# The Mystery of Life's Origin

## The Continuing Controversy

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Seattle Discovery Institute Press 2020

## Description

The origin of life from non-life remains one of the most enduring mysteries of modern science. *The Mystery of Life's Origin: The Continuing Controversy* investigates how close scientists are to solving that mystery and explores what we are learning about the origin of life from current research in chemistry, physics, astrobiology, biochemistry, and more. The book includes an updated version of the classic text *The Mystery of Life's Origin* by Charles Thaxton, Walter Bradley, and Roger Olsen, and new chapters on the current state of the debate by chemist James Tour, physicist Brian Miller, astronomer Guillermo Gonzalez, biologist Jonathan Wells, and philosopher of science Stephen C. Meyer.




## Library Cataloging Data

*The Mystery of Life's Origin: The Continuing Controversy* by Charles B. Thaxton, Walter L. Bradley, Roger L, Olsen, James Tour, Stephen Meyer, Jonathan Wells, Guillermo Gonzalez, Brian Miller, and David Klinghoffer

486 pages, 6 x 9 x 1.0 inches & 1.4 lb, 229 x 152 x 25 mm. & 0.65 kg

Library of Congress Control Number: 9781936599745

ISBN-13: 978-1-936599-74-5 (paperback), 978-1-936599-75-2 (Kindle), 978-1-936599-76-9 (EPUB)

BISAC: SCI013040 SCIENCE / Chemistry / Organic

BISAC: SCI013030 SCIENCE / Chemistry / Inorganic

BISAC: SCI007000 SCIENCE / Life Sciences / Biochemistry

BISAC: SCI075000 SCIENCE / Philosophy & Social Aspects

Publisher Information

Discovery Institute Press, 208 Columbia Street, Seattle, WA 98104

Internet: http://www.discoveryinstitutepress.com/

Published in the United States of America on acid-free paper.

Second Edition, First Printing, January 2020.

# Contents

# 14. Thermodynamic Challenges to the Origin of Life

*Brian Miller*

The thermodynamic barriers to the origin of life have become decidedly more well defined since this book's first publication. The initial challenges described in the original edition still stand. Namely, spontaneous natural processes always tend toward states of greater entropy, lower energy, or both. The change of entropy and energy are often combined into the change of free energy, and all spontaneous processes move toward lower free energy. However, the generation of a minimally functional cell on the ancient Earth required a local system of molecules to transition into a state of both lower entropy and higher energy. Therefore, it must move toward dramatically higher free energy. The chance of a system accomplishing this feat near equilibrium is astronomically small.[1]

Many origin-of-life researchers have responded to this challenge by arguing that a system driven far from equilibrium could self-organize into a functional cell through processes that are connected to such monikers as complex systems,[2] emergence,[3] synergetics,[4] or nonequilibrium dissipative systems.[5] The basic hope is that some new physical principles could overcome the barriers to life's origin mandated by classical thermodynamics. However, advances in nonequilibrium thermodynamics

have proven that the odds of a system driven far from equilibrium generating an autonomous cell are no greater than the odds for one near equilibrium.

Others have proposed that "natural engines" on the early Earth converted one form of energy into another that could drive a local system to sufficiently high free energy.[6] These approaches have proven equally disappointing. The only plausible explanation for the origin of life is intelligent agency.

## Fluctuation Theorems and the Origin of Life

One of the greatest challenges in systems driven far from equilibrium was describing them quantitatively. Then a breakthrough came in the 1990s with the advent of the fluctuation theorems. The first derived theorem was the Evans-Searles fluctuation theorem (ESFT).[7] It demonstrated in dissipative systems[8] that entropy can run in reverse. But probabilities drop exponentially with the magnitude of the entropy decrease[9] (note that the entropy, S, is presented in the units of nats, so its value is dimensionless):

$$\frac{p(S = A)}{p(S = -A)} = e^{A}$$

This theorem was used to solve the apparent contradiction of macroscopic processes progressing irreversibly toward greater entropy while the underlying physical dynamics are time-reversible. The ESFT demonstrated that the dynamics of individual particles in a given microstate (specific configuration of molecules) might be time-reversible, but the statistical tendency is for microstates to move in a direction that corresponds to an increase in entropy. Therefore, the average entropy production moving forward in time is always positive.[10]

In the context of the origin of life, the theorem demonstrates the implausibility of any realistic energy source, such as sunlight or heat from a thermal vent, driving a local system toward dramatically lower entropy.

