, which occurred under thermal conditions. Looking ahead several paragraphs, we note that a consequence of correctly designed conditions and further modeling of prebiotic processes should be isofunctionality of the resulting formations to either protocells or excitable cells (in the latter case, we are not speaking of isofunctionality as isomorphism, but of homomorphism on the graphs of functional dependencies within the framework of the category theory/set theory), and the origin of functions should be an emergent consequence of the pathways and conditions of obtaining the object that performs them.

A good example of the above theses is the synthesis of proteinoids and the assembly of proteinoid microspheres from them. This research area resulted from the works of Sydney Fox (1912–1998 [474]) and Kaoru Harada (1927–2010 [475]) on thermal copolymerization of amino acids in the second half of the 1950s [476,477]. In these works, the formation of microspheres (spherules) from synthetic proteinoid in hot water was observed [478]. We have already cited Sydney Fox's work suggesting studying the mechanisms of the origin of life within the framework of thermodynamics of nonequilibrium processes (dedicated to Lars Onsager). Therefore, obtaining proteinoids and spherules under hydrothermal conditions can be considered as a clear example of introducing nonequilibrium thermodynamics into the implementation of thermodynamic and thermophysical approaches in origin of life studies [479].

From the standpoint of biological modeling, in cases where their synthesis conditions are similar to the conditions of the protocell origin as the simplest living system, such spherules should exhibit a minimal set of (proto)biological functions or satisfy certain definitions of life, which typically include the same identification criteria, such as:

A. Structural regularity

B. Capacity for movement

C. Capacity for reproduction

D. Presence of expressible code

E. Catalysis and protometabolism based on it

F. Response to the typical chemical markers, as in biological structures

G. Excitability and reactivity.

All of the above criteria are present to varying degrees in proteinoid microspheres.

A. Structural Regularity

A common misconception related to the prevailing low methodological level of proteinoid research in the 1960s–1970s (since sequencing, available for mass use, had not yet been implemented, and X-ray structural analysis and X-ray protein crystallography were only taking their first steps) is the assertion about the stochastic nature of biopolymer/abiogenic heteropolymer sequences formed under thermal synthesis conditions and the alleged unpredictability and uncontrollability of their structure and sequence. However, in most cases this stems from reference to the earliest works of the pre-proteomics era, when obtaining thermal proteinoids could be considered "a project in molecular evolution for the undergraduate biochemistry laboratory" [480], and obtaining the most diverse forms of these structures at temperatures above 100 °C [481], achievable in any laboratory without additional conditions and equipment requirements, was identical to the statement about the meaninglessness of analyzing the structure of any forms of products spontaneously formed under the thermal synthesis conditions. Additional confidence in this was provided by inclusions of nonproteinous amino acids in thermally prepared proteinoid structures [482]. However, even based on the physical reasons (polyelectrolyte and phase-separation considerations), the detection of products of different charges and even neutral products of thermal proteinoid synthesis and the influence of the amino acid charge on the resulting product parameters [483] should have served as a prerequisite for reasoning about the differences in conformations and sequences of different proteinoid-based structures obtained via thermal synthesis. Actually, this was discovered, but somewhat later, when the interest in thermally synthesized proteinoids had waned, so, for many, these works went unnoticed. In 1981, an article by Fox's coauthors entitled "Formation of specific amino acid sequences during thermal polymerization of amino acids" appeared in the journal BioSystems [484], and in 2002 Fox and Ivanov published in Comptes Rendus de l'Academie Bulgare des Sciences (Доклади на Българската академия на науките) the article "Self-ordering of amino acids in the origin of life and its evolution: Universal regularities in protein primary structure" [485] (and a year later the next part entitled "Self-ordering of amino acids in the origin of life and its evolution: From ancient to contemporary proteins" [486]), in which the non-random nature of the primary protein structure in molecular evolution, originating at the point of geothermal proteinoid synthesis, was convincingly demonstrated. A more detailed examination of these and some other works demonstrating the presence of order in the structure of protobiopolymers within proteinoid microspheres, thermolabile coacervate droplets (which, as was shown back in the 1970s, can be biophysically identical or compatible with Fox's proteinoid microsphere model [487]) and related protobiological and biomimetic structures is beyond the scope of this review.

