



Why is Abiogenesis Such a Tough Nut to Crack?

David Lynn Abel

Abstract

Natural science explores the roles of the four known forces of physics, statistical mechanics, mass/energy phase changes, mass transfer, and the application of the laws of physics and chemistry to most any problem. But there is one problem a purely physico-chemical approach does not and logically cannot address: abiogenesis' pursuit and acquisition of *functionality*. The laws of motion do not perceive, value or pursue "usefulness." The physics definition of "work" has absolutely nothing to do with utility. Pragmatism is not an issue in an inanimate environment. Yet, every process in life is highly functional and extremely sophisticated in its achievement of function. No basis for evolution exists yet in abiogenesis. Neither molecular stability nor mass self-replication of an RNA analog produces the slightest "biosystem," let alone a proto-metabolism. Mere complexity doesn't DO anything. Any hope of real advancement in abiogenesis research requires addressing the problem of an inanimate environment having valued and pursued "usefulness" and "functionality" prior to computational success (the "halting problem"). What is our naturalistic mechanism for this?

Keywords: Protolife; Protocells; Abiogenesis; Life Origin; Origin of Life; Protometabolism; Protocellular Metabolomics

The Problem

We sometimes refer to natural processes with the phrase "Chance and Necessity"[1-10]. Necessity refers to law-governed, fixed, redundant behavior. Chance is not a cause of any effect. Chance is nothing more than an epistemological mathematical *description* of the likelihood of possible future events.

Laws are essentially compression algorithms. Reams of data can be reduced to nothing more than a simple equation: $F=ma$ or $E=mc^2$. The reason is that *regularity* of interactive and reactive outcomes can be counted on. With very minor statistical variation, things happen the same way every time given the same initial conditions. Physical outcomes are fixed and determined *by mathematical law*. (Never mind asking why physicality would be ruled by abstract, *non-physical*, purely formal mathematics [11-13]). Events happen the same way every time. That's the only reason physical laws help our investigations. We find it immensely valuable that so many contingencies can be reduced by laws and constraints. We can use those laws and constraints to predict relatively certain outcomes. They do not vary.

The problem for natural science is that not every phenomenon in reality is fixed and forced to occur the same way every time. Despite laws, very real contingencies still exist. And they are not all random contingencies

Affiliation:

Proto-Biocybernetics/Protocellular Metabolomics,
The Gene Emergence Project, The Origin of Life
Science Foundation, USA

Citation: David Lynn Abel. Why is Abiogenesis
Such a Tough Nut to Crack?. Archives of
Microbiology and Immunology. 8 (2024): 338-364.

Received: June 15, 2024

Accepted: July 26, 2024

Published: August 06, 2024

describable by statistics. Certain contingencies cannot only be “favored,” they can be outrightly “selected” for functionality. If we doubt the reality of “selection,” we doubt the reality of both evolution and engineering.

But selection in evolution is always passive and secondary to already existing optimal fitness. No mechanism has been defined for the active selection required in molecular evolution and abiogenesis to *produce* that fitness. The problem with naturalistic models of abiogenesis is that metabolomics is by no means a necessity. Metabolomics constitutes a constellation of highly integrated formal achievements. We don’t view the effects of law as “achievements” for good reason. Achievements connote wise choices needed to steer and control sophisticated function. Yet the pre-assumption of the all-sufficiency of law and constraints is exactly what the naturalistic abiogenesis axiom requires.

This axiom might be fine if we had adequate empirical evidence of spontaneous self-orchestration of any actual proto-metabolism. We think such evidence has been abundantly published. But it doesn’t take much critical analysis of Materials and Methods in any supposedly naturalistic abiogenesis paper to find abundant evidence of “investigator involvement” in experimental design and engineering. Like metabolism itself, these experiments represent clear formal achievements, not natural process. They only prove the exact opposite of what the investigators thought they were proving. Even then, the model provides only imagination, never repeatedly observed spontaneous natural-process creativity.

Physics cannot address the whole of reality. The laws of motion do not explain everything. “Usefulness, functionality, utility, benefit, success, pragmatism, biochemical pathways, biosystems, homeostatic metabolism, and computational halting” are just a few examples of life’s concepts that physico-dynamics cannot explain.

What is “functionality,” for example? Can *natural science* explain “functionality,” or its origin? We have a physics definition of “work.” Unfortunately, the physics definition of “work” has absolutely nothing to do with “function.” None of the four known forces of nature cares about “usefulness.” Where did utility and pragmatism come from? Certainly not the force of gravity.

Can natural science explain an inanimate environment *preferring* something—anything? Merely “favoring” something is less problematic. “Favoring” something presupposes it’s prior existence. With abiogenesis, no truly “hands-off” proto-life has ever been demonstrated to spontaneously generate for the environment to “favor” or passively select. No basis for “molecular evolution” exists apart from embarrassing stretches of the term’s meaning. All too common are purely formal, pseudo-naturalistic

explanations. Examples of loaded phrases include “so that. . .” or “in order to . . .” No such concepts are considered by inanimate physics and chemistry.

The environment might passively favor an especially stable molecule. But some of the most stable molecules are poisonous, even lethal, to life (e.g., heavy metals). What does molecular stability have to do with “biosystems,” “functionality,” or “metabolic success?”

An auto-catalytic RNA analog might have accidentally formed. But how does a pure population of any one molecule orchestrate metabolism, especially when it consumes all of the resources needed by all of the other required abiogenic players to form? Even mutually catalytic networks [14-18] would require steering and control to not only organize and propel a biochemical pathway to a useful end-product, but more importantly to integrate circuits, biosystems and finally a protometabolism. A heritable system would also have to be quickly devised for any Metabolism-First model to survive. But an inanimate environment doesn’t “devise” anything [19,20].

Life is computation. Computation is fundamentally formal, not physical. Life employs biosemiosis to convey instructive messages. The symbolic representationalism needed for biosemiosis is formal, not physical. Neither life’s computations nor its coded biosemiosis can be reduced to law and constraints, chance and necessity.

A prebiotic environment does not value or pursue “usefulness.” An inanimate environment cannot even sense “usefulness.” Physical interactions know nothing of pragmatism. How many evolutionary peer-reviewed papers have we all read proclaiming that “evolution has no goal”?

Even in Darwinian evolution, mutations do not offer the creative genius we suppose. They have no motives for improving already existing life. Mutations correspond more to typographical errors than thesis-writing. The programming parallel is, “Garbage in, garbage out.”

The point mutation that causes sickle cell anemia is often used as an example of a beneficial mutation. The benefit is malaria resistance. Few sickle cell anemia sufferers would agree that their mutation is beneficial. They would much rather be infected with the Plasmodium parasite, and be treated with anti-malarials like everybody else.

What exactly is the mechanism for mutations in Darwinian evolution to generate all of the undeniably ingenious cooperative schemes we observe even in the simplest known life forms? Even an imagined proto-metabolism would have required not only formal organization, but bona fide orchestration of a symphony of biochemical pathway cooperation.

And what is the basis for natural science expecting an inanimate environment to “select” *anything* “in order to” achieve or acquire functionality? One finds “*in order to* . . .” in the vast majority of abiogenic papers as the supposedly naturalistic mechanism for optimization. An inanimate environment does *nothing* “in order to.”

Also prominent in most abiogenesis papers are loaded terms such as “may have,” “could have,” “might have,” “suggests,” etc. The supposedly scientific mechanisms provided are found to be little more than wish-fulfillments.

The selection and favoring that serves as the basis for evolution theory is purely passive and secondary. In addition, evolution hasn’t even begun yet in abiogenesis. Darwinian evolution is nothing more than the differential survival and reproduction of the fittest already-programmed, already-cybernetically processed, already-computed, already-living organisms. No organisms exist in a prebiotic environment. Evolution theory is irrelevant to abiogenesis theory.

One cannot specialize in proto-cellular metabolomics, as this author does, without being confronted daily with the reality of “biosystems,” no matter how rudimentary we try to reduce them. Biochemical pathways, cycles and sophisticated interactomes cannot be reduced to chance and necessity [5]. They are undeniably steered toward utility. They are controlled, not merely constrained [21]. They all have a purpose. Fixed laws cannot explain the formal integration of circuits or the orchestration that even a proto-metabolism would require [22]. And let us not forget, no lab has ever produced this “hands-off” hypothetical proto-metabolism. Any hint of progress has always been “hands-on,” as readily demonstrated by the Materials and Methods section of any such paper. Certainly no one has ever observed spontaneous generation of even proto-life in the wild.

The most enduring models of the spontaneous generation of proto-life.

What are the most long-standing models in the literature that have persisted into the last three years of peer-reviewed publication? Such models are by now quite well-developed and refined. They are certainly worthy of open-minded, honest consideration.

Hundreds of papers leading up to the present emanate from four main categories of models: Inorganic, Organic Composomal, Co-evolution and Informational models. The last group acknowledges some degree of genetic-like instruction and programming control.

1. Inorganic models

One of the first inorganic models was that of Cairns-Smith [23-28]. He proposed that life began as structural patterns in clays which self-replicated during cycles of crystal growth

and fragmentation. This model died out decades ago. But the work of Martin and Russell around the turn of the millennium has not died out.

In 1994, H, Russell and later Martin [29-31] attempted in an early geochemistry model to envision physical compartmentation from the environment as a substitute for present-day cells, cell membranes and cell walls. Their focus was on self-contained redox reactions involving inorganic matter. They initially proposed that life evolved in structured iron monosulphide precipitates in a seepage site of a hydrothermal mound. They believed a redox, pH and temperature gradient existed between sulphide-rich hydrothermal fluid and iron(II)-containing waters of the Hadean ocean floor.

FeS and NiS can catalyze the synthesis of the acetyl-methylsulphide from carbon monoxide and methylsulphide which are constituents of hydrothermal fluid. The authors suggested pre-biotic syntheses occurred at the inner surfaces of these metal-sulphide-walled compartments. The model proposes that these compartments restrained reacted products from diffusion into the ocean, providing sufficient concentrations of reactants to forge the transition from geochemistry to biochemistry.

Through time, Martin and Russell [32-38] believed that RNA-world chemistry could have taken place within these naturally forming, catalytic walled compartments to give rise to replicating systems. Sufficient concentrations of precursors to support replication would have been synthesized in situ geochemically and biogeochemically, with FeS (and NiS) centers playing the central catalytic role. They inferred that the universal ancestor was not a free-living cell, but rather was confined to the naturally chemi-osmotic FeS compartments within which the synthesis of its constituents occurred. The first free-living cells were suggested to have been eubacterial and archaeobacterial chemoautotrophs that emerged more than 3.8 Gyr ago from their inorganic confines.

They believe that the emergence of prokaryotic lineages from inorganic confines occurred independently, facilitated by the independent origins of membrane-lipid biosynthesis: isoprenoid ether membranes in the archaeobacterial and fatty acid ester membranes in the eubacterial lineage. The eukaryotes, all of which are ancestrally heterotrophs and possess eubacterial lipids, are suggested to have arisen two billion (2 Gyr) ago through symbiosis involving an autotrophic archaeobacterial host and a heterotrophic eubacterial symbiont, the common ancestor of mitochondria and hydrogenosomes. The attributes shared by all prokaryotes are viewed as inheritances from their confined universal ancestor.

Others have contributed to this line of thought with modifications along the way [29-62].

More currently, Liu et al [63] suggest that life is an out-of-equilibrium system sustained by a continuous supply of energy. In extant biology, the generation of the primary energy currency is adenosine 5'-triphosphate. ATP's use in the synthesis of biomolecules requires enzymes. Before their emergence, alternative energy sources, perhaps assisted by simple catalysts, are believed to have mediated the activation of carboxylates and phosphates for condensation reactions. The authors showed that the chemical energy inherent in isonitriles can be harnessed to activate nucleoside phosphates and carboxylic acids through catalysis by acid and 4,5-dicyanoimidazole under mild aqueous conditions. Simultaneous activation of carboxylates and phosphates provides multiple pathways for the generation of reactive intermediates, including mixed carboxylic acid-phosphoric acid anhydrides, for the synthesis of peptidyl-RNAs, peptides, RNA oligomers and primordial phospholipids. Unified prebiotic activation chemistry could have enabled the joining of building blocks in aqueous solution from a common pool and enabled the progression of a system towards higher complexity, foreshadowing today's encapsulated peptide-nucleic acid system.

2. Organic Composomes and various Metabolism-First models

Doron Lancet and Daniel Segre at The Weizmann Institute of Science in Israel in 1998 originated the idea of Graded Auto-Catalytic Replication Domains (GARD)[18]. Segre and Lancet provided a rigorous kinetic analysis of simple chemical sets that manifest mutual catalysis. Catalytic closure was hypothesized to sustain self-replication up to a critical dilution rate related to the graded extent of mutual catalysis. The authors explored the behavior of vesicles containing GARD "species." Mutual catalysis was seen to be governed by a statistical distribution. Some GARD vesicles displayed a significantly higher replication efficiency than others. Thus, GARD was viewed as a simple model for primordial chemical selection of mutually catalytic sets.

The statistical possibility of many random, mutually catalytic interactions was pursued with relatively few parameters of molecular properties. They analyzed enhancing kinetic behavior of small heterogeneous assemblies of spontaneously aggregating molecules. The spontaneous growth and splitting of assemblies resulted in a complex population behavior. A statistical formalism for mutual rate enhancement was used to numerically simulate the detailed chemical kinetics within such assemblies.

Work along the lines of GARD has continued through the years [14-17,64-68]. Recently, Lancet and A.M. Segre have revisited some of the original theoretical models dealing with the chemical emergence of "life-like" properties in prebiotic systems. Special emphasis was given to models involving

random assemblies of mutually catalytic organic molecules, as opposed to scenarios in which individual molecular species are endowed with the capacity of self-replication. They believe that some of these metabolic reactions were initially catalyzed by less sophisticated and less specific catalysts, such as small organic molecules, metal ions, minerals, short RNA polymers, prebiotic amino acids or peptides. Smaller molecules could have persisted throughout evolution, gradually becoming incorporated into protein enzymes as catalytic cores or cofactors. They envision geochemically available prebiotic catalysts like transition metals, iron-sulfur clusters and organic cofactors.

The authors continue to investigate various generic constraints of autocatalytic networks and sustained autocatalysis of biopolymeric ensembles. They assume that a large repertoire of relatively simple organic compounds could have formed spontaneously prebiotically. Graph theory and a mean field approach was used to study the autocatalytic formation of amphiphilic assemblies (e.g., lipid vesicles or micelles)

The assemblies manifest a significant degree of homeostasis, resembling the previously predicted quasi-stationary states of biopolymer ensembles (Dyson, F. J. (1982) J. Mol. Evol. 18, 344-350). Such emergent catalysis-driven, compositionally biased entities may be viewed as having rudimentary "compositional genomes." The author's address the question of how mutually catalytic metabolic networks, devoid of sequence-based biopolymers, could exhibit transfer of chemical information and might undergo selection and evolution. This computed behavior may constitute a demonstration of natural selection in populations of molecules without genetic apparatus, suggesting a pathway from random molecular assemblies to a minimal protocell.

Amphiphilic molecules are thought to have contributed to an exclusively lipid-based origin of life. The proponents hope that modern trends in molecular complementarity, combinatorial chemistry and enzyme mimetics represent a source of conceptual and experimental information that might help extend their Amphiphile-GARD model. Lipid world micelles and vesicles play a considerable role in compartmentalization of these mutually catalytic sets of simple organic molecules. They are seen to have undergone selection, evolution, and transfer of chemical information.

