

Why Need a Model?

The Debate over the Origin of Life Theories and a Lesson from Simpson's Paradox

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Abstract:

We address the need for a model by considering two competing theories regarding the origin of life: (i) the Metabolism First theory and (ii) the RNA World theory. We discuss two inter-related points. (I) Models are valuable tools in understanding both the processes and intricacies of the origin of life issues. (II) Insights from models also help us to evaluate the core objection to origin of life theories called “the inefficiency objection” commonly raised by proponents of both the Metabolism First theory and the RNA World theory against each other. We use Simpson's paradox as a tool for challenging this objection. Finally, we discuss some of the consequences of our view.

1. Overview
2. Two competing theories about the origin of life
3. The inefficiency objection to two origin of life theories
4. Two types of Simpson's paradox and a lesson learned
5. Summing up

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“Chance *alone* is at the source of every innovation, of all creation in the biosphere. Pure chance, absolutely free, but blind, is at the very root of the stupendous edifice of evolution.... Which means its [*life's*] *a priori probability was virtually zero*....The universe was not pregnant with life nor the biosphere with man. Our number came up in the *Monte Carlo game*” (Jacques Monod, 1971. Emphases are ours.)

“...[L]ife may have originated when the mix of different molecules in the primordial soup passed a certain level of complexity and self-organized into living entities (if so, then life is not highly improbable chance event, but almost *inevitable*). ...Not we the *accidental*, but we the *expected*.” (Stuart Kauffman, 1995. Emphases are ours.)

Overview

Philosophy of science is replete with case studies describing both how scientists use models and the ways in which philosophers have interpreted the application of these models (Bailer-Jones, 2009, Epstein, 2008 & Van Fraassen, 1980). This is no mean achievement, since the multi-textured aspects of models help us to appreciate the significance of those case studies as well as why philosophers have chosen them instead of others in developing their stances toward science and scientific theories. In a certain sense, our approach is no different from theirs. For our case, we will *study* models dealing with both the processes and intricacies of the origin of life issues, a mostly uncharted territory for philosophers. We discuss two competing theories (models) of the origin of life, known as the Metabolism First Theory (MFT), and the RNA World Theory (RWT)

(section 2). Astrobiology is a growing field of research devoted exclusively to the study of the nature and distribution of life in and outside our solar system. Within this field, we include origin of life issues as case studies for how and under what conditions life arises.

Our primary purpose, however, lies elsewhere, i.e. in *our use of* models. We will first investigate the scientific discussions of the origin of life with the help of models, and then use insights from models to evaluate the core objection to the origin of life theories called “the inefficiency objection” commonly raised by proponents of MFT and RWT against each other. The inefficiency objection states that the chemical reactions proposed by competing theories are both too inefficient and not specific enough to explain the generation of early life (section 3). We will propose models that exploit dynamical cases of Simpson’s Paradox to assess the inefficiency objection, and conclude subsequently that the inefficiency objection is untenable (section 4). Simpson’s Paradox involves the reversal of the direction of a comparison or the cessation of an association when data from several groups are combined to form a single whole. Applications of the paradox will show that even though reactions in question could be inefficient locally (in sub-populations), they could emerge as efficient globally (in the overall population). This, in turn, suggests that the emergence of life is *chemically plausible* despite what both competing theorists have been arguing against each other.

Astute readers might have noticed already that we have been using models in various senses ranging from taking them to be representations of reality to treating them as theories/accounts that provide heuristics for probing reality. To admit that the model has multiple purposes is to be sensitive to the practice of science. This brings philosophy of science closer to its common root, i.e. how science is actually being done.

1. **Two competing theories about the origin of life**

Serious scientific experimentation on the origin of life can be traced to the first organic synthesis of urea by Friedrich Wohler in 1828. Wohler showed that it is possible to produce molecules formed in biological processes in the test tube (Solomons 2004). This production of an “organic”

molecule from “inorganic” ones is arguably the first step on the road to the origin of life. Darwin speculated in 1871 that life first started in a “warm little pond, with all sorts of ammonia and phosphoric salts, lights, heat, electricity, etc. present, so that a protein compound was chemically formed ready to undergo still more complex changes.” But the first theory that proposed a testable hypothesis was put forth by Alexander Oparin as early as 1922, which suggested that life formed within vesicles in a primordial soup (Oparin 2003).