As mentioned in Chapter 8 above, Harold Morowitz performed a crude estimate for the reduction of entropy in the formation of a cell associated with the generation of macromolecules (e.g. RNA, DNA, proteins). His approximation for the entropy reduction was on the order of .1 cal/deg-gm.[11] This quantity corresponds in a bacterium[12] to a reduction of greater than $10^{10}$ nats, which yields a probability from the ESFT for a bacterial cell spontaneously forming of less than 1 in $10^{10^9}$, a clear impossibility even if the first cell were orders of magnitude smaller.

A second theorem, known as the Crooks Fluctuation Theorem, was derived to study systems acted upon by nondissipative fields or forces that transition a system from an initial state to a final state with a different equilibrium free energy. In classical thermodynamics the transition can often be assumed to proceed slowly enough for the process to remain close to equilibrium. The work, W, performed could then equal the change in free energy, ΔF.[13] However, if the transition occurs away from equilibrium, some of the applied work will typically be lost as heat.

Now let A and –A designate work performed in forward and time-reversed transitions. Crooks's theorem establishes that the ratio of probabilities over A and –A is

$$\frac{p_f\left(W = A\right)}{p_r\left(W = -A\right)} = e^{\beta(A-\Delta F)}$$

where β is the inverse of the initial temperature of the system and the thermal bath surrounding it times the Boltzmann constant, and $A - \Delta F$ is the heat released during the transition into the thermal bath.

Similar to the ESFT, the Crooks theorem shows that there is a finite probability that, while work is performed on the system, the increase in free energy can exceed the amount of applied work: A – ΔF is negative. As a result, heat will be *absorbed* from the bath and converted to free energy, thus gaining energy for free. However, the probability drops exponentially with the magnitude of the heat absorbed.[14]

The Crooks theorem can be used to calculate the probability for a driven system absorbing sufficient heat from the environment to provide the needed increase in free energy for the origin of life. As mentioned in Chapter 7, Morowitz estimated that the formation of a cell would require a collection of prebiotic molecules absorbing roughly $10^{-9}$ joules ($10^{10}$ eV) of heat.[15] This value corresponds in the Crooks equation to a probability of occurring on the order of 1 in $10^{10^{11}}$, which is the same as in a system near equilibrium.

The odds do not improve if the process takes place in multiple steps separated by extended periods of time.[16] In fact, the challenges actually increase if each step towards life does not proceed immediately after the previous one, for the chances of the system moving toward higher entropy (or lower free energy) are far greater than moving in a life-friendly direction. Any progress could be completely squandered by a few deleterious thermal fluctuations or chemical interactions. Therefore, all origin-of-life scenarios appear thermodynamically implausible.

## The Inadequacy of "Natural Engines"

The only way to overcome the free energy challenge is for some mechanism to apply work in such a manner as to raise a system's free energy. Modern cells accomplish this goal by employing complex molecular machinery and finely-tuned chemical networks to convert one form of energy from the environment into high-energy molecules. The energy from the breakdown of these energy-currency molecules is directed toward powering targeted chemical reactions and other processes.[17] However, no such machinery could be synthesized until after life originated.

Many proposals have been offered for how various natural mechanisms could impart the needed work. Examples include meteorite crashes,[18] moving mica sheets,[19] shock waves,[20] volcanic hot springs,[21] and proton gradients.[22] However, none of these sources could have generated more than a tiny fraction of the required free energy. They primarily produce energy in the form of heat or light, but such raw energy bursts increase the entropy of a system,[23] causing it to move in a direction

opposite to that of life. Life requires a mechanism that can increase the free energy to allow for the energy of the system to increase while also decreasing the entropy.