The authors combined network-based algorithms with physico-chemical constraints on chemical reaction networks to systematically show how different combinations of parameters (temperature, pH, redox potential and availability of molecular precursors) could have affected the evolution of a proto-metabolism. Their analysis of possible trajectories suggested that a subset of boundary conditions converges to an organo-sulfur-based proto-metabolic network fueled

by a thioester- and redox-driven variant of the reductive tricarboxylic acid cycle that is capable of producing lipids and keto acids. They doubted whether environmental sources of fixed nitrogen and low-potential electron donors are necessary for the earliest phases of biochemical evolution. They used one of these networks to build a steady-state dynamical metabolic model of a protocell, and found that different combinations of carbon sources and electron donors can support the continuous production of a minimal ancient 'biomass' composed of putative early biopolymers and fatty acids [69].

Segre, Lancet and Shenhav's mutually catalytic assemblies, devoid of sequence-based biopolymers, are also envisioned to entail a primitive information transfer system, exclusively based on idiosyncratic chemical compositions. This is imagined as the inheritance of spontaneous "compositional genomes." Of course, their definition of "information" is very different from Szostak's "functional information" [70-75] or Abel's more refined "Prescriptive Information (PI)" [76-78].

A continuous flow of nutrients into and out of reaction vessels has shown that simple mixtures of thiols and [thioesters](#) could display a wide range of dynamical properties, such as biostability, oscillations and autocatalysis [79,80]. These authors believe that collectively autocatalytic cycles and biological networks could have emerged from simple mixtures of prebiotically plausible chemicals and mineral surfaces held out of equilibrium.

Many others have contributed to various chemical evolution and molecular evolution models [81-92].

The most recent papers on life-origin are quite varied [93-158].

The new synergistic discipline of Chemobrionics [46] addresses self-ordering precipitation processes, such as chemical gardens forming biomimetic micro- and nanotubular forms. Nonequilibrium physicochemical systems are studied. The assembly of material architectures under a flux of ions is exploited in various applications. Chemobrionics requires a combination of expertise in physics, chemistry, mathematical modeling, biology, and nanoengineering, complex theory, and nonlinear and materials sciences [46]. Unclear is where all this expertise came from in a prebiotic environment.

3. Co-evolution of eventual code biology and crude genetics

Another major thrust of abiogenic research right up to the present has been in the area of code biology and genetic code origin. The reality of multiple kinds of coding in all known life forms is difficult to deny. It is not merely metaphorical. It is quite real [20,78,159-166].

Wong, JT first published his co-evolution model 40 years ago [167]. His work on the model has continued through the decades [168-173]. Wong believes that genetic information arose from replicator induction by metabolite in accordance with the metabolic expansion law. Messenger RNA and transfer RNA stemmed from a template for binding the aminoacyl-RNA synthetase ribozymes employed to synthesize peptide prosthetic groups on RNAs in the Peptidated RNA World. Coevolution of the genetic code with amino acid biosynthesis is believed to have generated tRNA paralogs that identify a last universal common ancestor (LUCA) of extant life close to *Methanopyrus*, which in turn points to archaeal tRNA introns as the most primitive introns and the anticodon usage of *Methanopyrus* as an ancient mode of wobble. The prediction of the coevolution theory of the genetic code that the code should be a mutable code has led to the isolation of optional and mandatory synthetic life forms with altered protein alphabets [168].

Massimo DiGiulio has also led the way in code origin studies [174-202].

Romeu Guimaraes since the early 1990's has been refining his Self-Referential Genetic Code [203-214].

Marcello Barbieri has extensively emphasized the role of a myriad of codes in biology [215-235].

Biosemosis and code biology has become a major interest of many other quality investigators [78,136,153,155,236-244].

Critique of the best thus far abiogenesis models

Common to all of these models is the lack of natural-process *steering* toward proto-metabolic success. Controls are needed to organize, orchestrate and direct reactions toward biochemical pathway endpoints and successfully integrated biofunction. A causal mechanism for the generation of such controls is completely lacking in all naturalistic "chance and necessity" models. No scientific explanation is ever offered for the achievement of highly orchestrated metabolic success. No spontaneous integration of circuits is demonstrated. No basis is provided for systemization of any "biosystem." Only statistical possibility beyond all rational plausibility is provided. The only natural mechanisms offered are "could have been's," "may have been's" "suggests the possibility of..." No scientifically respectable mechanism of causation exists in any of these models to propel reactions toward functionality.

All known life is programmed and cybernetically computed. Computational "halting" is required. None of these models provide a source of "drive" toward formal fruitfulness. The goal of usefulness is just subconsciously presupposed in sharp contrast to our simultaneous contention that "evolution has no goal." Our supposedly scientific

hypothesis of achieved functionality boils down to little more than “happenstance.”

This author freely acknowledges that it seems grossly inadequate for a critique of thousands of abiogenesis papers to be so parsimonious. But science has always highly valued Occam’s razor in its evaluations of hypotheses, models and theories. It is highly significant that such a myriad of varied abiogenesis papers could all have the same basic flaw critique. The applicability of such parsimony to basically all naturalistic models lends great weight to the validity of this critique.

The flaw is this: Life requires controls, not just laws and constraints [5,21,160,165,245-248]. Abiogenesis models thus far have offered no explanation whatever for the blatantly obvious formal steering and controls that would have been required for orchestration of even the simplest proto-metabolism.

Not only abiogenesis, but all aspects of science require abstract formalisms.

The scientific method is formal, not physical. The tabulation of results and the formulation of conclusions is conceptual. “Laws” are abstract, formal mathematical equations and inequalities. All known life is programmed with sophisticated representational codes that are cybernetically processed. Life is literally computed. There is nothing physical about computation itself, though it may employ programmed physical machines (e.g., sub-cellular nanocomputers). Not only must the formal programming be explained, but the generation of the sophisticated molecular machinery that puts to shame any Turing machine.

Life is characterized by innumerable kinds of configurable switch-settings. The light switches on our walls are configurable switches. They are physical. But they are designed and engineered to be set only by formal Choice Causation, not by Physico-Dynamic Causation [11,76,78,159-161,164,247,249]. That is why we call them “configurable.” We can control how they are set to provide needed or desired functions. Gravity does not turn the light switch off; Choice Causation does. If the laws of motion controlled the lights, they would always be on, or always be off, by law.

The epigenetic controls that turn certain DNA segments on and off employ such configurable switches. The Choice Causation that controls many aspects of life can only be addressed by the field of engineering, not natural science.

The Periodic Table is formally organized. The codon table is altogether formal in its symbolic representation of instructions. Coding obeys shared arbitrary rules, not laws. Coding is layered and multidimensional [250], sometimes with instructions superimposed in opposite directions. No law of physics is going to explain this phenomenon.

Homeostatic metabolism is not achieved by law. It is achieved by Prescriptive Information (PI) [76-78,246,250-252]. All known life is programmed with Prescriptive Information (PI). Shannon’s statistical “information” doesn’t program anything. It merely measures choice *opportunities* [11,21,76,159-161,245,253,254]. Prescriptive Information provides function-producing instructions—pre-recorded programming choices that compute and halt.

Programming is useless without sophisticated equipment to process it. All known life is computed by molecular machines which must appear at the same place and time as the programming for either to have any usefulness. Each contributing component cannot appear separately over eons of time. And they must both come into existence “voluntarily,” obeying the same formal arbitrary rules. Laws cannot produce such arbitrarily-contingent rules. And laws cannot militate their obedience. Rules, unlike laws, can be readily broken. Biological systems are not forced to produce utility. They are steered and controlled toward formal pragmatic success, not merely constrained.

Nothing is more fundamental to life than Prescriptive Information (PI) [77,78]. Prescriptive Information choices are recorded into physical media similar to bar codes [162]. Recordation of instructions into a medium is secondary. The abstract, formal, nonphysical PI itself is what is primary. Turn a blind eye away from the fact of PI, and abiogenesis research is doomed. As in cybernetics, a functioning “controller” must exist.

Superb synthetic chemist Professor James Tour at Rice University enumerates many of the challenges that face abiogenic research in his 14-lecture series on abiogenesis [255]:

Remaining general synthetic chemistry challenges that remain for abiogenists to explain

- winenvironment has no sense of *sequencing* reactions needed for synthesis. Any organic chemist knows that the correct order of addition of each reagent is absolutely essential to have any hope of producing a purified adequate “yield.”
- Highly impure reagents dominate in prebiotic environments. These impurities ruin synthetic organic chemistry.
- Prebiotic environments cannot purify reactants, or achieve their delicate quantities needed for synthetic chemistry.
- Instead of using sequentially produced in-lab reagents in successive steps, extrinsically supplied homochiral populations of moieties must be ordered and used from Sigma-Adrich-like chemical plants. To produce a pure moiety, the engineered products themselves require

homochiral seeding. No such seeding or processes were available in prebiotic environments.

- Spontaneous reactions cannot do chemistry of mass mixtures because they gum up the works into worse than useless tars.
- Carbon forms strong bonds that do not hydrolyze easily, but can remodel with enzymes. Where did the highly specific functional enzymes come from in an inanimate environment?
- Hypothesized Silicon Life chemically dead-ends. The bonds are too rigid.
- Purely physicalistic abiogenic reactions in plausible prebiotic environments don't know how or when to stop.
- Highly intelligent chemists must keep separating out from ongoing reactions what is wanted and needed to prevent the inevitable tar end-product.
- It is very difficult to undo unhelpful reactions. Reactions cannot back up and do retakes with different moieties.
- Molecules form innumerable unwanted cross-reactions.
- "Helpful" molecules degrade almost as fast as they form. The half-life of Ribose is only five hours. All ribose would have been gone, even if it had formed, within two days in a magnesium rich early earth crust.
- Eschenmoser spent a lifetime trying to make functional RNA. He couldn't even produce five-carbon-sugar ribose naturalistically.
- The yield is often only 1-2% of most organic syntheses, creating a mass transfer crisis. This problem arises with any net movement of mass from one location or phase to another. Mass Transfer is involved in evaporation, drying, precipitation, absorption, membrane filtration, distillation, etc. With such low yields, even in carefully controlled synthetic chemistry labs, any environment soon runs out of resources.
- Aqueous environments prevent dehydration synthesis.
- Polypeptides cannot form in the presence of sugars or aldehydes.
- Amino acids and sugars cross react, resulting in insoluble polymers.

Molecules oxidize. Ammonia in a reducing environment is anything but helpful. A reducing environment is even more degrading. As of 2011, papers in such journals as Nature began presenting evidence and concluded that early earth's atmosphere was NOT reducing [251]. It does not really matter, however, whether it was a reducing or oxidizing environment. The necessary chemistry would not have spontaneously proceeded in either environment.

Amino acid mixes are not just of the 20 classic needed amino acids. Many other poisonous amino acids are mixed in that would have jammed abiogenesis.

Four fundamental kinds of molecules are needed for abiogenesis, not just proteins. Lipids, polysaccharides and nucleotides are also essential. All of these players present tremendous engineering problems to produce. Even then, they are only racemic.

The possible permutations of polysaccharides and lipids alone that can form is mind-boggling. Abiogenesis is not just a protein or nucleoside-formation problem. Selection of only the correct moieties is statistically prohibitive. Every published model of abiogenesis thus far can be shown to measure out with a Universal Plausibility Metric of ξ equaling <1.0 . This requires peer-review rejection of that model and manuscript for reason of scientific implausibility (The Universal Plausibility Principle) [252-254].

How many ways can 60 D-glucoses be linked together to make Starch?

Just six repeated units of D-glucose can form one trillion different branching and stereochemically distinct hexa-saccharides. Novice abiogenists don't appreciate the number of permutations from which the correct one must be isolated and used.

Nobody has ever made a self-purifying starch necessary for life in a relatively useful stereochemical form in a prebiotic-like environment. This doesn't even address a purely homochiral right-handed only ribose. Prebiotically plausible ribose generation models are all racemic and in such a mixture one could never find R-ribose exclusively.

Carbohydrate polymerization is statistically prohibitive without highly specific enzymes that were simply not present in a pre-biotic environment.

Polysaccharides have vast numbers of carbohydrate appendages. They have highly unique assemblies and important functional three-dimensional structures, the same as proteins. Polysaccharides (carbohydrates), therefore, contain enormous opportunity for information retention, which life fully uses.

Even when one already has D-glucose, it can have a large number of other possible forms mixed in as pollutants that terminate any hope of abiogenesis.

5-Carbon Carbohydrate is the hardest component of life to explain. Eschenmoser spent most of his career trying to make 5-carbon ribose so that he could start to make RNA. All he could make was 6-membered sugars rather than the five-membered sugars. So he tried to make an analog of ribose. He failed in the 70's and early 80's. Synthetic chemists have done better since, but only by literal chemical

engineering, not by “natural process,” and especially not by prebiotic natural process.

DNA tripartite needs ribose. Ribose is only one of the building blocks of the building blocks!

Virtually none of the building block precursors form spontaneously, especially not with enantiomeric excess. Homochirality of sugars and amino acids needs to be 100% for electron spin up or down to make life work.

Only two of the twenty amino acids can crystallize spontaneously to get only the L-optical isomer. Artificially manufactured L-amino acids are needed to crystallize additional L-amino acids. But even then, the yield is only around 1-2%. A 100% homochiral yield is needed.

Prebiotic reactions had no control over critically-needed stereochemistry.

Sophisticated enzymes not only make reactions possible, but speed them up by many orders of magnitude. Abiogenesis could never have occurred at the ridiculously slow pace of reactions apart from sophisticated enzymes. Early enzyme-like moieties would have been totally inadequate.

Enzymes check things out to make sure the reaction sequence is what is needed. Thus reaction rate does not constitute the only need for enzymes.

But enzymes, along with the other three essential classes of molecules needed for abiogenesis, cannot be made themselves without other enzymes, and without nucleosides.

Enzymes are even needed for polysaccharide and proper active transport lipids.

Dehydration synthesis of peptides and proteins cannot occur in an aqueous environment without very creatively designed and engineered enzymes.

All components must be *purely* enantiomeric for the required stereochemistry.

A pre-biotic environment can't generate homochirality.

Amino acids don't just have an A and a B prong. Half of the amino acids also have a C prong that winds up getting in the way. They couple in the main chain. Enzymes were needed from the very beginning of the process to make proper folding possible.

If you had a mixture of amino acids and sugars in the same place and time trying to make sugars, the amino acids have the same alcohol groups that would compete. The amine groups would compete in the same types of reaction and would preclude sugar formation.

The needed Electron Spin Selectivity (ESS)

- All living systems have chiral-induced *electron spin selectivity* critical for such function as active transport

through membranes. That is why the best synthetic chemists' yields are so pathetic, while subcellular life produces yields of 99.99999% purity.

- Electron spin polarization spins up or spins down. Homochirality only allows one electron spin to go through membrane channels, and not the other.
- Life can take two HO groups and produce *either* HOOH or $O_2 + 2 H^+$
- Chiral-induced electron spin selectivity permits selection of the correct option needed for abiogenesis.
- CISS correlates the electron spin with the homochiral twist direction.
- One surface is parallel, the other is anti-parallel. No such correlation existed in an inanimate environment to achieve needed function.

Folding of primary structures into functional secondary and tertiary structures

- Nobody has ever explained higher order structuring (engineering). Mere Gibbs-free energy minimization alone does not explain what needs to be explained for *functional* shapes to be produced.

The Levinthal 1.0 paradox asks how nature could have formed the needed sequencing of monomers in a linear chain of nucleosides or amino acids (primary structure) and have it wind up folding into the needed three-dimensional shape (secondary > tertiary structure) to become the needed specific enzyme [255,256].

Foldamers and chaperones are additional enzymes needed to assist the proper folding into the needed three-dimensional shape. But, how were *they* produced in a prebiotic environment?

Translational pausing is critical to protein folding [245,257-260]. Translational pausing is controlled, not constrained, by superimposed, multi-layered coding in the mRNA [245].