There are presently several theories putatively trying to address the origin of life. We focus on two: (i) the Metabolism First Theory (MFT) and (ii) the RNA World Theory (RWT). One way to state the debate between these two theories is in terms of which factor, “energy” or “heredity,” is the central theme behind the emergence of life. The MFT upholds energy as the central driving force for life’s emergence, whereas the RWT champions heredity. According to the MFT, the development of the first living system must have involved a sequence of chemical transformations which achieved a greater level of structure and complexity than its available starting materials. Within this framework, one possible starting point for the sequence to living things was considered to be the polymers of amino acids. The MFT suggests that the chemistry that leads to life could have occurred in a sequestered environment that contained some catalytic activity that would have expedited the production of other important bio-molecules. Many believe that minerals served a number of critical functions in this process. These functions include (i) protection, (ii) support, (iii) selection, and (iv) catalysis. Minerals could have acted as hosts for assembling chemical systems which protected these systems from dispersal and destruction. The surface of these minerals could have also acted as a support for molecules to accumulate and interact upon. It is conjectured that minerals might have acted as a selective agent and framework for certain biologically useful molecules. In short, MFT proponents contend that life originated through a metabolic process, and not via heredity.

Consider the RNA World Theory (RWT). In the 1960s, Francis Crick and several other bio-chemists suggested that the ancestor molecule that triggered the origin of life was neither DNA nor a protein, but perhaps RNA. According to their work, RNA might have catalyzed reactions necessary for replication as well as providing the genetic information necessary to replicate itself. Leslie Orgel, one of the supporters of this view, wrote

“[t]here were a few reasons why we favored RNA over DNA as the originator of the genetic system, even though DNA is now the main repository of hereditary information. One consideration was that the ribonucleotides in RNA are more readily synthesized than are the deoxyribonucleotides in DNA. Moreover, it was easy to envision ways that DNA could evolve from RNA and then, being more stable, take over RNA’s role as the guardian of heredity.”

The proponents of the RWT argue that RNA, rather than DNA or protein, was responsible for the sequence of events that generated the emergence of life. However, the hypothetical primordial RNA would have features not currently found in today’s RNA, such as the ability to self-replicate and the ability to catalyze every reaction necessary for cellular reproduction.

Note that like any science, in astrobiology, hypotheses are proposed, experiments constructed, theories refined according to the data, and subsequently new experiments developed. However, some aspects of astrobiology are speculative and rest on incomplete data, thus allowing for the development of competing theories. This is to be expected since astrobiology is an emerging field of science. The aspects of astrobiology that are speculative or rest on incomplete data pose challenges for testing these competing theories since they involve, in some sense, intractable issues (Bandyopadhyay, et. al. 2010). An evaluation of the correctness of these theories is intractable since we cannot time-travel to observe the unfolding of life. Fortunately, there is a long tradition in science of scientists transforming intractable problems into tractable ones (Earman, 1992; Hawking, 1988). Theories of astrobiology are no exception. The intractability of these two theories can be overcome to some extent by constructing models in labs to conceptualize the conditions leading to the emergence of life. Schoonen *et al* have shown that iron and nickel sulfides could have served as a template, catalyst and energy source for the production of biological molecules, thus supporting the MFT. For the RWT, Altman and Cech independently showed that RNA, unlike DNA, can perform some of the enzymatic functions needed for replication. In principle, RNA molecules could store genetic information and act as catalysts; consequently, they would make pre-existing proteins unnecessary for simpler life (Zaug, Been, and Cech 1986; Guerrier-Takada, Gardiner, Marsh, et al. 1983). These experimental data suggest that a pre-protein life could have existed before life became largely protein catalyzed.

2. The Inefficiency Objection to the Two Origin of Life Theories

Both theorists criticize one another for failing to provide a satisfactory account of the emergence of life on early earth. One of the fundamental objections they advance against one another is what we call “the inefficiency objection.” The inefficiency objection states that the reactions proposed by competing theories are both too inefficient and not specific enough to explain life’s emergence.

Orgel, a proponent of the RWT, examines various metabolic pathways to determine if such pathways could have existed under the conditions present on early Earth. He agrees with MFT proponents that it is logically possible to think that some metabolic cycle could have evolved which then generated early life. However, Orgel insists that scientists are solely concerned with “chemical plausibility.” He writes,

It must be recognized that assessment of the feasibility of any particular proposed prebiotic cycle must depend on arguments about *chemical plausibility*, rather on a decision about *logical possibility*. (Emphasis added; Orgel 2008).