To illustrate the challenge, the power production density (free energy increase per time per mass) of the simplest known cell for only maintenance[24] is on the order of 1 watt per gram (W/g), which is comparable to that of a high-performance sports car. A protocell would have to generate this amount in the latter stages[25] leading toward an autonomous cell just to overcome the thermodynamic drive back toward equilibrium, and even greater amounts would be required for replication.[26] For comparison, a leading proposal for energy production involves proton gradients in small crevices in hydrothermal vents powering life-friendly chemical reactions. However, experimental simulations of vents under ideal conditions only generate small quantities of formaldehyde,[27] which is believed to be a precursor to some of life's building blocks. The corresponding power production density is on the order of 1 nanowatt per gram (nW/g),[28] a billionth of what is needed. Moreover, the concentration of yielded formaldehyde is about a millionth of what would be required to drive any life-friendly reaction. As a result, alkaline vents could never supply even the smallest fraction of the power needed, and only minuscule amounts of the generated chemical energy[29] could be directed toward forming the first cell. Other scenarios perform no better.

Such an enormous disparity between the required and available energy production demonstrates the implausibility for a "natural engine" forming on the early Earth with sufficient capacity to support any origin-of-life scenario. Consequently, highly efficient molecular engines comparable to those in modern cells are needed from the very beginning to provide a continuous supply of energy-currency molecules capable of driving nonspontaneous cellular processes.

## The Necessity of Proteins

An additional challenge is that a minimally functional metabolism requires directing a highly specific set of chemical reactions and prevent-

ing interfering cross-reactions. The chance of a randomly selected set of reactions meeting such exacting criteria is infinitesimally small.[30]

Compounding the difficulty, individual reactions in the chemical pathways to synthesize life's building blocks and other metabolic reactions require multiple, mutually exclusive reaction conditions,[31] so no environment could support more than a few of them. In addition, many of the reactions are energetically unfavorable, so energy from the breakdown of the energy-currency molecules must be directed toward enabling them to move in the required direction. And even energetically favorable reactions are typically too slow to drive cellular operations. As a consequence, special protein molecules known as enzymes, or their equivalent, are essential to support cellular life since only they could sufficiently accelerate a highly specific set of reactions.[32]

Enzymes are long chains of amino acids that fold into specific three-dimensional structures with crevices known as active sites. These sites accelerate specific reactions' turnover rates by factors typically between $10^8$ and $10^{10}$, and the increase in many cases could be significantly higher.[33] Without their presence, the concentration of a reactant would typically need to be at least millions of times greater to maintain a comparable reaction rate. Achieving such high concentrations for nearly every cellular metabolite[34] would be highly implausible. The active sites also create the necessary physical and chemical conditions to support their target reactions, so a multitude of diverse reactions can be maintained in the same cellular environment simultaneously. In addition, the enzymes couple the breakdown of the energy-currency molecules to energetically unfavorable chemical reactions and other processes, so the energy from the former can power the latter. As a consequence, a complete suite of enzymes must have existed at the very earliest stages of life's origin.

Yet the challenges faced in any origin-of-life scenario related to the formation of enzymes and other proteins are immense. First, any natural process which yielded amino acids would also have produced a myriad of other molecules which would have blocked the formation of long functional chains.[35] Second, the probability of amino acids forming

a chain in even the most ideal conditions drops exponentially with its length, so none would likely have formed on the early Earth sufficiently long to correspond to nearly any of the essential proteins in a minimally functional cell.[36] Third, even if the probability for long-chain formation were significantly higher, all realistic processes on the early Earth would have yielded both left-handed and right-handed amino acids. However, functional proteins require amino acids of only one chirality. Even if some process could generate a solution of homochiral amino acids, it would spontaneously racemize (move toward equal quantities of both versions).[37] Every one of these hurdles appears insurmountable.