Alignment is not just a covalent bond problem, but a non-covalent spatial interaction problem also. The Levinthal 2.0 paradox addresses astronomical possibilities from which only a very few are usable. In many cases, this is where the Universal Plausibility Metric of life-origin models measures out to less than a ξ of < 1.0. The Universal Plausibility Principle is thus violated [254], requiring peer-review rejection of the model for lack of scientific *plausibility*. Mere possibility does not make a model scientifically plausible.

Coded Prescriptive Information is not just metaphorical.

- Nobody has solved the code problem for the sequencing of nucleotides.

No instructions (Prescriptive Information, PI) [21,71-73,156,158,231,241] exists in an inanimate, prebiotic environment. What was steering and controlling all this chemistry to avoid tar production?

Nucleic acid prescriptions have to be programmed with representational code. That instructional code then has to be instantiated into a replicable physical matrix in order to generate repeated production in the future. This is especially true for any newly needed enzyme. How did inanimate nature accomplish all this?

Gene editing (e.g., Crispr) is engineering, not natural science. How were genes edited into useful prescriptions prebiotically?

Production of the needed fatty acids, glycerol ethanolamine and lipids are all directed and engineered by coded Prescriptive Information [72,73].

Non-covalent interactions have to all be aligned because Prescriptive Information travels down these channels by electrostatic potentials.

Membranes

- A huge number of highly specific transmembrane proteins are needed.
- Glycoproteins, transport proteins, cholesterol, glycolipid, peripheral protein, internal protein, filaments of cytoskeleton, integral protein, surface protein, Alpha-helix protein, hydrophobic tails, hydrophilic heads, phospholipids, and highly specific carbohydrates are all needed.
- Lipase and many other enzymes are needed to make a real cell membrane. No enzymes of any kind are present in a micelle or vesicle environment. Not even enough functional peptides are there yet.
- The building blocks of lipids are fatty acids, phosphate, glycerol and ethanolamine. Very few of the incredible number of possible three-dimensional steric lipid formations fit the required bill for any conceivable active transport membrane or form of life to arise. Cell membranes have highly selective pores that allow only certain metabolites in, and preclude others from getting in. Then, there are critical excretory and secretory pumps.
- A bilipid layer micelle is a cartoon of an active transport membrane with highly selective pores. Not just osmotic gradients are required, but an incredible array of essential homeostatic requirements is maintained by cellular membranes in the simplest uni-cellular organisms.
- Outside lipids are different from inside lipids. Very complex layers of lipids exist even in organelles. They are highly organized with undeniably orchestrated functions,

not just self-ordered by law or constraint.

- Ionophore pores are highly selective. What exactly does selective mean? The answer to this question is not explainable by any law, constraint or the four known forces of physics. Selection has to be active, not passive, for a proto-cell to even faintly resemble life. A cell membrane requires thousands of different lipids and protein-lipid complexes.
- Monoacyl lipids are a catastrophe. Different diacyl lipids are required on the inside from the outside to perform the required proton gradient and pumps.
- Nobody knows how natural law could prebiotically make the outside of the cell membrane different from the inside in a functional sense. An inanimate environment sees no need to arrange the tails and heads so as to achieve function.

Lynn Margulis' model's [261-264] just presupposes organelles rather than explaining their origin. Membranes are critical to organelle function, too.

How are monoacyl lipids avoided in a prebiotic environment?

How were all the highly specific protein-lipid complexes made for selective transport.

How were nutrient ingestion, waste excretion, and secretion channels in the supposed "protocell" developed to make it even resemble a protocell rather than a pathetic vesicle or micelle.

A proton gradient is needed. How did prebiotic nature achieve that?

Protocells cannot be organized and engineered into existence by mere laws and constraints

- Bioengineers have clearly defined the minimum requirements for the simplest protocell to come to life. Of the 15 minimal essential components, absolutely none has been made in a prebiotically relevant environment!
- Chemists haven't even made pure yields of the four basic classes of molecules prebiotically, let alone the compounds of those basic classes.
- The protein-protein interactions alone in a simple yeast cell have $10^{79,000,000,000}$ possibilities. There are only 10^{90} elemental particles in the cosmos!

The needed manufacturing plant

- Inanimate nature must have had all 20 amino acids (or possibly 22), and only those amino acids, available in the same place at the same time to make most ANY enzyme.
- Even if you have all 20 at the same place and time, how

is the cross-linking problem solved caused by half of all amino acids having a C prong? Enzymes are required to keep that from happening. But in order for those enzymes to form, they themselves had the exact same problem.

- 2'5' dinucleotide contamination prevails. 2'5' dinucleotides cannot code for protein! 3'5' dinucleotides are essential for abiogenesis.
- Yet spontaneously formed RNA yields a mixture of 75-85% 2'-5' dinucleotides. This would have precluded naturalistic abiogenesis. If only 1% were 2'5', NO peptides can be instructed or constructed.
- Each amino acid has to have three nucleotides coding for it. If one out of three has a 2'5', no amino acid is coded.
- Small interfering RNA (siRNA) is formed from 2'5' RNA: siRNA stops translation. In RNA, the 2'5' linkages (30 to 70%) act like siRNA
- Chemists have to store reagents at -112 degrees F (!) to make 3'-5' dinucleotides
- Nucleobases need protection. The phosphate needs activation.
- To make nucleotides in the lab, glassware must be washed with 3% H₂O₂. Then, the glasswork requires ten washes with RNase free water. This could never have happened on early earth.
- Primed RNA has never duplicated more than 10% of itself.

A hands-off, spontaneous formose reaction is an implausible source of a pure dextro-ribose and RNA. Many of the chemical species generated in controlled laboratory conditions are nothing more than carboxylic acids [265]. To any qualified chemist, a spontaneous formose reaction is not the explanation hoped for.

You cannot get the moieties needed to do any sort of synthetic chemistry work needed for life to form even when the world's finest synthetic chemists are controlling the all of the many needed processes.

Dipyranose's interactome has 10⁷⁹ billion potential combinations. There are only 10⁹⁰ elementary particles in the cosmos! Where is this objective reality in the minds of naïve, simplistic thinkers when they argue, "The life-origin problem has largely been solved"?

Even if you have all 20 amino acids, they must be separated and isolated.

The smartest micelle-vesicle researchers cannot design and engineer even an adequate active transport membrane, let alone a real protocell. Any progress in that direction is always proven by Materials and Methods to be teleological (which, of course, we euphemistically try to reduce to "teleonomy.")

All of these papers defeat the very purpose for which they were written: to demonstrate the capabilities of *naturalistic* physicalism. What is demonstrated instead is humanistic creationism. No human agency, . . . no experimental success!.

Heritability

- Inorganic abiogenic Metabolism-First models have no heritability and no way to sustain any accidental "successes," not that a prebiotic environment would have known what a "success" was.
- How would an inorganic or organic composomal reaction sequence have been preferentially preserved, and by what means?

Eons of time

There's not enough time in 14 billion years, and not enough elementary particles in the cosmos, to overcome relevant probability bounds [266].

Inanimate nature could not have collected in piecemeal fashion all components through long periods of time. There would be no basis for secondary, passive selection without a superior final product to differentially survive. Organisms first have to be alive to differentially survive best.

Eons of time is not the savior of abiogenesis theory. Eons of time is it's greatest enemy.

The contention that "Cells were simpler back then."

- How simple were they, asks synthetic chemist Prof Tour [250]?
- The simplest holistically "living" cell would have had to manifest right from the beginning:
- DNA replication, repair; restriction, modification
- basic transcription machinery
- Amino-acyl tRNA synthesis:
- t-RNA maturation and modification
- Tremendously *conceptually* complex Ribosomes
- Ribosomal proteins and their organization and orchestration
- Ribosome function, maturation and modification
- Translation factors
- Controlled RNA degradation
- Protein processing, folding and secretion
- Superimposed, multilayered coding (Superimposed codes of Ontological Prescriptive Information (PI_o) [73,246] purposely slows or speeds up the translation-decoding process within the ribosome. Variable translation rates

help prescribe functional folding of the nascent protein [245]. Protein folding would have been critical right from the start.)

- Cellular replication is highly prescribed and controlled. It is not just “cell division.”
- Intra-cellular molecular transport
- Glycolysis
- Proton motive force generation
- Pentose phosphate pathway
- Lipid metabolism
- Biosynthesis of nucleotides and cofactors
- Minimization of heat release. The need to mitigate chiral-induced spin selectivity to prevent cellular heat stroke. Homochirality had to be there from the beginning. Homochirality could not have been developed through time. Any protocell would have burned up without chirality.
- Membrane transport is highly selective and exquisitely tailored to cellular needs.
- Micellar, vesicle and proto-cellular concepts are not immune to such requirements.
- Excretion of waste, ingestion of nutrients, secretion—all mediated by a true cell membrane that thoroughly embarrasses any lipid bilayer micelle/vesicle of a supposed protocell.
- No purified reagents, buffers, or catalysts were present in a prebiotic environment. Everything had to be manufactured from the simplest molecules: CH₄, NH₃, CO₂, O₂, H₂S, sulphate, H₂O, formaldehyde, carbonate, formate and cyanide. Many of these needed molecules are lethal to life.
- No source of phospholipids or nucleosides existed in an inanimate environment; no human-designed coupling agents or protecting groups; no H₂O₂ and distilled-water-rinsed and dried flasks; no purified solvents; no vacuum pumps or degassing steps; no ability to arrest or restart reactions when needed; no method of transfer of reagents from one flask to the next for critical sequential steps done in the required order, etc.
- The Materials and Methods in abiogenesis research papers are most often not *prebiotically relevant or plausible*.

Code, Prescriptive Information (PI) and biosemiosis considerations

A common contention is that the instructions to organize and orchestrate life came from a template, typically from

Table 1: Science seeks to optimize our epistemology of objective reality. The following basic dichotomies/contrasts are repeatedly observed within presumed objective reality

Forced regularities, laws and constraints	vs.	Opportunity for change despite law
Monotony/Sameness	vs.	Contingency/Possibilities
Noncreative automaticity	vs.	Originality/creativity/usefulness
Zero perception of and indifference to utility	vs.	Awareness & Valuation of utility
Zero effort toward achieving usefulness	vs.	Persistent pursuit of usefulness
Spontaneous occurrences	vs.	Purposefully orchestrated events
Constraints	vs.	Controls/Steering toward utility
Physics “Work”	vs.	Functional formal work
Complexity	vs.	Conceptional Complexity
Isness/Whatever happens to exist	vs.	Means/Methods/“In order to’s . . .”
Physicodynamic Causation	vs.	Choice Causation
Natural science mechanisms	vs.	Engineering mechanisms

a ribozyme or other RNA analog (an auto-catalytic RNA-like precursor). The question is, where did the *templated instructions* come from? Mere Clay surface? Since when does mere clay (e.g., montmorillonite) contain formal instructions to do *anything* sophisticated?

A short 200 mer protein has 20²⁰⁰ permutations. And that phase space would be racemic. The number of permutations is way larger than 10⁵⁰. Only a very small percentage of these permutations fold into functional tertiary structures [272]. Thus, most Protein-First models of abiogenesis are statistically prohibitive. But the real questions are, “How did inanimate nature sequence linear digital instructions out of this phase space?” How did prebiotic nature assign formal code assignments and meaning to those assignments? What were the scientific mechanisms for achieving transcription and translation? These are *not* chemical reaction problems. They are programming delegations. Coding and translation from one language into another is *not* physico-chemical. It is abstract. Biosemiosis can be instantiated into physical symbol vehicles (tokens) within a Material Symbol System [159,164,273-276]. But the coded instructions themselves are abstract, not physical. Prescriptive Information (PI) [11,21,76-78,160,162,245,249,250,254] cannot be reduced to physicality.

We have no explanation for the interactome’s *conceptual* complexity. To instruct sophisticated function requires abstract concept. Concept is formal, not physical. Concept can be instantiated into physicality according to rules and

arbitrary code assignments, but concept cannot be mustered by the laws of motion or mere physico-dynamic constraints [11,20,21,78,160-162,246,247,254]. Even a protometabolism would have required controls rather than constraints [11,21,76,160,161,254]. Controls emanate from concept, not fixed redundant law. They are choice contingent. Controls fall into the fundamental category of Choice Causation (CC), not Physicodynamic Causation (PC) [5,20,21,162,164,165,246-248,277,278].

Materials and Methods invariably prove the opposite of what physicalist abiogenists wanted to prove. Experimental design consistently betrays “investigator involvement.” Every reactant is carefully and actively selected. Reactions are steered to desired end-points. While the title of the paper invokes the contention of “natural process,” the experimental achievements are all invariably engineered by agent-controlled lab techniques. Exact measurements, deliberate and careful sequencing of reactions and critical removals of reactants at the needed times from the reaction environment are the most common features of agent-controlled experimental design. Neglect of these details, and organic labs become tar factories every time.

Panspermia Considerations

Panspermia appeals to the possibility that life formed elsewhere in the cosmos and was somehow transported to earth (e.g., on meteorites). Panspermia was originally suggested by Hoyle and Wickramasinghe [279,280]. It has been a hot topic of discussion ever since right up to the present time [281-295].

Astrobiology is the study of the origin, evolution, distribution, and future of life in the Universe, not just on earth [296-309]. Astrobiology encompasses panspermia.

Why is astrobiology so interested in the possibility of panspermia? Models of abiogenesis on earth quickly incur gross violations of relevant probability bounds. Worse yet, the Universal Plausibility Metric often invokes the Universal Plausibility Principle, thereby necessitating the rejection of most abiogenesis models on earth by peer review (not that most editors abide by this well documented Principle!). When statistical prohibitiveness becomes evident, a common appeal is to the notion of panspermia. The larger-than-earth phase space increases probability bounds and renders any seemingly statistically prohibitive model more plausible. But does it?

One of the components in calculating the Universal Plausibility Metric is time restriction since the Big Bang. The age of the earth is believed to be 3.9 billion years. The age of the cosmos is believed to be 14 billion years. Panspermia theory increases the odds of spontaneous abiogenesis somewhere in the cosmos by a factor of around 3.5 compared

to abiogenesis hypotheses on earth. When the probability of abiogenesis on earth is calculated to be one chance in 10^{90} , or far worse, for example, multiplying that statistically prohibitive unlikelihood by a mere factor of 3.5 effectively does *nothing* to overcome the statistical prohibitiveness of that model.

A little background might be helpful in understanding the time probability bound inherent in the Universal Plausibility Metric [257,259]. The shortest time any physico-dynamic transition requires before a chemical reaction can take place is 10 femtoseconds [310-314]. A femtosecond is 10^{-15} seconds. Complete chemical reactions, however, rarely take place faster than the picosecond range (10^{-12} secs). Most biochemical reactions, even with highly sophisticated enzymatic catalysis, take place no faster than the nano (10^{-9}) and usually the micro (10^{-6}) range. To be exceedingly generous (perhaps overly permissive of the capabilities promoted by any chance hypothesis), the Universal Plausibility Metric uses 100 femtoseconds as the shortest chemical reaction time. This is mathematically converted to 10^{43} possible transactions per second as the fastest chemical reactions could conceivably take place in the best of theoretical scenarios. Those possible reactions per second are then multiplied by the 10^{17} second age of the cosmos since the Big Bang. The result is a limit on even quantum reaction possibilities with reference to time. This becomes a major factor in the required rejection by peer review of implausible chance hypotheses. Such models are defined *quantitatively*, not merely subjectively, to be scientifically irresponsible by the Universal Plausibility Principle [257,259].

The idea of panspermia is also highly controversial for chemical and informational reasons, and thus fosters many other objections [315-318]. Digiulio seems to reject the notion of panspermia altogether [319].