One of the metabolic cycles important to MFT is the reverse citric acid cycle (rTCA). This process is used by some organisms to synthesize reduced carbon compounds from CO₂ in the atmosphere. This type of reaction is an alternative to the Calvin Cycle observed in plants. Wachterhauser has suggested this cycle as a possible candidate for the production of reduced carbon in a prebiotic setting. Orgel has used this cycle to investigate whether it is chemically plausible to demonstrate that life could have generated from such metabolic cycles. While the TCA takes complex carbon molecules in the form of sugars and oxidizes them to CO₂ and water, the reverse TCA fixes CO₂ and water to make useable carbon compounds. Orgel states that each metabolic cycle, including the reverse TCA, “must be evaluated in terms of the efficiencies and specificities.” He concludes that early reactions were not efficient and the existence of side reactions would disrupt the reverse TCA. These side reactions would siphon off carbon captured in earlier steps of the reverse TCA cycle, reducing the efficiency of the total cycle.

Robert Shapiro, a MFT theorist, questions the RWT. In a series of articles spanning more than twenty years, he has argued that RNA, the versatile class of molecules, is a “highly implausible start for life” (Shapiro, 2007), [and although] “no physical law need not be broken for spontaneous RNA formation to happen,...the chances against it are ... immense (Shapiro,

2007.)” To appreciate Shapiro’s arguments against the RWT and some of the subsequent comments by his opponent, we discuss some of the components of the RWT beginning with precursors to nucleic acids.

According to the critics of the RWT, RNA nucleotides are difficult to synthesize, and are very easily destroyed when synthesized in lab conditions. One of the examples Shapiro considers is the autocatalytic formose reaction for the pre-biotic synthesis of ribose. Ribose is the sugar that connects the phosphate backbone to the nucleobase head. The synthesis of ribose should be an integral step to the prebiotic production of RNA necessary for an RNA world. However, Shapiro writes, “[t]he evidence that is currently available does not support the availability of ribose on the prebiotic earth, except perhaps for brief periods of time, in low concentration as part of a complex mixture, and under conditions unsuitable for nucleotide synthesis.” He argues that although the Urey-Miller experiment yields amino acids, it fails to provide nucleotides, the building blocks of RNA. He states that the reactions that yield RNA precursors are too “inefficient,” and produce these precursors in very low number. Recent work has, however, shown that borate minerals are able to stabilize ribose in early earth conditions against the inevitable Browning reactions which transform sugars into largely non-functional polymeric mixtures of non-essential molecules for the emergence of life (Ricardo, et. al. 2004). However, Shapiro’s principle argument that reactions for RNA precursors are inefficient could still be salvaged. Although borate minerals are able to stabilize ribose, their paper shows that the rate of the formation of ribose as a natural outcome of the chemical polymerization of formaldehyde remains inefficient compared to the rate of the non-ribose molecules which are produced in an 8:2 ratio of non-ribose to ribose (Ricardo, et. al. 2004). Therefore, ribose synthesis is still likely to be too inefficient to produce large concentrations of RNA precursors.

Three inter-related points deserve mention since they are shared by both Orgel and Shapiro despite their vehement opposition to each other’s theory. First, both agree that the reactions cited by their opponent to occur on early earth are logically possible. Therefore, the point of disagreement is not about the logical possibility of those reactions to take place on early earth. It is rather a point of chemical plausibility of those reactions in early earth. Neither Orgel or Shapiro holds the view that that these reactions violate laws of physics or chemistry, but each argues that the reactions cited by the other are chemically improbable. Both think that since those

reactions are improbable, they are therefore chemically implausible. The third and final point, on which surprisingly both agree, concerns what we have called the inefficiency objection. If we read the objection that adherents to both theories raise against each other, then we find that they argue that the early earth reactions invoked by adherents of either the RWT or the MFT are both too inefficient and not specific enough to explain the spark of life on early earth.

3. Two Types of Simpson’s Paradox and a Lesson Learned

We have defined Simpson’s Paradox (SP) as the reversal of the direction of a comparison or the cessation of an association when data from several groups are combined to form a single whole (See Bandyopadhyay et. al., 2011 and Blyth, 1972). We call this the Static version of the paradox. Here is a familiar example of the static version.