An additional challenge, which is rarely acknowledged, is the excessive time requirement for a protein and a cell membrane located in the same small pool of water to make contact through the random motion of diffusion. The main search mechanism would have to be diffusion, since water sufficiently agitated to mix molecules at microscales would likely eviscerate any cell membrane.[38] An estimate for the timescale begins by calculating the time required for an enzyme to traverse the diameter of a cell using the protein's diffusion coefficient (100 $\mu m^2/s$)[39] and the width of a bacterium (1 $\mu m^3$). The average time approximates to one millisecond. Therefore, an enzyme could only sample a volume of 1 $\mu m^3$ every millisecond, even ignoring the fact that diffusion would cause resampling of the same micro-volumes repeatedly. A lower estimate for enzyme-membrane contact would then be on the order of tens of millions of years.

Yet a protein's lifespan is on the order of weeks to years, based on the half-life of peptide bonds in water,[40] and the actual breakdown time measured in bacteria is typically considerably less, only on the order of hours.[41] Therefore, any protein formed on the early Earth would denature long before finding its way into a protocell. The problem for RNA is even greater since it is considerably less stable.[42]

## The Information Challenge

An even greater challenge is that the protein molecules that compose the molecular engines and the enzymes consist of chains of amino acids in precise sequences, so a prerequisite for life is large quantities of functional information.[43] Specifically, the amino acids have to be arranged in the right order in the same way the letters in a sentence must be arranged properly to convey the intended meaning.[44] The sequential order is crucial for the chains to fold into the correct three-dimensional structures to properly perform their intended functions.

The centrality of information is becoming increasingly apparent with theoretical analyses on its role in enacting causal control over outcomes, such as a metabolic pathway synthesizing a specific amino acid at the correct time in the needed quantities.[45] The term "control information" has even been designated to those entities within cells (e.g. nucleotide sequences in DNA) that direct the acquisition and use of matter, energy, and information to enable biological functions. And the implementation of this information has been recognized as essential for maintaining a cell's highly specified low-entropy state.[46]

An extreme lower bound for the prerequisite information required for the origin of life can be calculated from the needed proteins' *algorithmic specified complexity* (ASC). The ASC measure was developed to quantify the functional, semantic, or meaningful information in a pattern,[47] and it provides an upper limit on the probability for a pattern with a given ASC measure to occur by any undirected process: $P\,[ASC(X,C,P) \geq \alpha] \leq 2^{-\alpha}$.[48] The minimal information calculation proceeds by first estimating the minimal number of required proteins in an autonomous cell and then estimating the ASC for a single protein. The product of these two numbers is the lower bound for the first cell.

Several research groups have attempted to identify for the simplest viable cell the minimal set of proteins. Removing just one of these essential proteins would result in the metabolism ceasing to function, and the cell would degrade irreversibly into simple chemicals. Similarly, systems

engineers, such as those at NASA, have analyzed the minimal functional requirements for a self-replicating machine.[49] The results from both classes of studies converge on several essential functional components:

- Large repositories of information and information processing.
- Manufacturing centers that construct all of the essential pieces.
- Assembly and installation processes.
- Energy production and distribution machinery.
- Automated repair and replacement of parts.
- Global communication and coordination with feedback control systems.
- Sensing of environment and calculation of needed responses.
- Self-replication, which draws upon nearly all other essential functions.