B. Capacity for emergent dynamics and movement

The statement found in the critical works by some authors that the microspheres obtained by Sydney Fox and coauthors were in a stationary and equilibrium state is not true, since already in the 1960s dynamic phenomena in spherules/microspheres from thermal proteinoid were observed [488].

C. Reproduction

Regarding division and budding of proteinoid microspheres, it was observed in numerous works by Sydney Fox and coauthors [489–492]. However, for full genetic similarity, the possibility of conjugation for recombination of genetic material is required. This phenomenon was also observed in thermal proteinoid microspheres back in the 1970s [493]. But what is the genetic code carrier in the case of recombination? The answer to this question is found in the next section.

D. Presence of an expressible code

Based on various simplified versions of interpretation (widespread because of the name of the research object—proteinoids, which implies phase-separated systems not containing nucleic acids), several critics generally outline the inadequacy of Fox's theory due to the absence of any genetic code carriers (DNA, RNA, etc.) within proteinoid microspheres. However, this indicates insufficient competence and level of knowledge of the material being criticized, since already in the 1960s Fox and his colleagues performed binding of basic proteinoids with thermally synthesized polynucleotides [494] and condensation of the adenylates of amino acids common to protein [495] (it is noteworthy that somewhat later, in the 1970s, the effect of coprecipitation of thermal proteinoids with polyribonucleotides was also demonstrated [496]). In the early 1970s, the synthesis of oligonucleotides by proteinoid microspheres using a standard bioenergetic macroergic compound—ATP [497] was demonstrated, and in the early 1980s, formation of peptides from amino acids by single or multiple additions of ATP to the suspensions of nucleoproteinoid microparticles [498] was published. In the 1970s, Fox considered the compatibility of primordial genetic mechanisms with coacervate droplets and proteinoid microspheres [499]. In 1980 Fox and coauthors analyzed the possibility of cellular peptide synthesis in proteinoid or complex proteinoid-nucleic systems [500], which indicated the prospect of assembling anabolism networks in proteinoid microspheres, as well as in coacervates (later this idea was implemented in the hypercycle models in coacervates [501–503]).

In the early 1980s, the thermodynamic basis of spontaneous structure formation, appealing to nonequilibrium thermodynamics that had developed by that time, developed to the point where synergetic approaches could be applied to analyzing the behavior of such hybrid nucleic-proteinoid systems, postulating their self-organization as a model of protobiogenesis and the origin of protohypercycles [504]. From the perspective of evolutionary cybernetics and evolutionary molecular biophysics, considering the possibilities and limitations not only of the direct but also of reverse code transcription, it would be tempting and promising for further research to also find the possibilities of proteinoid reverse machinery in the development of a transcribable code. In this aspect (beyond the scope of this review), we refer the reader to a conceptual work that did not come from Fox's collective: "The genetic anticode: The role of thermal proteinoids in the development of an hypothesis" [505].

E. Catalysis and Protometabolism

The very fact of applying kinetic models, such as hypercycles, sizers, and quasispecies, to analyzing a possible behavior of transcriptional and translational systems in proteinoid microspheres and their post-synthetic (but not post-translational, if there is no modern-type translation apparatus with RNA) derivatives

indicates the presence of catalytic (autocatalytic and cross-catalytic) cycles with a connectivity number of at least two. However, to reproduce cellular metabolism in proteinoid-based systems, it is necessary to demonstrate a larger nomenclature and variability of processes, including shunting pathways and feedback loops for reconfiguring metabolic networks. Catalytic activities of thermally prepared polyaminoacids were known already at the turn of the 1960s–1970s [506,507], and in 1980 Fox institutionalized in the title of his article the term "metabolic microspheres" [508] (see also [509]). At the same time, it was postulated that the capacity for regulated metabolism in the long term leads to the evolution and progress of metabolic organization through feedback and selection.

F. Biochemical Markers and Biosignatures

Based on the obvious biochemistry concepts, given the chemical similarity between proteinoids and amino acid fractions of cytoplasm, they should be stained/labeled identically by the dyes and labels for the corresponding amino acids or proteins. This is indeed the case, known since the first half of the 1960s, when it was first shown (by Fox and Yuyama) that microspheres from thermal polyamino acids are stained by Gram stain, like ordinary bacteria [510].