Simpson’s Paradox (Static Version)

CV	Dept. 1	Dept. 2	Acceptance Rates		Overall Acceptance Rates		
	Accept	Reject	Accept	Reject	Dept. 1	Dept. 2	
F	180	20	100	200	90%	33%	56%
M	480	120	10	90	80%	10%	70%

Table I

In Table 1, “CV” includes two categorical variables, “F” for “females” and “M” for “men.” “A” and “R” represent “the rates of acceptance/rejection” for two departments, D₁, and D₂. This is a formulation of the paradox in which the association in the subpopulations is reversed in the combined population. Although the acceptance rates for females are higher than for males in each department, in the combined population, the rates are reversed. We call this the Static version because it involves a static one-time cross-section of a dataset without constant updates in light of the impact of new data. However, there is another version of the paradox called the Dynamic Version which has been recently described in (Chuang et. al 2009). In molecular dynamic cases of SP, we observe, over a period of time, the reversal of the direction of a major molecular product evolving as a whole when minor molecular products are pooled together from

their sub-reactions. We will be exploiting the theme behind the dynamic version of the paradox to contend that the inefficiency objection is untenable. First, we will provide an example to illustrate both how a dynamic case of the paradox works and why Orgel's objection is not necessarily true. Then we will apply the same treatment to Shapiro's objection. Since the molecular dynamical case involves a change in growth-rate, we first define the notion of growth rate (G) as

, where N_2 is the number of molecules at a later time and N_1 represents the number at an earlier time. One example of the dynamic case of the paradox is represented by Table II, with growth rates between 1.17 and 1.57, depending on the groups being compared. Here, we observe the growth rate change, of, for example, "acetyl-CoA" in sub-reactions over a period of time. In the reverse TCA cycle, the functional molecules are represented by acetyl-CoA, the product of the 8 steps of the reverse TCA cycle which gains two carbons in the acetyl functional group via reduction of CO_2 . Non-functional molecules are created every time an entire cycle is not completed. An inefficient reaction causes loss of the carbon captured earlier in the reverse TCA. For this example, we have made three assumptions following Orgel (Orgel, 2008). (1) Each reaction within the reverse TCA is 90% efficient. (2) Acetyl-CoA is stable enough in its environment that it does not undergo any appreciable loss. (3) The supply of CO_2 is not limiting. According to Orgel's example, a 90% efficiency per reaction should not produce an adequate supply of acetyl-CoA, because after 8 reactions of 90% efficiency, the efficiency of the total cycle of acetyl-CoA is less than 45%, meaning that the cycle produces only non-functional molecules more than half of the time. This presumably led Orgel to conclude that a non-catalyzed reverse TCA is chemically implausible.

Consider Table II in which CV represents two categorical variables, F (acetyl-CoA) and NF (non-functional molecules). R1 and R2 represent different individual reaction groups and T_1 and T_2 represent two time points where a count is made. For example, in R1, we began with 1100 molecules altogether; 1000 functional and 100 non-functional molecules. In R1, NF grew at a rate of $(n \times 1.57)$ from its original number (n) over time T_i to T_{i+1} whereas F grew at a rate of $(n \times 1.43)$ over the same period. In R2, we began with 1100 molecules altogether; 100 functional and 1000 non-functional molecules. NF grew at a rate of $(n \times 1.285)$, whereas F grew at a rate of $(n \times 1.17)$. We see that although acetyl-CoA is a minor product within each subpopulation, the overall

growth rate for F is 1.41, which is greater than NF growth of 1.31 for the global population. This possible scenario casts doubt on the inefficiency objection raised by Orgel against the MFT.

Simpson's Paradox (Dynamic Version)

CV	R1		R2		Growth Rates		Overall Growth Rates		
	T1	T2	T1	T2	R1	R2			
F	1000	1430	100	117	1.43	1.17	1.41		
NF	100	157	1000	1285	1.57	1.285	1.31		

Table II

Table II is visually represented in Figure 1. Here, the “dark” line stands for “functional molecules” and the “grey” line represents “non-functional molecules.” Even though the dark lines are shorter in length than the grey lines in R1 and R2, in the overall population, the former dominate over the latter showing the required reversal to reject the inefficiency objection to the MFT.