Very sophisticated molecules are sometimes found on meteorites, but they are not enantiomerically pure. Rarely, you can get up to 70% enantiomeric excess, but still way too contaminated to spontaneously contribute to life, which would require 100% enantiomeric excess.

Meteorites do not have the right chemical mixture to be relevant to life origin. Nobody has shown that meteorites or interstellar space have the right usable components to contribute to abiogenesis because they would have been too inseparable in a prebiotic environment. Any organic reactions would have produced TAR. Natural process cannot use such a mixture of compounds. Only racemic compounds are found on meteorites. These mixtures are simply not productive of anything relevant to life.

In short, neither panspermia nor the more general astrobiology have thus far provided the missing clues, or solved the Universal Plausibility Principle elimination of wild imaginations.

Discussion

One reason the abiogenesis problem is such a tough nut to crack is the mind-boggling *constellation* of challenges. It would be bad enough if all we had to address was the homochirality problem in a prebiotic environment. But there are hundreds of more challenges of equal perplexity, all requiring orchestration of a “Rachmaninoff piano concerto” by inanimate nature.

We are literally just scratching the surface of the many outright *engineering* requirements necessary for abiogenesis. When these engineering requirements are swept under the rug, ignored or fallaciously denied, what hope is there for abiogenesis research to finally make any real progress?

All of these statistically prohibitive “natural” events are conveniently converted into certainties by blind-belief, unsubstantiated concepts such as “Emergence” and “Self-Organization.” We somehow manage to forget that all of these individual statistically prohibitive probabilities have to be multiplied together to predict the likelihood of even a protocell. All probability bounds are grossly exceeded [271], and certainly the Universal Plausibility Principle [257,259].

How could anything organize itself into existence? It would have to already exist to organize itself into existence. “Self-organization” is a tautology at best. But far worse, it is a logical impossibility. “Self-organization” is an utterly self-contradictory nonsense term and notion that has no place in scientific literature.

Spontaneous “emergence” of such highly integrated circuits and biochemical pathways that yield usefulness only on the thirteenth step (e.g., the Krebs cycle) is nothing more than a pipe dream. Nothing exists in peer-reviewed literature that demonstrates spontaneous emergence of sophisticated products, let alone life. Self-ordering can spontaneously emerge (e.g., tornadoes), but not bona fide formal organization. Whenever “emergence” is pontificated, the Materials and Methods section of the paper exposes embarrassing extensive investigator involvement in experimental design and execution that alone made any supposed “emergence” possible.

Everything about life is steered and controlled toward “success.” And it had to be that way from the start.

The only thing truly scientific we can say is to admit that we don’t have a clue how life came into existence from the standpoint of natural process *alone*. But we dare not admit that. That would threaten our *purely metaphysical* worldview that “*physicalism is sufficient*.” That would be “unscientific!” Never mind that mathematics, logic and the scientific method themselves are all non-physical.

What we repeatedly observe even in the simplest-known

life forms is not just *apparent* engineering. We observe blatant, undeniable, actual engineering. Life is computation. Life is cybernetic processing of bona fide programming. Life is controlled, not constrained [21]. Life originates only from the far side of The Cybernetic Cut [254,320]. Life is not just complex. Life is *conceptually* complex. Life’s molecular machines, transport molecules, and nanocomputers put Turing machines and cell phones to shame. Life IS engineering, whether we insist on putting on blind folds to the fact, or not.

How far would we get explaining the origin of smart phones using nothing but the laws of motion, the four known forces of physics, chemistry and initial constraints? Would anyone in their right mind seriously expect to be able to elucidate the origin of a smart phone limiting their investigation to nothing but spontaneous physico-chemical interactions alone? What would be the source of such idiocy? Certainly not anything scientific or rational.

The simplest known life, such as an organism like *Micoplasma genitalium*, which is not even free-living, puts to shame the latest smart phone in its engineering. The same is true of just the ribosome, or any organelle.

Has any scientist ever observed a smart phone spontaneously generate from “hands off” physics and chemistry alone? Would there be some reason we would feel justified in appealing to eons of time to explain the causation of smart phones? Time is not a cause of any effect. The prohibition is one of logic theory absolutes, not best-thus-far induction. Law cannot generate engineering phenomena in any amount of time. Multiverse notions are purely metaphysical constructs, not science.

Conclusion

Why is abiogenesis such a tough nut to crack? Because we tie our hands behind our backs metaphysically before ever beginning any scientific investigation. We proclaim by purely metaphysical faith that physicality and natural law are alone sufficient. We philosophically deny the reality of steering and control as opposed to mere law and constraint.

For kids, we sponsor “Science and Engineering Fairs.” Why the dichotomy?

We know full well that some phenomena can be addressed by natural science; other phenomena can be addressed only by the field of engineering. What’s the difference in subject matter? Engineering involves Choice Causation rather than just Physico-Dynamic Causation alone [5,11,20,21,76,78,159-165,245,247-249,253,254,273,278,321].

We have no problem granting each domain of investigation, natural science vs. engineering, its space and methodological route to progress—until, that is, it comes to life origin science. Any engineering realities are immediately disallowed no matter how obvious and undeniable.

We spend all day long studying how much more *conceptually* complex, not just complex, life is than smart phones. But for purely metaphysical reasons, not scientific reasons, we refuse to admit the obvious, that explaining life and life origin is an engineering problem, not just a natural science problem.

As long as we disallow legitimate engineering questions and answers relating to abiogenesis, the field is going nowhere but into deeper frustration and disappointment!

We are slow learners indeed! Pure physicalism is a Kuhnian Paradigm Rut [322] far worse than the one in Copernicus' day!

Acknowledgements

This paper relies heavily upon the abiogenesis work of synthetic chemist Prof. James Tour of Rice University. Many seasoned abiogenists are simply not aware of the innumerable daunting chemical challenges that exist in areas of abiogenic research not immediately their own.

References

- Garcon, N. Chance and necessity. Hum Vaccin 2008, 4, 173-175, doi:10.4161/hv.4.3.6226.
- Koonin, E.V. Chance and necessity in cellular response to challenge. Mol Syst Biol 2007, 3, 107, doi:msb4100152 10.1038/msb4100152.
- de Duve, C. Chance and necessity revisited. Cell Mol Life Sci 2007, 64, 3149-3158, doi:10.1007/s00018-007-7442-y.
- Pal, C.; Papp, B.; Lercher, M.J.; Csermely, P.; Oliver, S.G.; Hurst, L.D. Chance and necessity in the evolution of minimal metabolic networks. Nature 2006, 440, 667-670.
- Trevors, J.T.; Abel, D.L. Chance and necessity do not explain the origin of life (Also available at www.DavidAbel.us Last accessed 7/20/3034). Cell Biol Int 2004, 28, 729-739, doi:S1065-6995(04)00141-6.
- Sariola, H. [The chance and necessity of life]. Duodecim; laaketieteellinen aikakauskirja 2002, 118, 2425-2431.
- Carroll, S.B. Chance and necessity: the evolution of morphological complexity and diversity. Nature 2001, 409, 1102-1109.
- Schuster, P.; Fontana, W. Chance and necessity in evolution: lessons from RNA. Physica D 1999, 133, 427-452.
- Lorsch, J.R.; Szostak, J.W. Chance and necessity in the selection of nucleic acid catalysts. Acc Chem Res 1996, 29, 103-110.
- Monod, J. Chance and Necessity; Knopf: New York, 1972.
- Abel, D.L. What utility does order, pattern or complexity prescribe? (<http://DavidAbel.us> Last accessed in July, 2024). In The First Gene: The Birth of Programming, Messaging and Formal Control, Abel, D.L., Ed.; LongView Press--Academic, Biol. Res. Div.: New York, N.Y., 2011; pp. 75-116.
- Hamming, R.W. The unreasonable effectiveness of mathematics. The American Mathematical Monthly 1980, 87, 81-90.
- Wigner, E.P. The unreasonable effectiveness of mathematics in the natural sciences. Comm. Pure Appl. 1960, 13.
- Shenhav, B.; Oz, A.; Lancet, D. Coevolution of compositional protocells and their environment. Philos Trans R Soc Lond B Biol Sci 2007, 362, 1813-1819, doi:10.1098/rstb.2007.2073.
- Shenhav, B.; Segre, D.; Lancet, D. Mesobiotic emergence: molecular and ensemble complexity in early evolution. Adv. Complex Syst 2003, 6.
- Segre, D.; Lancet, D. Composing Life. EMBO Rep 2000, 1, 217-222.
- Segre, D.; Ben-Eli, D.; Lancet, D. Compositional genomes: prebiotic information transfer in mutually catalytic noncovalent assemblies. Proc Natl Acad Sci U S A 2000, 97, 4112-4117.
- Segre, D.; Lancet, D.; Kedem, O.; Pilpel, Y. Graded autocatalysis replication domain (GARD): kinetic analysis of self-replication in mutually catalytic sets. Orig Life Evol Biosph 1998, 28, 501-514.
- Tessera, M. Is pre-Darwinian evolution plausible? Biology Direct 2018, 13, doi:https://doi.org/10.1186/s13062-018-0216-7.
- Abel, D.L. The capabilities of chaos and complexity (Also available at www.DavidAbel.us Last accessed July, 2024). Int. J. Mol. Sci. 2009, 10, 247-291 doi: https://doi.org/10.3390/ijms10010247.
- Abel, D.L. Constraints vs. Controls: Progressing from description to prescription in systems theory (<http://DavidAbel.us> Last accessed 6/2024). Open Cybernetics and Systemics Journal 2010, 4, 14-27, doi:10.2174/1874110X01004010014.
- Thaxton, C.B., Bradley, Walter L, Olsen, Roger L, Tour, James;, et al. The Mystery of Life's Origin Discovery Institute: 2020.
- Cairns-Smith, A.G. Chemistry and the missing era of evolution. Chemistry 2008, 14, 3830-3839, doi:10.1002/chem.200701215.

24. Cairns-Smith, A.G. Seven Clues to the Origin of Life, Canto ed.; Cambridge University Press: Cambridge, 1990; p. 130.
25. Cairns-Smith, A.G. Genetic Takeover and the Mineral Origin of Life; Cambridge University Press: Cambridge, 1982.
26. Cairns-Smith, A.G. Takeover mechanisms and early biochemical evolution. *Biosystems* 1977, 9, 105-109.
27. Cairns-Smith, A.G.; Walker, G.L. Primitive metabolism. *Curr Mod Biol* 1974, 5, 173-186.
28. Cairns-Smith, A.G. The origin of life and the nature of the primitive gene. *J Theor Biol* 1966, 10, 53-88.
29. Kaschke, M.; Russell, M.J.; Cole, W.J. [FeS/FeS₂], a redox system for the origin of life (some experiments on the pyrite-hypothesis). *Orig Life Evol Biosph* 1994, 24, 43-56.
30. MacLeod, G.; McKeown, C.; Hall, A.J.; Russell, M.J. Hydrothermal and oceanic pH conditions of possible relevance to the origin of life. *Orig Life Evol Biosph* 1994, 24, 19-41.
31. Russell, M.J.; Hall, A.J. The emergence of life from iron monosulphide bubbles at a submarine hydrothermal redox and pH front. *Journal Geological Society London*, 1997, 154, 377-402.
32. Russell, M.J.; Hall, A.J.; Martin, W. Serpentinization as a source of energy at the origin of life. *Geobiology* 2010, 8, 355-371, doi:10.1111/j.1472-4669.2010.00249.x.
33. Martin, W.; Baross, J.; Kelley, D.; Russell, M.J. Hydrothermal vents and the origin of life. *Nat Rev Microbiol* 2008, 6, 805-814, doi:10.1038/nrmicro1991.
34. Russell, M.J.; Martin, W. The rocky roots of the acetyl-CoA pathway. *Trends in biochemical sciences* 2004, 29, 358-363.
35. Martin, W.; Russell, M.J. On the origins of cells: a hypothesis for the evolutionary transitions from abiotic geochemistry to chemoautotrophic prokaryotes, and from prokaryotes to nucleated cells. *Philos Trans R Soc Lond B Biol Sci* 2003, 358, 59-83; discussion 83-85.
36. Martin, W.; Russell, M. On the origins of cells: a hypothesis for the evolutionary transitions from abiotic geochemistry to chemoautotrophic prokaryotes, and from prokaryotes to nucleated cells. . *Philosophical Transactions of the Royal Society, B* 2002, doi:10.1098/rstb.2002.1183.
37. Dagan, T.; Martin, W. The tree of one percent. *Genome Biol* 2006, 7, doi:10.1186/gb-2006-7-10-118.
38. Koonin, E.V.; Martin, W. On the origin of genomes and cells within inorganic compartments. *Trends Genet* 2005, 21, 647-654, doi:10.1016/j.tig.2005.09.006.
39. Lane, N.; Allen, J.F.; Martin, W. How did LUCA make a living? Chemiosmosis in the origin of life. *Bioessays* 2010, 32, 271-280, doi:10.1002/bies.200900131.
40. Hazkani-Covo, E.; Zeller, R.M.; Martin, W. Molecular poltergeists: mitochondrial DNA copies (numts) in sequenced nuclear genomes. *PLoS genetics* 2010, 6, doi:10.1371/journal.pgen.1000834.
41. Dagan, T.; Martin, W. Ancestral genome sizes specify the minimum rate of lateral gene transfer during prokaryote evolution. *Proc Natl Acad Sci U S A* 2007, 104, doi:10.1073/pnas.0606318104.
42. Timmis, J.N.; Ayliffe, M.A.; Huang, C.Y.; Martin, W. Endosymbiotic gene transfer: organelle genomes forge eukaryotic chromosomes. *Nature reviews* 2004, 5, doi:10.1038/nrg1271.
43. Martin, W.; Rujan, T.; Richly, E.; Hansen, A.; Cornelsen, S.; Lins, T.; Leister, D.; Stoebe, B.; Hasegawa, M.; Penny, D. Evolutionary analysis of Arabidopsis, cyanobacterial, and chloroplast genomes reveals plastid phylogeny and thousands of cyanobacterial genes in the nucleus. *Proc Natl Acad Sci U S A* 2002, 99, doi:10.1073/pnas.182432999.
44. Martin, W. Mosaic bacterial chromosomes: a challenge en route to a tree of genomes. *Bioessays* 1999, 21, doi:10.1006/bio.1999.2-b.
45. Martin, W.; Brinkmann, H.; Savonna, C.; Cerff, R. Evidence for a chimeric nature of nuclear genomes: Eubacterial origin of eukaryotic glyceraldehyde-3-phosphate dehydrogenase genes. *Proc Natl Acad Sci U S A* 1993, 90, doi:10.1073/pnas.90.18.8692.
46. Cardoso, S.S.S.; Cartwright, J.H.E.; Cejkova, J.; Cronin, L.; De Wit, A.; Giannerini, S.; Horvath, D.; Rodrigues, A.; Russell, M.J.; Sainz-Diaz, C.I.; et al. Chemobionics: From Self-Assembled Material Architectures to the Origin of Life. *Artif Life* 2020, 26, 315-326, doi:10.1162/artl_a_00323.
47. Camprubi, E.; de Leeuw, J.W.; House, C.H.; Raulin, F.; Russell, M.J.; Spang, A.; Tirumalai, M.R.; Westall, F. The Emergence of Life. *Space Science Reviews* 2019, 215, 56, doi:10.1007/s11214-019-0624-8.
48. Russell, M.J.; Barge, L.M.; Bhartia, R.; Bocanegra, D.; Bracher, P.J.; Branscomb, E.; Kidd, R.; McGlynn, S.; Meier, D.H.; Nitschke, W.; et al. The Drive to Life on Wet and Icy Worlds. *Astrobiology* 2014, 14, 308-343, doi:10.1089/ast.2013.1110.
49. Schoepp-Cothenet, B.; van Lis, R.; Atteia, A.; Baymann, F.; Capowiez, L.; Ducluzeau, A.; Duval, S.; Ten Brink,