G. Excitability and Reactivity/Active Behavior of Microspheres

The problem of the origins of behavior in macromolecules and protocells [511] was posed by Fox at the turn of the 1970s–1980s and, also based on the physical chemistry of thermal proteins in the first life, was positioned as a prerequisite of the "mind-body" problem in the early 1990s [512]. However, this problem was not positively solved by him in those years, but only posed in a philosophical context. Nevertheless, these assumptions were based on quite material experimental results. Thus, in the early 1980s, Przybylski and Fox published the results of measurements of electrical/electrophysiological membrane phenomena in spherules/microspheres from proteinoid and lecithin [513], including membrane potentials and action potentials [514]. Such proteinoid-based microspheres with shells were positioned by them as excitable artificial cells, and the registered wave phenomena were considered as oscillatory potentials in simulated protocells [515,516]. Sometimes the same data were interpreted "reductionistically" as manifestations of the electrical double layer activity or as a function of lecithin coating. However, reproducibility of the corresponding results on "alecithal" (lecithin-free) and membraneless proteinoid structures settled the disputes. Thus, independently of Przybylski and Fox, electric excitability of proteinoid microspheres composed of basic and acidic proteinoids was demonstrated by Matsuno [517], and shortly thereafter Vaughan, Przybylski, and Fox proposed considering thermal proteinoids as excitability-inducing materials [518].

Initially, the concept of "excitability" as applied to thermal proteinoids was interpreted only in the aspect of registering electrical potentials (modeling electrophysiological potentials of a cell or a protocell). However, subsequently this concept began to expand actively, and the number of excitation agents grew qualitatively. For example, in the late 1980s, an authors' team including Galina I. Lozovaya (a coauthor of Alexander I. Oparin and Kira B. Serebrovskaya in the papers on coacervates) began to work with dyes in proteinoid microspheres and porphyrin-proteinoid complexes as models of prebiotic photosensitizers [519]. At the same time, the

emergence of melanoidins was discovered in experiments on proteinoid thermal synthesis, which indicated the possibility of manifestation of photoabsorption properties in proteinoids already at the emergent point of their origin under natural prebiological conditions [520]. During the same period, proteinoid microspheres were considered as implementers of another extremely important protobioenergetic process, prebiological photophosphorylation [521].

On the other hand, in addition to the physical aspect of excitability of proteinoids and spherules based on them, Fox and coauthors proposed an ideology of pharmacological or pharmacochemical reactivity of these structures, and initially pharmaceutics in this aspect was associated with molecular evolution [522]. We will not delve into this topic in this review; however, it should be noted that these ideas have not lost significance to the present day, especially in the aspect of targeted drug delivery based on proteinoid microspheres as carriers [523], which may be of crucial importance in externally stimulated theranostics based on proteinoid systems. The very method of thermal synthesis of proteinoid microspheres, in which assembly (including with a pharmaceutical agent regulating the structure and phase composition of the microspheres) is, according to Fox, a manifestation of reactivity and the start of "the origins of behavior in macromolecules" (which can be assessed as a manifestation of emergence, since during structural self-assembly, superadditive properties of a (bio)colloid system are formed, and the response to external stimulus during its preparation programs the reactivity of its functioning or physiological function).

Attempts of some critics to call representations of reactivity or emergence of behavior in proteinoid-based protocells/proteinoid microspheres or spherules based on behavior and reactivity in macromolecules archaic, morally outdated, and having no right to exist in modern science are mostly based on superficial study of both the criticized primary source and the current level of this rapidly developing science area (or tendentious "metaphysical" interpretation of the terms "behavior" and "reaction"). In fact, at present, the data of Przybylski and Fox have been successfully reproduced and the following experimental results have been achieved (in order of increasing complexity):

1. Low-frequency electrical waves have been re-registered not only on single proteinoid microspheres, but also in ensembles of proteinoid microspheres [524].

2. Effects of light-induced spiking in proteinoids [525] have been discovered, including in systems with PANI (polyaniline – conducting polymer and organic semiconductor from the polyarenes groups, conducting electric current due to conjugated bonds) [526,527].