Shapiro has raised a similar objection involving the inefficiency of RNA production for the RWT. He has argued that ribose reactions are inefficient since ribose reactions cannot generate an adequate amount of the RNA precursors required for production of polymerized RNA. Three assumptions are made for this example of the paradox. (1) The ratios of percent yields of each reaction are as reported in (Ricardo, et. al., 2004). So, conditions that produce these yields must be present. While the ratios of these percent yields must stay fixed to those reported reaction

times, reaction rates can vary (such as might happen if the reaction temperature has changed during the time of the experiment). (2) Ribose is stable enough not to undergo appreciable loss. (3) The supply of precursors must not be limiting. Based on these assumptions, we have produced Table III. We show that although functional molecules (ribose) grow less rapidly than non-ribose products, the ribose can still emerge as the major product globally against the non-functional molecules. This indicates that the production of functional molecules from prebiotic precursors can be far more *chemically plausible* globally than indicated by the detractors of each theory (RWT and MFT). If a reaction can be globally efficient as shown by SP, then the inefficiency objection to the origin of life theories is untenable, and thus the emergence of life on early earth seems more probable. In Table III, while the ratio of the growth rates (about 1.2: 1.8 as in Ricardo et. al. 2004) remains the same in sub-reactions, the overall growth rates display another dynamical case of Simpson’s Paradox.

Simpson’s Paradox (Dynamic Version)

CV	R1		R2		Growth Rates		Overall Growth Rates		
	T1	T2	T1	T2	R1	R2			
R	10	12	1000	2000	1.2	2		1.99	
NR	1000	1795	10	29	1.795	2.9		1.81	

Table III

Table III is visually represented in Figure II. Here, the “dark” line represents “R” (ribose) and the “grey” line represents “NR” (non-ribose). Although the dark lines in R1 and R2 are shorter than the grey lines, in the overall population, the dark line dominates over the grey line. This reversal allows us to jettison the inefficiency objection to the MFT.

The lesson from Simpson's paradox is that life could emerge from the accumulation of minor products of sub-reactions. These products become major products globally, and thus contribute to the emergence of life. The use of dynamic versions of the paradox does not just show that it is logically possible for functional molecules to emerge as a major product globally; it also shows that it is chemically plausible for functional molecules to emerge as a major product globally since this emergence is not improbable.

Work by Russell *et al* has more direct implications for this work. They state that compartments that form at hydrothermal vents could act as membranes that sequester some molecules, but allow others to pass through (Russell *et al* 1997). Similar compartments have been used to show enzyme free polynucleotide replication (Baaske *et al* 2007). We mention the idea of prebiotic hydrothermal compartments to explain a scenario under which a Simpson's paradox can occur. In this scenario, each compartment acts as an individual sub-reaction chamber producing molecules in yields similar to those reported. However, in this scenario these compartments somehow release the products of their reaction, either via destruction of the compartment or through leaky walls. This ultimately creates a global population of molecules. Thus, hydrothermal vents provide conditions under which a plausible scenario for the Simpson's Paradox can affect chemical yields.

6. Summing Up

We began our discussion with two leading theories of the origin of life, the MFW and RWT. Within the dispute between these two theories, we found a common thread shared by them which we called the inefficiency objection. According to this objection, the reactions proposed by competing theories are both too inefficient and not specific enough to explain the generation of early life. One assumption on which this objection rests is that the chemical implausibility of certain key reactions implies that the emergence of life is highly improbable. We applied dynamical versions of the paradox to show that this assumption is false. We demonstrated that the emergence of life is not at all improbable relative to each theory given a plausible scenario of

the paradox; therefore, chemical plausibility of life is a likely fact, and not just a dream. Since the inefficiency objection relies on the assumption of implausibility, the objection has turned out to be false. The implication of our critique is that one alleged roadblock to the emergence of life on early earth has been thus removed. There is a further significance of our work that is tied to contemporary probability-based debates about the emergence of life in the universe.

Remember what Jacques Monod said in the beginning quote. He said that since the emergence of life is a Monte Carlo simulation of numerous factors, there is a “virtually zero” probability that life could have ever occurred. In contrast, Stuart Kauffman holds the position that the emergence of life is “inevitable,” implying that its emergence is possible with a probability of almost one. We would, however, like to distance ourselves from these two extreme positions: (i) Monod’s pessimism and (ii) Kauffman’s optimism. We have adopted a stance somewhere in the middle ground by suggesting that life is a likely event; neither its probability is zero, nor its probability almost one. We would rather allow the emergence of life to have a range of probabilities, since this approach reflects the wide range of conditions present both on earth and throughout the universe.

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