- F.; Russell, M.; Nitschke, W. On the universal core of bioenergetics. *Biochim Biophys Acta* 2012.
50. McGlynn, S.E.; Kanik, I.; Russell, M.J. Peptide and RNA contributions to iron-sulphur chemical gardens as life's first inorganic compartments, catalysts, capacitors and condensers. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences* 2012, 370, 3007-3022, doi:10.1098/rsta.2011.0211.
 51. Branscomb, E.; Russell, M.J. Turnstiles and bifurcators: The disequilibrium converting engines that put metabolism on the road. *Biochim Biophys Acta* 2012, doi:S0005-2728(12)01042-0.
 52. Simoncini, E.; Russell, M.; Kleidon, A. Modeling Free Energy Availability from Hadean Hydrothermal Systems to the First Metabolism. *Origins of Life and Evolution of Biospheres* 2011, 41, 529-532, doi:10.1007/s11084-011-9251-4.
 53. Russell, M., (Ed.) *Abiogenesis: How Life Began. The Origins and Search for Life.* Cosmology Science Publishers: Cambridge, 2011.
 54. Mielke, R.E.; Robinson, K.J.; White, L.M.; McGlynn, S.E.; McEachern, K.; Bhartia, R.; Kanik, I.; Russell, M.J. Iron-Sulfide-Bearing Chimneys as Potential Catalytic Energy Traps at Life's Emergence. *Astrobiology* 2011, 11, 933-950, doi:10.1089/ast.2011.0667.
 55. Mielke, R.E.; Russell, M.J.; Wilson, P.R.; McGlynn, S.E.; Coleman, M.; Kidd, R.; Kanik, I. Design, fabrication, and test of a hydrothermal reactor for origin-of-life experiments. *Astrobiology* 2010, 10, 799-810, doi:10.1089/ast.2009.0456.
 56. Baaske, P.; Weinert, F.M.; Duhr, S.; Lemke, K.H.; Russell, M.J.; Braun, D. Extreme accumulation of nucleotides in simulated hydrothermal pore systems. *Proc Natl Acad Sci U S A* 2007, 104, 9346-9351, doi:10.1073/pnas.0609592104.
 57. Russell, M.J. Geochemistry. The importance of being alkaline. *Science* 2003, 302, 580-581.
 58. Bonfio, C.; Russell, D.A.; Green, N.J.; Mariani, A.; Sutherland, J.D. Activation chemistry drives the emergence of functionalised protocells. *Chem Sci* 2020, 11, 10688-10697, doi:10.1039/d0sc04506c.
 59. Bonfio, C.; Russell, D.A.; Green, N.J.; Mariani, A.; Sutherland, J.D. Activation chemistry drives the emergence of functionalised protocells. *Chemical Science* 2020, 11, 10688-10697, doi:10.1039/D0SC04506C.
 60. Mariani, A.; Russell, D.A.; Javelle, T.; Sutherland, J.D. A Light-Releasable Potentially Prebiotic Nucleotide Activating Agent. *Journal of the American Chemical Society* 2018, 140, 8657-8661, doi:10.1021/jacs.8b05189.
 61. Nalbantoglu, O.U.; Russell, D.J.; Sayood, K. Data Compression Concepts and Algorithms and their Applications to Bioinformatics. *Entropy (Basel)* 2010, 12, 34, doi:10.3390/e12010034.
 62. Griffiths, P., E.; Gray, R., D. Discussion: Three Ways to Misunderstand Developmental Systems Theory. *Biology and Philosophy* 2005, 20, 417-425.
 63. Liu, Z.; Wu, L.F.; Xu, J.; Bonfio, C.; Russell, D.A.; Sutherland, J.D. Harnessing chemical energy for the activation and joining of prebiotic building blocks. *Nat Chem* 2020, 12, 1023-1028, doi:10.1038/s41557-020-00564-3.
 64. Segre, A.M.L., Doron. A Statistical Chemistry Approach to the Origin of Life. *CHEMTRACTS-BIOCHEMISTRY AND MOLECULAR BIOLOGY* 2019, 12, 382-397.
 65. Kahana, A.; Schmitt-Kopplin, P.; Lancet, D. Enceladus: First Observed Primordial Soup Could Arbitrate Origin-of-Life Debate. *Astrobiology* 2019, 19, 1263-1278, doi:10.1089/ast.2019.2029.
 66. Lancet, D.; Shenhav, B. Compositional lipid protocells: reproduction without polynucleotides. In *Protocells: Bridging Nonliving and Living Matter*, Rasmussen, S., Bedau, M.A., Chen, L., Deamer, D., Krakauer, D.C., Packard, N.H., Stadler, P.F., Eds.; MIT Press: Cambridge, MA, 2009.
 67. Inger, A.; Solomon, A.; Shenhav, B.; Olender, T.; Lancet, D. Mutations and lethality in simulated prebiotic networks. *J Mol Evol* 2009, 69, 568-578, doi:10.1007/s00239-009-9281-y.
 68. Segre, D.; Ben-Eli, D.; Deamer, D.W.; Lancet, D. The lipid world. *Orig Life Evol Biosph* 2001, 31, 119-145.
 69. Goldford, J.E.; Hartman, H.; Marsland, R., 3rd; Segre, D. Environmental boundary conditions for the origin of life converge to an organo-sulfur metabolism. *Nat Ecol Evol* 2019, 3, 1715-1724, doi:10.1038/s41559-019-1018-8.
 70. Sharov, A.A. Functional Information: Towards Synthesis of Biosemiotics and Cybernetics. *Entropy (Basel)* 2010, 12, 1050-1070, doi:10.3390/e12051050.
 71. Sharov, A.A. Role of Utility and Inference in the Evolution of Functional Information. *Biosemiotics* 2009, 2, 101-115, doi:10.1007/s12304-008-9032-2.
 72. Sharov, A. Role of utility and inference in the evolution of functional information. *Biosemiotics* 2009, 2, 101-115.
 73. Hazen, R.M.; Griffin, P.L.; Carothers, J.M.; Szostak, J.W. Functional information and the emergence of

- biocomplexity. *Proc Natl Acad Sci U S A* 2007, 104 Suppl 1, 8574-8581.
74. McIntosh, A.C. Functional Information and Entropy in living systems. In *Design and Nature III: Comparing Design in Nature with Science and Engineering*, Brebbia CA, Suchrov LJ, P, P., Eds.; WIT Press: U.K., 2006.
75. Szostak, J.W. Functional information: Molecular messages. *Nature* 2003, 423, 689.
76. 76. Abel, D.L. Primordial Prescription: The Most Plaguing Problem of Life Origin Science LongView Press Academic: New York, N. Y., 2015.
77. D'Onofrio, D.J.; Abel, D.L.; Johnson, D.E. Dichotomy in the definition of prescriptive information suggests both prescribed data and prescribed algorithms: biosemiotics applications in genomic systems (Also available at www.DavidAbel.us last accessed 7/20/2024). *Theor Biol Med Model* 2012, 9, 8, doi:10.1186/1742-4682-9-8.
78. Abel, D.L. The biosemiosis of prescriptive information (also available at www.DavidAbel.us Last accessed July, 2024). *Semiotica* 2009, 2009, 1-19, doi:10.1515/semi.2009.026.
79. Goldford, J.E.; Segrè, D. Modern views of ancient metabolic networks. *Current Opinion in Systems Biology* 2018, 8, 117-124, doi:<https://doi.org/10.1016/j.coisb.2018.01.004>.
80. Jacobs, C.; Segre, D. Organization principles in genetic interaction networks. *Adv Exp Med Biol* 2012, 751, 53-78, doi:10.1007/978-1-4614-3567-9_3.
81. Ali, A. Extraterrestrial abiological synthesis of organics in space and its significance to chemical evolution and the origin of life: Comment on "A never-ending story in the sky: The secrets of chemical evolution" by Cristina Puzzarini and Vincenzo Barone. *Phys Life Rev* 2020, 32, 107-110, doi:10.1016/j.plprev.2019.08.010.
82. Bywater, R. On dating stages in prebiotic chemical evolution. *Naturwissenschaften* 2012, 99, 167-176.
83. Shanker, U.; Bhushan, B.; Bhattacharjee, G.; Kamaluddin. Formation of nucleobases from formamide in the presence of iron oxides: implication in chemical evolution and origin of life. *Astrobiology* 2011, 11, 225-233, doi:10.1089/ast.2010.0530.
84. Marlière, P.e.a. Chemical Evolution of a Bacterium's Genome. *Angewandte Chemie* 2011, 123, 7247-7252.
85. Pohorille, A. Was the emergence of life on earth a likely outcome of chemical evolution? *OLEB* 2010, 40, 362-365.
86. Maurer, S.E.; Deamer, D.W.; Boncella, J.M.; Monnard, P.-A. Chemical Evolution of Amphiphiles: Glycerol Monoacyl Derivatives Stabilize Plausible Prebiotic Membranes. *Astrobiology* 2009, 9, 979-987, doi:doi:10.1089/ast.2009.0384.
87. Hazen Robert, M. Chemical Evolution: An Introduction. In *Chemical Evolution II: From the Origins of Life to Modern Society*; ACS Symposium Series; American Chemical Society: Washington DC, 2009; pp. 3-13.
88. Branciamore, S.; Gallori, E.; Szathmary, E.; Czarán, T. The origin of life: chemical evolution of a metabolic system in a mineral honeycomb? *J Mol Evol* 2009, 69, 458-469, doi:10.1007/s00239-009-9278-6.
89. Bender Christopher, J. Chemical Evolution and Biomimetic Chemistry. In *Chemical Evolution II: From the Origins of Life to Modern Society*; ACS Symposium Series; American Chemical Society: Washington DC, 2009; pp. 313-331.
90. Rauchfuss, H.; Mitchell, T.N. Chemical Evolution and the Origin of Life; Springer-Verlag: Heidelberg, 2008.
91. Rauchfuss, H. Chemical Evolution and the Origin of Life Springer Varberg, Sweeden, 2008.
92. Melendez-Hevia, E.; Montero-Gomez, N.; Montero, F. From prebiotic chemistry to cellular metabolism--the chemical evolution of metabolism before Darwinian natural selection. *J Theor Biol* 2008, 252, 505-519.
93. Wienand, K.; Kampschulte, L.; Heckl, W.M. Creating a foundation for origin of life outreach: How scientists relate to their field, the public, and religion. *PLoS One* 2023, 18, e0282243, doi:10.1371/journal.pone.0282243.
94. Tirard, S. Abiogenesis. In *Encyclopedia of Astrobiology*, Gargaud, M., Irvine, W.M., Amils, R., Claeys, P., Cleaves, H.J., Gerin, M., Rouan, D., Spohn, T., Tirard, S., Viso, M., Eds.; Springer Berlin Heidelberg: Berlin, Heidelberg, 2023; pp. 30-31.
95. Tagami, S.; Li, P. The origin of life: RNA and protein co-evolution on the ancient Earth. *Dev Growth Differ* 2023, 65, 167-174, doi:10.1111/dgd.12845.
96. Subbotin, V.; Fiksel, G. Aquatic Ferrous Solutions of Prebiotic Mineral Salts as Strong UV Protectants and Possible Loci of Life Origin. *Astrobiology* 2023, 23, 741-745, doi:10.1089/ast.2023.0011.
97. Prosdociimi, F.; de Farias, S.T. Origin of life: Drawing the big picture. *Prog Biophys Mol Biol* 2023, 180-181, 28-36, doi:10.1016/j.pbiomolbio.2023.04.005.
98. Papineau, D.; Devine, K.; Nogueira, B.A. Self-Similar Patterns from Abiotic Decarboxylation Metabolism through Chemically Oscillating Reactions: A Prebiotic

- Model for the Origin of Life. Life (Basel) 2023, 13, doi:10.3390/life13020551.
99. Meyer, M.O.; Yamagami, R.; Choi, S.; Keating, C.D.; Bevilacqua, P.C. RNA folding studies inside peptide-rich droplets reveal roles of modified nucleosides at the origin of life. *bioRxiv* 2023, doi:10.1101/2023.02.27.530264.
 100. Fine, J.L.; Pearlman, R.E. On the origin of life: an RNA-focused synthesis and narrative. *RNA* 2023, 29, 1085-1098, doi:10.1261/rna.079598.123.
 101. Fields, C.; Levin, M. Regulative development as a model for origin of life and artificial life studies. *Biosystems* 2023, 229, 104927, doi:10.1016/j.biosystems.2023.104927.
 102. Ernst, L.; Barayeu, U.; Hader, J.; Dick, T.P.; Klatt, J.M.; Keppler, F.; Rebelein, J.G. Methane formation driven by light and heat prior to the origin of life and beyond. *Nat Commun* 2023, 14, 4364, doi:10.1038/s41467-023-39917-0.
 103. Bada, J.L. Volcanic Island lightning prebiotic chemistry and the origin of life in the early Hadean eon. *Nat Commun* 2023, 14, 2011, doi:10.1038/s41467-023-37894-y.
 104. Babajanyan, S.G.; Wolf, Y.I.; Khachatryan, A.; Allahverdyan, A.; Lopez-Garcia, P.; Koonin, E.V. Coevolution of reproducers and replicators at the origin of life and the conditions for the origin of genomes. *Proc Natl Acad Sci U S A* 2023, 120, e2301522120, doi:10.1073/pnas.2301522120.
 105. Zlenko, D.V.; Zanin, A.M.; Stovbun, S.V. Molecular Self-Assembly as a Trigger of Life Origin and Development. *Orig Life Evol Biosph* 2022, doi:10.1007/s11084-022-09620-z.
 106. Vanchurin, V.; Wolf, Y.I.; Koonin, E.V.; Katsnelson, M.I. Thermodynamics of evolution and the origin of life. *Proc Natl Acad Sci U S A* 2022, 119, doi:10.1073/pnas.2120042119.
 107. Spang, A.; Mahendrarajah, T.A.; Offre, P.; Stairs, C.W. Evolving Perspective on the Origin and Diversification of Cellular Life and the Virosphere. *Genome Biol Evol* 2022, 14, doi:10.1093/gbe/evac034.
 108. Spang, A.; Mahendrarajah, T.A.; Offre, P.; Stairs, C.W. Evolving perspective on the origin and diversification of cellular life and the virosphere. *Genome Biol Evol* 2022, doi:10.1093/gbe/evac034.
 109. Seebacher, F.; Beaman, J. Evolution of plasticity: metabolic compensation for fluctuating energy demands at the origin of life. *J Exp Biol* 2022, 225, doi:10.1242/jeb.243214.
 110. Rull, V. On predictions and laws in biological evolution. *EMBO reports* 2022, 23, e54392, doi:https://doi.org/10.15252/embr.202154392.
 111. Qu, K.; Xu, J.; Xue, Y.; Guo, J.; Gao, Z.; Song, Y.Y.; Mei, Y. Near Infrared Light-Driven Photothermal Effect on Homochiral Au/TiO₂ Nanotube Arrays for Enantioselective Desorption. *Anal Chem* 2022, 94, 588-592, doi:10.1021/acs.analchem.1c04981.
 112. Prinz, R. A simple measure for biocomplexity. *Biosystems* 2022, 217, 104670, doi:https://doi.org/10.1016/j.biosystems.2022.104670.
 113. Mukouyama, Y., Tanaka K, Nakanishi S, Nakato Y. Dynamic Self-organization in an Open Reaction Network as the Fundamental Principle for the Emergence of Life. . Available online: <https://chemrxiv.org/engage/chemrxiv/article-details/6230259f702f040a90bca37b> (accessed on
 114. Moldavanov, A.V. Energy infrastructure of evolution for system with infinite number of links with environment. *Biosystems* 2022, 213, 104607, doi:https://doi.org/10.1016/j.biosystems.2022.104607.
 115. Marijuán, P.C.; Navarro, J. The biological information flow: From cell theory to a new evolutionary synthesis. *Biosystems* 2022, 213, 104631, doi:https://doi.org/10.1016/j.biosystems.2022.104631.
 116. Malaterre, C.; Jeancolas, C.; Nghe, P. The Origin of Life: What Is the Question? *Astrobiology* 2022, doi:10.1089/ast.2021.0162.
 117. Lin, H.; Jimenez, E.I.; Arriola, J.T.; Muller, U.F.; Krishnamurthy, R. Concurrent Prebiotic Formation of Nucleoside-Amidophosphates and Nucleoside-Triphosphates Potentiates Transition from Abiotic to Biotic Polymerization. *Angew Chem Int Ed Engl* 2022, 61, e202113625, doi:10.1002/anie.202113625.
 118. Levit, G.S.; Hossfeld, U.A. Self-Organization Meets Evolution: Ernst Haeckel and Abiogenesis. In *Self-Organization as a New Paradigm in Evolutionary Biology: From Theory to Applied Cases in the Tree of Life*, Dambricourt Malassé, A., Ed.; Springer International Publishing: Cham, 2022; pp. 11-32.
 119. Kuhne, I.A.; Ozarowski, A.; Sultan, A.; Esien, K.; Carter, A.B.; Wix, P.; Casey, A.; Heerah-Boo luck, M.; Keene, T.D.; Muller-Bunz, H.; et al. Homochiral Mn(3+) Spin-Crossover Complexes: A Structural and Spectroscopic Study. *Inorg Chem* 2022, 61, 3458-3471, doi:10.1021/acs.inorgchem.1c03379.
 120. Kondratyeva, L.G.; Dyachkova, M.S.; Galchenko, A.V. The Origin of Genetic Code and Translation in the