3. Thermosensory spiking activity of proteinoid microspheres cross-linked by actin filaments [528] has been observed.

4. Effects of pharmaceutical (such as ion channel blockers) and anesthetic (e.g., chloroform) agents on proteinoid microspheres and their proteinoid biochemical substrate as a chemical target of action have been demonstrated [529,530].

5. Transfer functions of proteinoid microspheres have been obtained/reconstructed [531]. Hybrid systems based on proteinoids and colloidal/dispersed semiconductors such as ZnO have also been created, for which equivalent operating circuits can be reconstructed, including under short-wavelength (UV) irradiation [532].

6. Memfractance of proteinoids has been investigated [533].

7. Proto-neural networks from thermal proteins/thermal proteinoids have been constructed [534,535], in which proteinoid microspheres from abiotic polypeptides perform the role of proto-neurons [536].

8. Electroactive composite films integrating Kombucha, Chlorella, and synthetic proteinoids have been developed [537], and similar systems integrating biological structures with biological reactivity and abiogenic proteinoid microstructures. In such composite ensembles, many of the forms of reactivity considered above have been registered, for example, light-induced spiking response in proteinoid-actin-kombucha systems [538].

9. An ideology of "proteinoid computers" has been proposed [539].

10. Analogous to Pavlovian reflex learning in living systems or machine learning, a concept of learning in ensembles of proteinoid microspheres has been formulated [540].

11. The possibility of interactions between proteinoids and simulated neural networks has been proven [541].

12. Recognition of sounds by ensembles of proteinoids has been realized in a specialized artificial system created using outputs from a computer DAC [542]. Given that sounds or modulated electrical signals of acoustic frequencies (amplitude and frequency modulation of a carrier wave) are not originally the immanent sources of excitation under conditions of obtaining proteinoid and hybrid proteinoid-nucleic systems (although they are physically direct excitors for microsphere reactivity, based on the analysis of transfer functions of proteinoid microspheres), one can speak of their reactivity being emergent and potentially progressively going beyond reflecting the environmental parameters present at the moment of their formation. This interpretation refers us to the analogy with protobiophysics/biophysics of reactivity of primary thermal proteins in the first life within the framework of the "mind-body" problem, corresponding to Fox's ideas cited from the same-named article above.

At the same time, the dependence of proteinoid and proteinoid microsphere reactivity on thensynthesis conditions anew raises the question posed in this article, considered and illustrated by numerous other examples in the preceding text: how to correctly reproduce/model the conditions of obtaining prebiotic evolving systems and protocells under thermal conditions so that functionally biosimilar and biomimetically reactive systems form, rather than equilibrium/rapidly relaxing and incapable of "protobiological" response structures?

Already in the Fox's works with coauthors in the 1970s the problem of the origin of stable protocells in a primitive alkaline ocean [543] was posed (it is quite obvious that there also existed conditions of hydrotherms or compositions of the protoocean and primordial broth that could not have led to the assembly of biochemically balanced and "protophysiologically" active protocells). It is also necessary to analyze not only chemical but also isotopic composition of the liquid. Based on the analogies and biochemical similarity of

prebiological and biological processes in microheterogeneous systems, it is possible to move from “biological fractionation of isotopes” [544–546] to “prebiological/prebiotic fractionation of isotopes” and “protobiological fractionation of isotopes,” taking into account in the words of E. M. Galimov from the chapter title from the above cited book, “Geological aspects of thermodynamically ordered isotopic distributions in biological products”. Therefore, it is necessary to instrumentally ensure variation of different parameters of a primitive ocean for screening the conditions of prebiological synthesis that clearly favor the selection of biomorphic microstructures with biosimilar behavior.

Many believe that in hydrothermal synthesis and assembly of proteinoids or proteinoid microspheres, the composition or pressure of the atmosphere above the liquid surface can be neglected. However, this is not the case. In the 1970s, Rohlfing (a former graduate student of Fox’s and an eyewitness to the first proteinoids and microspheres [547]) and coauthors convincingly demonstrated that although both acidic and basic proteinoids formed microspheres in atmospheres of carbon dioxide, carbon monoxide, methane, hydrogen sulfide, hydrogen, nitrogen, and oxygen (applied separately), as well as in an atmosphere of nitrogen and carbon dioxide (though higher proportions of carbon dioxide led to fewer proteinoid microspheres from basic proteinoids), neither type of acidic nor basic proteinoids formed spheres under a 10-min exposure to ammonia or in an atmosphere of methane, hydrogen, and ammonia (although brief exposure did not prevent sphere formation from basic proteinoids) [548]. The mechanism of this effect was discovered empirically, as control experiments showed that both qualitative and quantitative effects in the generation of proteinoids and proteinoid microspheres were due to pH, not the specific gas or ion.