In the context of a minimal cell, these requirements correspond to over 300 protein-coding genes in a parasite[50] and probably double that amount in a free-living prokaryote.[51]

The ASC associated with a single protein can be estimated from the probability for a random sequence of amino acids to properly fold into a structure that performs a specific cellular function. That value for only one portion of a relatively small protein was calculated to be on the order of 1 in $10^{77}$.[52] This estimate equates to an ASC value of over 250 bits,[53] so the minimal ASC for one copy of the over 300 required proteins is over 75,000 bits. This value can be compared with the maximum ASC value that could have been generated from the total number of protein sequences that could have occurred in the entire history of the Earth. The most wildly optimistic estimates have assumed that all of the available atoms of nitrogen, carbon, and oxygen on the planet contributed to amino acid sequences of at least modest length.[54] The upper estimates are less than $10^{60}$, which corresponds to a maximum ASC value of roughly 200 bits.[55]

Clearly, the required prerequisite information vastly exceeds what could have been generated by any undirected process. In fact, even if 1

in 10 amino acid sequences corresponded to a functional protein, the cumulative ASC value would still exceed the maximum limit.

In reality, the required information is significantly greater than the previous analysis suggests, for it does not include several other constraints and requirements.[56] For instance, the metabolism must start with sufficient numbers of enzymes, energy-currency molecules, and intermediate metabolites.[57] In addition, multiple copies of most proteins are needed,[58] such as those that are assembled into multiprotein complexes.[59]

Compounding the problem, proteins have a limited lifespan, so they must constantly be replaced. Proteins do not self-replicate, and RNAs are too unstable for long-term information storage.[60] Therefore, the minimal requirements for a cell must include the protein sequences being encoded into DNA, and the cell must possess the DNA-protein translational machinery to access the encoded information and implement it in the manufacture of new proteins. In addition, a functional metabolism requires the cell to tightly control each reaction using feedback loops, and this meticulous coordination is to a large extent accomplished through the regulation of the genes through gene-specific promoter, operator, and enhancer regions.[61] They direct the timing and quantities of proteins manufactured.

Studies on metabolic networks[62] have demonstrated that a functional metabolism requires an "intricate network of mutual interactions" that "depends crucially on the numerical values of kinetic parameters and regulatory interactions," so the additional information associated with these regulatory regions in DNA must be significant. Future studies will undoubtedly only increase the chasm between the information that could be produced by any natural process and that required in a minimally functional cell at its instantiation.

In summary, the formation of the original cell cannot plausibly be explained by any undirected process. In addition, its minimal requirements demonstrate unmistakable signs of intelligence. In any other context, the identification of a nanotechnology vessel capable of energy production, information processing, and the other identified require-

ments would immediately be recognized as a product of design by any reasonable criteria. In particular, cellular structures and operations demonstrate unmistakable evidence of foresight, coordination, and goal-directedness, which are telltale signs of intelligent agency.