- Framework of Current Concepts on the Origin of Life. *Biochemistry (Mosc)* 2022, 87, 150-169, doi:10.1134/S0006297922020079.
121. Klopogge, J.T.T.; Hartman, H. Clays and the Origin of Life: The Experiments. *Life (Basel)* 2022, 12, doi:10.3390/life12020259.
 122. Kharitonov, E.; Cherepanov, G.; Ostrenko, K. In Silico Predictions on the Productive Life Span and Theory of Its Developmental Origin in Dairy Cows. *Animals (Basel)* 2022, 12, doi:10.3390/ani12060684.
 123. Heylighen, F.; Beigi, S.; Busseniers, E. The role of self-maintaining resilient reaction networks in the origin and evolution of life. *Biosystems* 2022, 219, 104720, doi:10.1016/j.biosystems.2022.104720.
 124. Fontecilla-Camps, J.C. Nickel and the origin and early evolution of life. *Metallomics* 2022, 14, doi:10.1093/mtomcs/mfac016.
 125. Fiore, M.; Chieffo, C.; Lopez, A.; Fayolle, D.; Ruiz, J.; Souler, L.; Oger, P.; Altamura, E.; Popowycz, F.; Buchet, R. Synthesis of Phospholipids Under Plausible Prebiotic Conditions and Analogies with Phospholipid Biochemistry for Origin of Life Studies. *Astrobiology* 2022, 22, 598-627, doi:10.1089/ast.2021.0059.
 126. Fiore, M.; Chieffo, C.; Lopez, A.; Fayolle, D.; Ruiz, J.; Souler, L.; Oger, P.; Altamura, E.; Popowycz, F.; Buchet, R. Synthesis of Phospholipids Under Plausible Prebiotic Conditions and Analogies with Phospholipid Biochemistry for Origin of Life Studies. *Astrobiology* 2022, doi:10.1089/ast.2021.0059.
 127. Dong, J.; Liu, L.; Tan, C.; Xu, Q.; Zhang, J.; Qiao, Z.; Chu, D.; Liu, Y.; Zhang, Q.; Jiang, J.; et al. Free-standing homochiral 2D monolayers by exfoliation of molecular crystals. *Nature* 2022, 602, 606-611, doi:10.1038/s41586-022-04407-8.
 128. Deamer, D.; Cary, F.; Damer, B. Urability: A Property of Planetary Bodies That Can Support an Origin of Life. *Astrobiology* 2022, doi:10.1089/ast.2021.0173.
 129. de la Pena, M.; Gago-Zachert, S. A life of research on circular RNAs and ribozymes: towards the origin of viroids, deltaviruses and life. *Virus Res* 2022, 314, 198757, doi:10.1016/j.virusres.2022.198757.
 130. Chatterjee, S.; Yadav, S. The Coevolution of Biomolecules and Prebiotic Information Systems in the Origin of Life: A Visualization Model for Assembling the First Gene. *Life (Basel)* 2022, 12, doi:10.3390/life12060834.
 131. Castelveccchi, D. Origin of life theory involving RNA-protein hybrid gets new support. *Nature* 2022, 605, 409, doi:10.1038/d41586-022-01303-z.
 132. Carrasco, C.J.; Montilla, F.; Alvarez, E.; Galindo, A.; Perez-Aranda, M.; Pajuelo, E.; Alcudia, A. Homochiral imidazolium-based dicarboxylate silver(I) compounds: synthesis, characterisation and antimicrobial properties. *Dalton Trans* 2022, doi:10.1039/d1dt04213k.
 133. Bromberg, Y.; Aptekmann, A.A.; Mahlich, Y.; Cook, L.; Senn, S.; Miller, M.; Nanda, V.; Ferreiro, D.U.; Falkowski, P.G. Quantifying structural relationships of metal-binding sites suggests origins of biological electron transfer. *Science Advances* 2022, 8, eabj3984, doi:10.1126/sciadv.abj3984.
 134. Bose, T.; Fridkin, G.; Davidovich, C.; Krupkin, M.; Dinger, N.; Falkovich, A.H.; Peleg, Y.; Agmon, I.; Bashan, A.; Yonath, A. Origin of life: protoribosome forms peptide bonds and links RNA and protein dominated worlds. *Nucleic Acids Res* 2022, 50, 1815-1828, doi:10.1093/nar/gkac052.
 135. Altamura, E.; Fiore, M. The Origin and Early Evolution of Life: (Prebiotic) Systems Chemistry Perspective. *Life (Basel)* 2022, 12, doi:10.3390/life12050710.
 136. Zámečník, L. Causal and non-causal explanations in code biology. *Biosystems* 2021, 209, 104499, doi:https://doi.org/10.1016/j.biosystems.2021.104499.
 137. Wilson, D.F.; Matschinsky, F.M. Metabolic Homeostasis in Life as We Know It: Its Origin and Thermodynamic Basis. *Frontiers in physiology* 2021, 12, 658997, doi:10.3389/fphys.2021.658997.
 138. Villafane-Barajas, S.A.; Ruiz-Bermejo, M.; Rayo-Pizarroso, P.; Galvez-Martinez, S.; Mateo-Marti, E.; Colin-Garcia, M. A Lizardite-HCN Interaction Leading the Increasing of Molecular Complexity in an Alkaline Hydrothermal Scenario: Implications for Origin of Life Studies. *Life (Basel)* 2021, 11, doi:10.3390/life11070661.
 139. Tang, S. The Origin(s) of Cell(s): Pre-Darwinian Evolution from FUCAs to LUCA : To Carl Woese (1928-2012), for his Conceptual Breakthrough of Cellular Evolution. *J Mol Evol* 2021, 89, 427-447, doi:10.1007/s00239-021-10014-4.
 140. Solymosi, I.; Krishna, S.; Nuin, E.; Maid, H.; Scholz, B.; Guldi, D.M.; Perez-Ojeda, M.E.; Hirsch, A. Diastereoselective formation of homochiral flexible perylene bisimide cyclophanes and their hybrids with fullerenes. *Chem Sci* 2021, 12, 15491-15502, doi:10.1039/d1sc04242d.
 141. Smith, H.H.; Hyde, A.S.; Simkus, D.N.; Libby, E.; Maurer, S.E.; Graham, H.V.; Kempes, C.P.; Sherwood Lollar, B.; Chou, L.; Ellington, A.D.; et al. The Grayness

- of the Origin of Life. *Life* (Basel) 2021, 11, doi:10.3390/ life11060498.
142. Slijepcevic, P. Serial Endosymbiosis Theory: From biology to astronomy and back to the origin of life. *Biosystems* 2021, 202, 104353, doi:10.1016/j.biosystems.2021.104353.
 143. Rubio-Sanchez, R.; O'Flaherty, D.K.; Wang, A.; Coscia, F.; Petris, G.; Di Michele, L.; Cicuta, P.; Bonfio, C. Thermally Driven Membrane Phase Transitions Enable Content Reshuffling in Primitive Cells. *J Am Chem Soc* 2021, 143, 16589-16598, doi:10.1021/jacs.1c06595.
 144. Rodríguez Higuera, C. Quantification and Realism: Locating Semiosis in the Description of Biological Systems. *Biosemiotics* 2021, 14, 1-12, doi:10.1007/s12304-021-09439-7.
 145. Rasmussen, B.; Muhling, J.R.; Fischer, W.W. Greenalite Nanoparticles in Alkaline Vent Plumes as Templates for the Origin of Life. *Astrobiology* 2021, 21, 246-259, doi:10.1089/ast.2020.2270.
 146. Prosdociimi, F.; Jose, M.V.; de Farias, S.T. The Theory of Chemical Symbiosis: A Margulian View for the Emergence of Biological Systems (Origin of Life). *Acta Biotheor* 2021, 69, 67-78, doi:10.1007/s10441-020-09388-7.
 147. Pawlak, K.; Wnetrzak, M.; Mackiewicz, D.; Mackiewicz, P.; Błażej, P. Models of genetic code structure evolution with variable number of coded labels. *Biosystems* 2021, 210, 104528, doi:https://doi.org/10.1016/j.biosystems.2021.104528.
 148. Paredes, O.; Morales, J.A.; Mendizabal, A.P.; Romo-Vázquez, R. Metacode: One code to rule them all. *Biosystems* 2021, 208, 104486, doi:https://doi.org/10.1016/j.biosystems.2021.104486.
 149. Osumah, A.; Krishnamurthy, R. Diamidophosphate (DAP): A Plausible Prebiotic Phosphorylating Reagent with a Chem to BioChem Potential? *Chembiochem* 2021, 22, 3001-3009, doi:10.1002/cbic.202100274.
 150. Moelling, K.; Broecker, F. Viroids and the Origin of Life. *Int J Mol Sci* 2021, 22, doi:10.3390/ijms22073476.
 151. Michaelian, K. The Dissipative Photochemical Origin of Life: UVC Abiogenesis of Adenine. *Entropy* 2021, 23, 217.
 152. Mamajanov, I. Single-molecule origin of life scenario: Necessity and feasibility: Comment on "Insoluble organic matter in chondrites: Archetypal melanin-like PAH-based multifunctionality at the origin of life?" by Marco d'Ischia et al. *Phys Life Rev* 2021, 38, 143-144, doi:10.1016/j.plrev.2021.04.007.
 153. Major, J.C. Archetypes and code biology. *Biosystems* 2021, 208, 104501, doi:https://doi.org/10.1016/j.biosystems.2021.104501.
 154. Liao, W.Q.; Zeng, Y.L.; Tang, Y.Y.; Peng, H.; Liu, J.C.; Xiong, R.G. Multichannel Control of Multiferroicity in Single-Component Homochiral Organic Crystals. *J Am Chem Soc* 2021, 143, 21685-21693, doi:10.1021/jacs.1c11000.
 155. Lacková, L.; Faltýnek, D. The lower threshold as a unifying principle between Code Biology and Biosemiotics. *Biosystems* 2021, 210, 104523, doi:https://doi.org/10.1016/j.biosystems.2021.104523.
 156. Kun, Á. The major evolutionary transitions and codes of life. *Biosystems* 2021, 210, 104548, doi:https://doi.org/10.1016/j.biosystems.2021.104548.
 157. Kordium, V.A. Defining life and evolution: Essay on the origin, expansion, and evolution of living matter. *Biosystems* 2021, 209, 104500, doi:10.1016/j.biosystems.2021.104500.
 158. Konjevoda, P.; Štambuk, N. Relational model of the standard genetic code. *Biosystems* 2021, 210, 104529, doi:https://doi.org/10.1016/j.biosystems.2021.104529.
 159. Abel, D.L. Linear Digital Material Symbol Systems (MSS) (<http://DavidAbel.us> Last accessed in July, 2024). In *The First Gene: The Birth of Programming, Messaging and Formal Control*, Abel, D.L., Ed.; LongView Press--Academic, Biol. Res. Div.: New York, N.Y., 2011; pp. 135-160.
 160. Abel, D.L. The three fundamental categories of reality (<http://DavidAbel.us> Last accessed in July, 2024). In *The First Gene: The Birth of Programming, Messaging and Formal Control*, Abel, D.L., Ed.; LongView Press--Academic: Biolog. Res. Div.: New York, N.Y., 2011; pp. 19-54.
 161. Abel, D.L. What is ProtoBioCybernetics? (<http://DavidAbel.us> Last accessed in July, 2024). In *The First Gene: The Birth of Programming, Messaging and Formal Control*, Abel, D.L., Ed.; LongView Press--Academic: Biolog. Res. Div.: New York, N.Y., 2011; pp. 1-18.
 162. Abel, D.L., (Ed.) *The First Gene: The Birth of Programming, Messaging and Formal Control*. LongView Press--Academic: Biolog. Res. Div.: New York, NY, 2011; p. 389.
 163. Abel, D.L. The GS (Genetic Selection) Principle (Also available at www.DavidAbel.us Last accessed July, 2024). *Frontiers in Bioscience* 2009, 14, 2959-2969 doi:10.2741/3426.