According to another work by Rohlfing [549], proteinoid “polyamino acids prepared at low pressure (0.02, 10^{-4} atm) were obtained in appreciably greater yield than those synthesized at 1 atm; amino acid composition was somewhat influenced by low pressure,” which, according to the authors’ conceptual conclusion, “indicates that polyamino acids could have been formed thermally under a variety of possible prebiotic atmospheres and on planetary bodies of low atmospheric pressure” (the value of this conclusion is enhanced by the fact that the experiments used not only terrestrial amino acids but also fragments detected in hydrolyzed extracts of three extraterrestrial samples [550]). Therefore, it is undoubtedly necessary that for more heuristically valuable work with thermal synthesis of proteinoid microstructures or microspheres, one must also reproduce in the appropriate chambers the gas composition and pressure above the modeled portion of the “landscape of hydrosphere.” For this, one should further improve and metrologically integrate the installations in which such reactive macromolecular (or supramolecular) (proto) biopolymer structures and phase-separated microstructures are synthesized.

Rohlfing wrote [547] that the “arena” in which the analysis of the origin of life takes place should be multidisciplinary, and for those involved in the chamber engineering this means that installations for modeling the origin of life should also be multiphysical and multiparametric. The full quote: “The origins arena is multidisciplinary (as, of course, are others), where there is a role for physicists, geologists, chemists (perhaps especially organic chemists and biochemists), biologists, paleontologists, cosmologists, and undoubtedly a few other specialists. It is not easy to be good, especially experimentally, in all of these; most researchers stick to

their area of experimental expertise and probably tend to overemphasize in their own mind the importance of that special area. However, in a multidisciplinary area, a fragmented viewpoint often is not a very useful one; an overall perspective of the whole discipline and the connections and relationships between subdisciplines is important not only for balance but also for planning and interpreting experiments (cf. ‘evolutionary continuity,’ below)” [547].

Therefore, striving for comprehensive reproduction of the origin of different forms of proteinoids and proteinoid microspheres (possessing reactivity to various physical and chemical factors, which is a prerequisite for the emergence of many biological functions in them), we should not limit ourselves to only partial reproduction of geophysical or hydrophysical conditions on the early planet. We must create installations that take into account the knowledge about the conditions of their possible synthesis accumulated by any specialists—both experimenters and naturalists who found such structures in meteorites or fossil rocks of the Archean/Hadean era, as well as by the specialists who assigned such microstructures to the known forms of abiogenic biopolymer associates (which in some cases were erroneously called “nanobacteria,” despite their almost abiogenic nature and undifferentiated morphology, which does not allow one to speak about any cytology and cytophysiological ultrastructure of such formations).

It is quite obvious that the problem of full-functional modeling of biological and, in particular, evolutionarily significant cytological functions based on proteinoids is not experimentally solved, and the introduction of additional constituents into them is not a fully validated or combinatorially screened (even at the level of preliminary assessments based on computational chemistry) task. The experimental completion of such work depends on the modeling conditions, which requires the design of installations, some requirements for which were outlined above. But the approximation to truth that was historically achieved since the pioneering Fox’s works in this field [551], consisting in simulating almost all the main functions attributed to the prebiological and protophysiological systems, undoubtedly inspires optimism in the designers of thermophysical installations for the synthesis of programmable and controllable thermal proteinoid microspheres (in systems with multi-channel feedbacks).

12. Conclusion

Thus, it is possible to move from formal thermodynamics, used to describe the origin of life at different abstract levels (from the Boltzmann molecular level to the informational Kolmogorov or Shannon approaches) [552–555], to engineering thermodynamics and engineering thermophysics, which enables the development of experimental instruments, simulation chambers, and facilities for validating various hypotheses of prebiotic thermal synthesis or for developing models of protobiological structures based on thermodynamic and thermochemical criteria.

Conflict of interest: The authors declare that they have no conflict of interest.

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