## Endnotes

1. The probability for *E. coli*, as calculated by Morowitz, is $10^{-10^{11}}$; for the discussion see Chapter 7 above, section "Closed Systems Near Equilibrium", and for the number see H. J. Morowitz, *Energy Flow in Biology* (New York: Academic Press, 1968), 67.
2. A. Lazcano, "Complexity, Self-Organization and the Origin of Life: The Happy Liaison?," in *Origins of Life: Self-Organization and/or Biological Evolution?*, eds. Marie-Christine Maurel and Maryvonne Gerin (Les Ulis, France: EDP Sciences, 2009), 13–22, https://doi.org/10.1051/orvie/2009002.
3. Noam Lahav, Shlomo Nir, and Avshalom C. Elitzur, "The Emergence of Life on Earth," *Progress in Biophysics and Molecular Biology* 75, no. 1–2 (January 2001): 75–120, https://doi.org/10.1016/S00796107(01)00003-7.
4. Werner Ebeling and Rainer Feistel, "About Self-Organization of Information and Synergetics," in *Complexity and Synergetics*, eds. Stefan C. Müller, Peter J. Plath, Günter Radons, and Armin Fuchs (Cham: Springer International Publishing, 2018), 3–8, https://doi.org/10.1007/978-3-319-64334-2_1.
5. James J. Kay, "Ecosystems as Self-Organizing Holarchic Open Systems: Narratives and the Second Law of Thermodynamics" in *Handbook of Ecosystems Theories and Management*, eds. Sven Erik Jorgensen and Felix Muller (Boca Raton, FL: CRC Press, 2000),135–160.
6. Nick Lane, "Proton Gradients at the Origin of Life," *BioEssays* 39, no. 6 (2017); Anthonie W. J. Muller, "Thermosynthesis as Energy Source for the RNA World: A Model for the Bioenergetics of the Origin of Life," *BioSystems* 82, no. 1 (2005): 93–102.
7. Denis J. Evans and Debra J. Searles, "The Fluctuation Theorem," *Advances in Physics* 51, no. 7 (2002): 1529–85, https://doi.org/10.1080/0001873021015513. Technically, the entropy cannot be calculated far from equilibrium since the temperature is not well defined. The canonical version of the ESFT uses the entropy-like quantity known as the dissipation function. It is a more generalized version of spontaneous entropy production which can be defined in systems driven far from equilibrium. See James C. Reid et al., "The Dissipation Function: Its Relationship to Entropy Production, Theorems for Nonequilibrium Systems and Observations on Its Extrema," in *Beyond the Second Law: Entropy Production and Non-Equilibrium Systems*, ed. Joseph J. Vallino et al. (New York: Springer, 2014), 31–47.
8. Dissipative systems are driven by dissipative fields which do not change the ground state energy of the system. Instead, the energy which enters the system due to these fields can completely turn into heat and diffuse out into the surrounding environment. Examples include the application of an electric field to a resistor or of light to a solution of interacting chemicals. In contrast, the energy imparted due to the application of a nondissipative or elastic field can be stored in the system as potential energy. For instance, the application of an electric field to solid sodium chloride increases the potential energy corresponding to intermolecular forces between the constituent molecules. See Denis J. Evans, Debra J.

Searles, and Stephen R. Williams, *Fundamentals of Classical Statistical Thermodynamics: Dissipation, Relaxation, and Fluctuation Theorems* (Weinheim, Germany: Wiley-VCH, 2016), 23.

9. The probability density ratio for $p(S)/p(-S)$ can be converted to an upper bound for the probability of entropy, S, taking on the negative value of –A or less by recognizing that $p(S) < p(-S)e^{-A}$ for values of S less than –A. Therefore, $P(S < -A) < P(S > A)e^{-A} < e^{-A}$.
10. Some physicists have argued that the proposed solution is incomplete and must be combined with the fact that our universe started in a low entropy state. See P. C. W. Davies, "The Arrow of Time," *Astronomy and Geophysics* 46, no. 1 (February 1, 2005): 1.26–1.29, https://doi.org/10.1046/j.1468-4004.2003.46126.x.
11. H. J. Morowitz, *Energy Flow in Biology* (New York: Academic Press, 1968), 97.
12. The approximate weight of a bacterium is $10^{-12}$g, which yields a drop in entropy on the order of $10^{-13}$ joules/deg. See Ron Sender, Shai Fuchs, and Ron Milo, "Revised Estimates for the Number of Human and Bacteria Cells in the Body," *PLoS Biology* 14, no. 8 (2016), https://doi.org/10.1371/journal.pbio.1002533.
13. The change in the Helmholtz free energy (F) equals the change in the internal energy of a system (U) minus the temperature times the change in entropy (S): $\Delta F = \Delta U - T\Delta S$. In a system where the volume is held constant, ΔF for spontaneous processes is always negative. If the pressure is held constant, then spontaneous processes correspond to a negative change in the Gibbs free energy (G), which is equal to the change in enthalpy (H) minus the temperature times the change in entropy: $\Delta G = \Delta H - T\Delta S$. The change in enthalpy represents the change in energy of a transition adjusted for the work performed on the environment due to a change in volume: $\Delta H = \Delta U + P\Delta V$. Positive changes in enthalpy represent heat being absorbed from the environment and negative changes represent heat being released. Physicists and chemical engineers typically work with the Helmholtz free energy while chemists typically work with the Gibbs free energy.
14. The same general approach can be applied to the Crooks FT as was applied to the Evans-Searles FT to demonstrate that the probability for the heat being absorbed with a value of Q or greater drops exponentially with Q.
15. Morowitz, *Energy Flow in Biology,* 65. The estimate was performed by calculating the difference between the average bond energies in a bacterium and those in the molecules in the environment of the ancient Earth.
16. The entropy and the free energy are state functions, so they are path-independent. The probabilities are exponentials of those functions. To appreciate the significance, imagine breaking the path from nonlife to life into three steps, which constantly move toward lower entropy (or higher free energy). Then, $-\Delta S = -\Delta S1 - \Delta S2 - \Delta S3$, and the probabilities associated with random fluctuations driving each step would be $e^{-\Delta S1}$, $e^{-\Delta S2}$, and $e^{-\Delta S3}$. The chance for all three fluctuations taking place consecutively is then $e^{-\Delta S1} \cdot e^{-\Delta S2} \cdot e^{-\Delta S3} = e^{-\Delta S1-\Delta S2-\Delta S3} = e^{-\Delta S}$. The probability for the three steps is the same as for one combined step.
17. The Crooks formalism originally assumed that the work, W, results from physical forces or applied fields. However, it can be reformulated to include contributions from chemical work resulting from high-energy reactants. See Riccardo Rao and Massimiliano Esposito, "Conservation Laws and Work Fluctuation Relations in Chemical Reaction Networks," *The Journal of Chemical Physics* 149, no. 24 (December 28, 2018): 245101, https://doi.org/10.1063/1.5042253.