164. Abel, D.L.; Trevors, J.T. More than metaphor: Genomes are objective sign systems (also available from www.DavidAbel.us Last accessed 7/2024). *Journal of BioSemiotics* 2006, 1, 253-267.
165. Abel, D.L.; Trevors, J.T. Three subsets of sequence complexity and their relevance to biopolymeric information. *Theoretical Biology and Medical Modeling* 2005, 2, 29-45 www.DavidAbel.us (Last accessed Nov, 2023), doi:<https://tbiomed.biomedcentral.com/articles/10.1186/1742-4682-2-29>.
166. Abel, D.L. Is Life Reducible to Complexity? In *Fundamentals of Life*, Palyi, G., Zucchi, C., Caglioti, L., Eds.; Elsevier: Paris, 2002; pp. 57-72 www.DavidAbel.us.
167. Wong, J.T. Evolution of the genetic code. *Microbiol Sci* 1988, 5, 174-181.
168. Wong, J.T.-F.; Ng, S.-K.; Mat, W.-K.; Hu, T.; Xue, H. Coevolution Theory of the Genetic Code at Age Forty: Pathway to Translation and Synthetic Life. *Life* (Basel, Switzerland) 2016, 6, 12, doi:10.3390/life6010012.
169. Mat, W.K.; Xue, H.; Wong, J.T. Genetic code mutations: the breaking of a three billion year invariance. *PLoS One* 2010, 5, e12206, doi:10.1371/journal.pone.0012206.
170. Mat, W.K.; Xue, H.; Wong, J.T. The genomics of LUCA. *Front Biosci* 2008, 13, 5605-5613, doi:10.1093/fbs/13.10.5605 [pii].
171. Wong, J.T.; Chen, J.; Mat, W.K.; Ng, S.K.; Xue, H. Polyphasic evidence delineating the root of life and roots of biological domains. *Gene* 2007, 403, 39-52, doi:S0378-1119(07)00403-9 [pii]10.1016/j.gene.2007.07.032.
172. Wong, J.T. Question 6: coevolution theory of the genetic code: a proven theory. *Orig Life Evol Biosph* 2007, 37, 403-408.
173. Wong, J.T. Coevolution theory of the genetic code at age thirty. *Bioessays* 2005, 27, 416-425.
174. Di Giulio, M. The evolutionary stages of the complexity of biological catalysts mark and clarify the phases of the origin of the genetic code: A model for the origin of the reading frame with codons from proto-mRNAs with different frames. *Biosystems* 2021, 207, 104449, doi:<https://doi.org/10.1016/j.biosystems.2021.104449>.
175. Di Giulio, M. An RNA Ring was Not the Progenitor of the tRNA Molecule. *J Mol Evol* 2020, 88, 228-233, doi:10.1007/s00239-020-09927-3.
176. Di Giulio, M. LUCA as well as the ancestors of archaea, bacteria and eukaryotes were progenotes: Inference from the distribution and diversity of the reading mechanism of the AUA and AUG codons in the domains of life. *Biosystems* 2020, 198, 104239, doi:10.1016/j.biosystems.2020.104239.
177. Di Giulio, M. The key role of the elongation factors in the origin of the organization of the genetic code. *Biosystems* 2019, 181, 20-26, doi:10.1016/j.biosystems.2019.04.009.
178. Di Giulio, M. A comparison between two models for understanding the origin of the tRNA molecule. *J Theor Biol* 2019, 480, 99-103, doi:10.1016/j.jtbi.2019.07.020.
179. Di Giulio, M.; Moracci, M.; Cobucci-Ponzano, B. RNA editing and modifications of RNAs might have favoured the evolution of the triplet genetic code from an ennuplet code. *J Theor Biol* 2014, 359, 1-5, doi:10.1016/j.jtbi.2014.05.037.
180. Di Giulio, M. The genetic code did not originate from an mRNA codifying polyglycine because the proto-mRNAs already codified for an amino acid number greater than one. *J Theor Biol* 2014, doi:10.1016/j.jtbi.2014.09.006.
181. Di Giulio, M. A polyphyletic model for the origin of tRNAs has more support than a monophyletic model. *J Theor Biol* 2013, 318, 124-128, doi:10.1016/j.jtbi.2012.11.012.
182. Di Giulio, M. The origin of the genetic code in the ocean abysses: new comparisons confirm old observations. *J Theor Biol* 2013, 333, 109-116, doi:10.1016/j.jtbi.2013.05.019.
183. Di Giulio, M. The origin of the genetic code: matter of metabolism or physicochemical determinism? *J Mol Evol* 2013, 77, 131-133, doi:10.1007/s00239-013-9593-9.
184. Di Giulio, M. The last universal common ancestor (LUCA) and the ancestors of archaea and bacteria were progenotes. *J Mol Evol* 2011, 72, 119-126, doi:10.1007/s00239-010-9407-2.
185. Branciamore, S.; Di Giulio, M. The presence in tRNA molecule sequences of the double hairpin, an evolutionary stage through which the origin of this molecule is thought to have passed. *J Mol Evol* 2011, 72, 352-363, doi:10.1007/s00239-011-9440-9.
186. Di Giulio, M. A model of the origin of the 5S ribosomal RNA molecule. *J Mol Evol* 2010, 71, 1-2, doi:10.1007/s00239-010-9358-7.
187. Di Giulio, M.; Kreitman, M. Research on the origin of life. Introduction. *J Mol Evol* 2009, 69, 405, doi:10.1007/s00239-009-9284-8.
188. Di Giulio, M.; Amato, U. The close relationship

- between the biosynthetic families of amino acids and the organisation of the genetic code. *Gene* 2009, 435, 9-12, doi:S0378-1119(09)00009-2.
189. Di Giulio, M. A methanogen hosted the origin of the genetic code. *J Theor Biol* 2009, 260, 77-82, doi:S0022-5193(09)00257-4.
 190. Di Giulio, M. A comparison among the models proposed to explain the origin of the tRNA molecule: A synthesis. *J Mol Evol* 2009, 69, 1-9, doi:10.1007/s00239-009-9248-z.
 191. Di Giulio, M. Transfer RNA genes in pieces are an ancestral character. *EMBO Rep* 2008, 9, 820; author reply 820-821, doi:embor2008153.
 192. Di Giulio, M. The origin of genes could be polyphyletic. *Gene* 2008, 426, 39-46, doi:S0378-1119(08)00341-7.
 193. Di Giulio, M. Permuted tRNA genes of Cyanidioschyzon merolae, the origin of the tRNA molecule and the root of the Eukarya domain. *J Theor Biol* 2008, 253, 587-592, doi:S0022-5193(08)00206-3.
 194. Di Giulio, M. An extension of the coevolution theory of the origin of the genetic code. *Biol Direct* 2008, 3, 37, doi:10.1186/1745-6150-3-37.
 195. Archetti, M.; Di Giulio, M. The evolution of the genetic code took place in an anaerobic environment. *J Theor Biol* 2007, 245, 169-174, doi:S0022-5193(06)00435-8.
 196. Di Giulio, M. The non-monophyletic origin of the tRNA molecule and the origin of genes only after the evolutionary stage of the last universal common ancestor (LUCA). *J Theor Biol* 2006, 240, 343-352, doi:S0022-5193(05)00427-3.
 197. Widmann, J.; Di Giulio, M.; Yarus, M.; Knight, R. tRNA creation by hairpin duplication. *J Mol Evol* 2005, 61, 524-530, doi:10.1007/s00239-004-0315-1.
 198. Di Giulio, M. Structuring of the genetic code took place at acidic pH. *J Theor Biol* 2005, 237, 219-226, doi:S0022-5193(05)00173-6.
 199. Di Giulio, M. The ocean abysses witnessed the origin of the genetic code. *Gene* 2005, 346, 7-12, doi:S0378-1119(04)00602-X.
 200. Di Giulio, M. The origin of the genetic code: theories and their relationships, a review. *Biosystems* 2005, 80, 175-184.
 201. Di Giulio, M. The origin of the tRNA molecule: implications for the origin of protein synthesis. *Journal of theoretical biology* 2004, 226, 89-93.
 202. Di Giulio, M. The coevolution theory of the origin of the genetic code. *Physics of Life Reviews* 2004.
 203. Guimaraes, R.C. Self-Referential Encoding on Modules of Anticodon Pairs—Roots of the Biological Flow System. *Life* (Chicago, Ill.: 1978) 2017, 7, 39, doi:10.20944/preprints201703.0031.v2.
 204. Guimaraes, R.C. Emergence of information patterns: in the quantum and biochemical realms. *Quantum Biosystems* 2015, 6, 148-159.
 205. Guimaraes, R.C. The self-referential genetic code is biologic and includes the error minimization property. *Origins of Life and Evolution of Biospheres* 2015, 03/2015, 82-86.
 206. Guimarães, R.C. Essentials in the Life Process Indicated by the Self-Referential Genetic Code. *Origins of Life and Evolution of Biospheres* 2015, 2015, 1-11.
 207. Guimarães, R. The Self-Referential Genetic Code is Biologic and Includes the Error Minimization Property. *Origins of Life and Evolution of Biospheres* 2015, 45, 69-75, doi:10.1007/s11084-015-9417-6.
 208. Jose, M.V.; Morgado, E.R.; Guimaraes, R.C.; Zamudio, G.S.; de Farias, S.T.; Bobadilla, J.R.; Sosa, D. Three-Dimensional Algebraic Models of the tRNA Code and 12 Graphs for Representing the Amino Acids. *Life* (Basel) 2014, 4, 341-373, doi:10.3390/life4030341.
 209. Guimaraes, R.C. Essentials in the life process indicated by the self-referential genetic code. *Orig Life Evol Biosph* 2014, 44, 269-277, doi:10.1007/s11084-014-9380-7.
 210. Guimarães, R.C. Formation of the Genetic Code. Update: Nov 2012. Webinar May 2013. 2013.
 211. Guimaraes, R.C. Metabolic basis for the self-referential genetic code. *Origins of life and evolution of the biosphere* 2011, 41, 357-371, doi:10.1007/s11084-010-9226-x.
 212. Guimaraes, R.C. Metabolic Basis for the Self-Referential Genetic Code. *Origins of life and evolution of the biosphere* 2010, doi:10.1007/s11084-010-9226-x.
 213. Guimaraes, R.C.; Moreira, C.H.; de Farias, S.T. A self-referential model for the formation of the genetic code. *Theory Biosci* 2008, 127, 249-270, doi:10.1007/s12064-008-0043-y.
 214. Guimaraes, R.C. The Genetic Code as a Self-Referential and Functional System. *International Conference on Computation, Communications and Control Technologies* 2004, 7, 160-165.
 215. Barbieri, M. Overview of the third special issue in code biology. *Biosystems* 2021, 210, 104553, doi:https://doi.org/10.1016/j.biosystems.2021.104553.

216. Barbieri, M. A general model on the origin of biological codes. *Biosystems* 2019, 181, 11-19, doi:10.1016/j.biosystems.2019.04.010.
217. Barbieri, M. What is code biology? *Biosystems* 2018, 164, 1-10, doi:https://doi.org/10.1016/j.biosystems.2017.10.005.
218. Barbieri, M. First Special Issue in Code Biology *BioSystems* 2018, 164.
219. Barbieri, M. From the Common Ancestor to the First Cells: the Code Theory. . *Biological Theory* 2016, *Biological Theory* 102-112.
220. Barbieri, M. What is information? *Philosophical transactions. Series A, Mathematical, physical, and engineering sciences* 2016, 374, doi:10.1098/rsta.2015.0060.
221. Barbieri, M. Codepoiesis – the deep logic of life. . *Biosemtotics* 2012, 5, 297-299.
222. Barbieri, M. Cosmos and History: Life is semiosis; The biosemiotic view of nature. *The Journal of Natural and Social Philosophy* 2008, 4, 29-51.
223. Barbieri, M. Biosemiotics: a new understanding of life. *Naturwissenschaften* 2008, 95, 577-599.
224. Barbieri, M., (Ed.) *The Codes of Life: The Rules of Macroevolution (Biosemiotics)*. Springer: Dordrecht, The Netherlands, 2007.
225. Barbieri, M., (Ed.) *BioSemiotic Research Trends*. Nova Science Publishers, Inc.: New York, 2007.
226. Barbieri, M. Is the cell a semiotics system? In *Introduction to Biosemiotics: The New Biological Synthesis*, Barbieri, M., Ed.; Springer: Dordrecht, The Netherlands, 2007; pp. 179-208.
227. Barbieri, M. Has biosemiotics come of age? In *Introduction to Biosemiotics: The New Biological Synthesis*, Barbieri, M., Ed.; Springer: Dordrecht, The Netherlands, 2007; pp. 101-114.
228. Barbieri, M. Semantic Biology and the Mind-Body Problem: The Theory of the Conventional Mind. *Biological Theory* 2006, 1, 352-356, doi:doi:10.1162/biot.2006.1.4.352.
229. Barbieri, M., (Ed.) *Introduction to Biosemiotics: The New Biological Synthesis*. Springer-Verlag: Dordrecht, The Netherlands, 2006.
230. Barbieri, M. Is the Cell a Semiotic System? In *Introduction to Biosemiotics: The New Biological Synthesis*, Barbieri, M., Ed.; Springer-Verlag New York, Inc.: Secaucus, NJ, USA, 2006.
231. Barbieri, M. Life is 'artifact-making'. *Journal of Biosemiotics* 2005, 1, 113-142.
232. Barbieri, M. The definitions of information and meaning: Two possible boundaries between physics and biology [in English]. *Revista di Biologia / Biology Forum* 2004, 97, 91-110.
233. Barbieri, M. Biology with information and meaning. *History & Philosophy of the Life Sciences* 2004, 25, 243-254.
234. Barbieri, M. *The Organic Codes: An Introduction to Semantic Biology*; Cambridge University Press: Cambridge, 2003.
235. Barbieri, M. The ribotype theory of the origin of life. *Riv Biol* 1982, 75, 515-561.
236. Johnson, D.E. Biocybernetics and Biosemiosis. In *Biological Information: New Perspectives*, Marks II, R.J., Behe, M.J., Dembski, W.A., Gordon, B.L., Sanford, J.C., Eds.; World Scientific: Cornell University Proceedings, 2013; pp. 402-414.
237. Barlow, P.W. The primal integrated realm and the derived interactive realm in relation to biosemiosis, and their link with the ideas of J.W. von Goethe. *Commun Integr Biol* 2012, 5, 434-439, doi:10.4161/cib.21253.
238. Cowley, S.J. Language and biosemiosis: Towards unity? *Semiotica* 2006, 2006, 417-443.
239. Zamecnik, L. Causal and non-causal explanations in code biology. *Biosystems* 2021, 209, 104499, doi:10.1016/j.biosystems.2021.104499.
240. Petoukhov, S.V. Algebraic harmony and probabilities in genomes. Long-range coherence in quantum code biology. *Biosystems* 2021, 209, 104503, doi:10.1016/j.biosystems.2021.104503.
241. Lackova, L.; Faltynek, D. The lower threshold as a unifying principle between Code Biology and Biosemiotics. *Biosystems* 2021, 210, 104523, doi:10.1016/j.biosystems.2021.104523.
242. Gare, A. Code biology and the problem of emergence. *Biosystems* 2021, 208, 104487, doi:10.1016/j.biosystems.2021.104487.
243. Hofmeyr, J.S. The Second Special Issue on Code Biology - An overview. *Biosystems* 2020, 187, 104050, doi:10.1016/j.biosystems.2019.104050.
244. Hofmeyr, J.S. The first Special Issue on code biology - A bird's-eye view. *Biosystems* 2018, 164, 11-15, doi:10.1016/j.biosystems.2017.12.007.
245. Abel, D.L. Is life unique? (also available from www.

- DavidAbel.us Last accessed 7/2024). *Life* 2012, 2, 106-134, doi:DOI 10.3390/life2010106
246. Abel, D.L. The 'Cybernetic Cut': Progressing from Description to Prescription in Systems Theory (Also available at www.DavidAbel.us Last accessed July, 2024). *The Open Cybernetics and Systemics Journal* 2008, 2, 252-262, doi:1874-110X/08.
 247. Abel, D.L. The capabilities of chaos and complexity In *Proceedings of the Society for Chaos Theory: Society for Complexity in Psychology and the Life Sciences, International Conference at Virginia Commonwealth University, Richmond, VA., Aug 8-10, 2008.*
 248. Abel, D.L.; Trevors, J.T. Self-Organization vs. Self-Ordering events in life-origin models (also available from www.DavidAbel.us Last accessed 7/2024). *Physics of Life Reviews* 2006, 3, 211-228, doi:10.1016/j.plrev.2006.07.003.
 249. Abel, D.L. The Genetic Selection (GS) Principle (<http://DavidAbel.us> Last accessed in July, 2024). In *The First Gene: The Birth of Programming, Messaging and Formal Control*, Abel, D.L., Ed.; LongView Press--Academic: New York, N.Y., 2011; pp. 161-188.
 250. D'onofrio, D.J.; Abel, D.L. Redundancy of the genetic code enables translational pausing. *Frontiers in Genetics* 2014, 5, 140 Open access doi:10.3389/fgene.2014.00140 1 Also at www.DavidAbel.us (Last accessed: 6/2024).
 251. Abel, D.L. Prescriptive Information (PI) [Scirus SciTopic Page]. Available online: www.DavidAbel.us (accessed on 7/20/2024).
 252. Corning, P.A. Control information theory: the 'missing link' in the science of cybernetics. *Systems Research and Behavioral Science* 2007, 24, 297-311, doi:10.1002/sres.808
 253. Abel, D.L. Moving 'far from equilibrium' in a prebiotic environment: The role of Maxwell's Demon in life origin (<http://DavidAbel.us> Last accessed in July, 2024). In *Genesis - In the Beginning: Precursors of Life, Chemical Models and Early Biological Evolution*, Seckbach, J., Gordon, R., Eds. Seckbach, J., Ed.; Springer: Dordrecht, 2012; pp. 219-236.
 254. Abel, D.L. The Cybernetic Cut and Configurable Switch (CS) Bridge (<http://DavidAbel.us> Last accessed in July, 2024). In *The First Gene: The Birth of Programming, Messaging and Formal Control*, Abel, D.L., Ed.; LongView Press--Academic, Biol. Res. Div. 55-74 New York, N.Y., 2011; pp. 55-74
 255. Tour, P.J. 14-Part Series on the Chemistry of Abiogenesis (Last accessed in 9/2023). Available online: https://www.youtube.com/watch?v=4rwPilmWu4&list=PLILWudw_84t22BWvWsoXCmaXNllbfJ2h7&index=3 (accessed on
 256. Trail, D.; Watson, E.B.; Tailby, N.D. The oxidation state of Hadean magmas and implications for early Earth's atmosphere. *Nature* 2011, 480, 79-82, doi:10.1038/nature10655.
 257. Abel, D.L. The Universal Plausibility Metric and Principle (<http://DavidAbel.us> Last accessed in July, 2024). In *The First Gene: The Birth of Programming, Messaging and Formal Control*, Abel, D.L., Ed.; LongView Press--Academic: New York, N.Y., 2011; pp. 305-324 <http://DavidAbel.us> (last accessed in 306/2024)
 258. Abel, D.L. The Universal Plausibility Metric (UPM) & Principle (UPP) [Scirus SciTopic Page]. Available online: <http://DavidAbel.us> (accessed on 7/20/2024).
 259. Abel, D.L. The Universal Plausibility Metric (UPM) & Principle (UPP) (also available at www.DavidAbel.us Last accessed 7/20/2024). *Theor Biol Med Model* 2009, 6, 27
 260. Durup, J. On "Levinthal paradox" and the theory of protein folding. *Journal of Molecular Structure: THEOCHEM* 1998, 424, 157-169.
 261. S`ali, A., Shakhnovich, E. & Karplus, M. . How does a protein fold? *Nature* 1994, 369 (I6477), 248-251.
 262. Bali, V.; Bebok, Z. Decoding mechanisms by which silent codon changes influence protein biogenesis and function. *The international journal of biochemistry & cell biology* 2015, 64, 58-74, doi:10.1016/j.biocel.2015.03.011.
 263. Liu, B.; Qian, S.B. Translational reprogramming in cellular stress response. *Wiley Interdiscip Rev RNA* 2013, doi:10.1002/wrna.1212.
 264. Perdrizet, G.A.; Artsimovitch, I.; Furman, R.; Sosnick, T.R.; Pan, T. Transcriptional pausing coordinates folding of the aptamer domain and the expression platform of a riboswitch. *Proceedings of the National Academy of Sciences* 2012, doi:10.1073/pnas.1113086109.
 265. Li, G.-W.; Oh, E.; Weissman, J.S. The anti-Shine-Dalgarno sequence drives translational pausing and codon choice in bacteria. *Nature* 2012, 484, 538 doi:<https://www.nature.com/articles/nature10965>.
 266. Margulis, L. Origins of species: acquired genomes and individuality. *Biosystems* 1993, 31, 121-125.
 267. Margulis, L. Biodiversity: molecular biological domains,

- symbiosis and kingdom origins. *Biosystems* 1992, 27, 39-51.
268. Lazcano, A.; Guerrero, R.; Margulis, L.; Oro, J. The evolutionary transition from RNA to DNA in early cells. *J Mol Evol* 1988, 27, 283-290.
 269. Margulis, L. *Symbiosis in Cell Evolution: Life and Its Environment on the Early Earth*; W.H. Freeman: San Francisco, CA, 1981.
 270. Omran, A.; Menor-Salvan, C.; Springsteen, G.; Pasek, M. The Messy Alkaline Formose Reaction and Its Link to Metabolism. *Life (Basel)* 2020, 10, doi:10.3390/life10080125.
 271. Dembski, W. *The Design Inference: Eliminating Chance Through Small Probabilities*; Cambridge University Press: Cambridge, 1998.
 272. Axe, D.D. Estimating the prevalence of protein sequences adopting functional enzyme folds. *J Mol Biol* 2004, 341, 1295-1315.
 273. Abel, D.L.; Trevors, J.T. More than Metaphor: Genomes are Objective Sign Systems. In *BioSemiotic Research Trends*, Barbieri, M., Ed.; Nova Science Publishers: New York, 2007; pp. 1-15 Downloadable from <http://DavidAbel.us> (Last accessed Aug, 2023).
 274. Rocha, L.M. Evolution with material symbol systems. *Biosystems* 2001, 60, 95-121.
 275. Rocha, L.M. The physics and evolution of symbols and codes: reflections on the work of Howard Pattee. *Biosystems* 2001, 60, 1-4.
 276. Rocha, L.M. Syntactic autonomy: or why there is no autonomy without symbols and how self-organizing systems might evolve them. *Annals of the New York Academy of Sciences* 2000, 207-223.
 277. Abel, D.L. Complexity, self-organization, and emergence at the edge of chaos in life-origin models (also available from www.DavidAbel.us Last accessed 7/2024). *Journal of the Washington Academy of Sciences* 2007, 93, 1-20, doi:https://www.jstor.org/stable/24536323.
 278. Abel, D.L. Life origin: The role of complexity at the edge of chaos (pdf of PowerPoint available from www.DavidAbel.us Last accessed 7/2024). In *Proceedings of the Washington Academy of Science 2006*, Lecture delivered at the Headquarters of the National Science Foundation, Arlington, VA, 2006.
 279. Hoyle, F.; Wickramasinghe, N.C. The case for life as a cosmic phenomenon. *Nature* 1986, 322, 509-511.
 280. Hoyle, F.; Wickramasinghe, N.C. *Space Travelers*; University College Cardiff Press: Cardiff, 1981.
 281. Mitton, S. A Short History of Panspermia from Antiquity Through the Mid-1970s. *Astrobiology* 2022, 22, 1379-1391, doi:10.1089/ast.2022.0032.
 282. McKay, C.P.; Davies, P.C.W.; Worden, S.P. Directed Panspermia Using Interstellar Comets. *Astrobiology* 2022, 22, 1443-1451, doi:10.1089/ast.2021.0188.
 283. Manini, P.; d'Ischia, M. The new frontier of an IOM-based panspermia hypothesis: Perspectives and feasibility: Response to commentary on "Insoluble organic matter in chondrites: Archetypal melaninlike PAH-based multifunctionality at the origin of life?". *Phys Life Rev* 2022, 42, 49-51, doi:10.1016/j.plrev.2022.06.005.
 284. Desch, S.J.; Jackson, A.P. Some Pertinent Issues for Interstellar Panspermia Raised after the Discovery of 1I/Oumuamua. *Astrobiology* 2022, 22, 1400-1413, doi:10.1089/ast.2021.0199.
 285. Adams, F.C.; Napier, K.J. Transfer of Rocks Between Planetary Systems: Panspermia Revisited. *Astrobiology* 2022, 22, 1429-1442, doi:10.1089/ast.2021.0187.
 286. Traspas, A.; Burchell, M.J. Tardigrade Survival Limits in High-Speed Impacts-Implications for Panspermia and Collection of Samples from Plumes Emitted by Ice Worlds. *Astrobiology* 2021, 21, 845-852, doi:10.1089/ast.2020.2405.
 287. Slijepcevic, P.; Wickramasinghe, C. Reconfiguring SETI in the microbial context: Panspermia as a solution to Fermi's paradox. *Biosystems* 2021, 206, 104441, doi:10.1016/j.biosystems.2021.104441.
 288. Schulze-Makuch, D.; Fairen, A.G. Evaluating the Microbial Habitability of Rogue Planets and Proposing Speculative Scenarios on How They Might Act as Vectors for Panspermia. *Life (Basel)* 2021, 11, doi:10.3390/life11080833.
 289. Wickramasinghe, N.C.; Wickramasinghe, D.T.; Steele, E.J. Cometary panspermia and origin of life? *Adv Genet* 2020, 106, 5-20, doi:10.1016/bs.adgen.2020.03.003.
 290. Steele, E.J. Introduction-Panspermia, 2020. *Adv Genet* 2020, 106, 1-4, doi:10.1016/bs.adgen.2020.04.001.
 291. Steele, E.J.; Gorczynski, R.M.; Lindley, R.A.; Liu, Y.; Temple, R.; Tokoro, G.; Wickramasinghe, D.T.; Wickramasinghe, N.C. Lamarck and Panspermia - On the Efficient Spread of Living Systems Throughout the Cosmos. *Prog Biophys Mol Biol* 2019, 149, 10-32, doi:10.1016/j.pbiomolbio.2019.08.010.
 292. Sleator, R.D.; Smith, N. Directed panspermia: a 21st century perspective. *Sci Prog* 2017, 100, 187-193, doi:10.3184/003685017X14901006155062.

293. Lingam, M.; Loeb, A. Enhanced interplanetary panspermia in the TRAPPIST-1 system. *Proc Natl Acad Sci U S A* 2017, 114, 6689-6693, doi:10.1073/pnas.1703517114.
294. Hollinger, M. Life from Elsewhere - Early History of the Maverick Theory of Panspermia. *Sudhoffs Arch* 2016, 100, 188-205.
295. Parsons, P. Exobiology: Dusting off panspermia. *Nature* 1996, 383, 221-222.
296. Malaterre, C.; Lareau, F. The Emergence of Astrobiology: A Topic-Modeling Perspective. *Astrobiology* 2023, 23, 496-512, doi:10.1089/ast.2022.0122.
297. De Mol, M.L. Astrobiology in Space: A Comprehensive Look at the Solar System. *Life (Basel)* 2023, 13, doi:10.3390/life13030675.
298. Wu, J.H.; McGenity, T.J.; Rettberg, P.; Simoes, M.F.; Li, W.J.; Antunes, A. The archaeal class Halobacteria and astrobiology: Knowledge gaps and research opportunities. *Front Microbiol* 2022, 13, 1023625, doi:10.3389/fmicb.2022.1023625.
299. Theiling, B.P.; Chou, L.; Da Poian, V.; Battler, M.; Raimalwala, K.; Arevalo, R., Jr.; Neveu, M.; Ni, Z.; Graham, H.; Elsila, J.; et al. Science Autonomy for Ocean Worlds Astrobiology: A Perspective. *Astrobiology* 2022, 22, 901-913, doi:10.1089/ast.2021.0062.
300. Shapshak, P. Neutrino communication, intergalactic transit, and Astrobiology. *Bioinformation* 2022, 18, 72-75, doi:10.6026/97320630018072.
301. Helman, D.S. Finding or Creating a Living Organism? Past and Future Thought Experiments in Astrobiology Applied to Artificial Intelligence. *Acta Biotheor* 2022, 70, 13, doi:10.1007/s10441-022-09438-2.
302. de la Higuera, I.; Lazaro, E. Viruses in astrobiology. *Front Microbiol* 2022, 13, 1032918, doi:10.3389/fmicb.2022.1032918.
303. Cowan, D.A.; Ferrari, B.C.; McKay, C.P. Out of Thin Air? Astrobiology and Atmospheric Chemotrophy. *Astrobiology* 2022, 22, 225-232, doi:10.1089/ast.2021.0066.
304. Seaton, K.M.; Cable, M.L.; Stockton, A.M. Analytical Chemistry in Astrobiology. *Anal Chem* 2021, 93, 5981-5997, doi:10.1021/acs.analchem.0c04271.
305. Mendez, A.; Rivera-Valentin, E.G.; Schulze-Makuch, D.; Filiberto, J.; Ramirez, R.M.; Wood, T.E.; Davila, A.; McKay, C.; Ceballos, K.N.O.; Jusino-Maldonado, M.; et al. Habitability Models for Astrobiology. *Astrobiology* 2021, 21, 1017-1027, doi:10.1089/ast.2020.2342.
306. Onofri, S.; Balucani, N.; Barone, V.; Benedetti, P.; Billi, D.; Balbi, A.; Brucato, J.R.; Cobucci-Ponzano, B.; Costanzo, G.; Rocca, N.; et al. The Italian National Project of Astrobiology-Life in Space-Origin, Presence, Persistence of Life in Space, from Molecules to Extremophiles. *Astrobiology* 2020, 20, 580-582, doi:10.1089/ast.2020.2247.
307. Kumar, D.; Steele, E.J.; Wickramasinghe, N.C. Preface: The origin of life and astrobiology. *Adv Genet* 2020, 106, xv-xviii, doi:10.1016/S0065-2660(20)30037-7.
308. Lazcano, A.; Hand, K.P. Astrobiology: Frontier or fiction. *Nature* 2012, 488, 160-161.
309. Zagorski, Z.P. Question 2: relation of panspermia-hypothesis to astrobiology. *Orig Life Evol Biosph* 2007, 37, 351-355, doi:10.1007/s11084-007-9074-5.
310. Zewail, A.H. The Nobel Prize in Chemistry. For his studies of the transition states of chemical reactions using femtosecond spectroscopy: Press Release. 1999, doi:http://nobelprize.org/nobel_prizes/chemistry/laureates/1999/press.html.
311. Pedersen, S.; Herek, J.L.; Zewail, A.H. The Validity of the "Diradical" Hypothesis: Direct Femtosecond Studies of the Transition-State Structures. *Science* 1994, 266, 1359-1364.
312. Zewail, A.H. The Birth of Molecules. *Scientific American* 1990, December, 40-46.
313. Sundstrom, V. Femtobiology. *Annual Review of Physical Chemistry* 2008, 59, 53-77, doi:10.1146/annurev.physchem.59.032607.093615.
314. Sundström, V., (Ed.) Nobel Symposium: Femtochemistry & Femtobiology: Ultrafast Reaction Dynamics at Atomic-Scale Resolution. World Scientific: Singapore, 1996.
315. Willerslev, E.; Hansen, A.J.; Ronn, R.; Nielsen, O.J. Panspermia--true or false? *Lancet* 2003, 362, 406; author reply 407-408, doi:10.1016/S0140-6736(03)14039-1.
316. Ponce de Leon, S.; Lazcano, A. Panspermia--true or false? *Lancet* 2003, 362, 406-407; author reply 407-408, doi:10.1016/s0140-6736(03)14040-8.
317. Bhargava, P.M. Panspermia--true or false? *Lancet* 2003, 362, 407; author reply 407-408, doi:10.1016/S0140-6736(03)14041-X.
318. Secker, J.; Wesson, P.S.; Lepock, J.R. Astrophysical and biological constraints on radiopanspermia. *J R Astron Soc Can* 1996, 90, 184-192.
319. Di Giulio, M. Biological evidence against the panspermia theory. *J Theor Biol* 2010, 266, 569-572, doi:S0022-5193(10)00374-7.

320. Abel, D.L. The Cybernetic Cut: Progressing from Description to Prescription in Systems Theory [Scirus SciTopic Page] Available online: www.DavidAbel.us (accessed on 7/20/2024).
321. Abel, D.L. Examining specific life-origin models for plausibility (<http://DavidAbel.us> Last accessed in July, 2024). In The First Gene: The Birth of Programming, Messaging and Formal Control, Abel, D.L., Ed.; LongView Press Academic: 2011; pp. 231-272.
322. Kuhn, T.S. The Structure of Scientific Revolutions, 2nd 1970 ed.; The University of Chicago Press: Chicago, 1970.