18. Carsten Bolm et al., "Mechanochemical Activation of Iron Cyano Complexes: A Prebiotic Impact Scenario for the Synthesis of α-Amino Acid Derivatives," *Angewandte Chemie International Edition* 57, no. 9 (February 23, 2018): 2423–26, https://doi.org/10.1002/anie.201713109.

19. Helen Greenwood Hansma, "Possible Origin of Life between Mica Sheets: Does Life Imitate Mica?," *Journal of Biomolecular Structure & Dynamics* 31, no. 8 (2013): 888–95, https://doi.org/10.1080/07391102.2012.718528.

20. Charles S. Cockell, "The Origin and Emergence of Life under Impact Bombardment," *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 361, no. 1474 (October 29, 2006): 1845–55; discussion 1856, https://doi.org/10.1098/rstb.2006.1908.

21. Muller, "Thermosynthesis as Energy Source for the RNA World: A Model for the Bioenergetics of the Origin of Life."

22. Nick Lane, John F. Allen, and William Martin, "How Did LUCA Make a Living? Chemiosmosis in the Origin of Life," *BioEssays* 32, no. 4 (2010): 271–80, https://doi.org/10.1002/bies.200900131.

23. S. R. De Groot, *Non-Equilibrium Thermodynamics* (Mineola: Dover Publications, 2013), 20–23.

24. The simplest known organism is *Mycoplasma pneumoniae*. Its energy production for maintenance is roughly 50,000 ATP/s—see Judith A. H. Wodke et al., "Dissecting the Energy Metabolism in *Mycoplasma Pneumoniae* through Genome-Scale Metabolic Modeling," *Molecular Systems Biology* 9 (2013): 653, https://doi.org/10.1038/msb.2013.6. ATP molecules provide 30,000 J/mol of energy—see Victor W. Rodwell et al., *Harper's Illustrated Biochemistry* (New York: McGraw-Hill Education, n.d.), 107. The size of *Mycoplasma* is around .15 mm—see Laleh Nikfarjam and Parvaneh Farzaneh, "Prevention and Detection of Mycoplasma Contamination in Cell Culture," *Cell Journal* 13, no. 4 (2012): 204. Therefore, the energy production density is on the order of 1 W/g.

25. *Mycoplasma pneumoniae* is a parasite, so it lacks many of the metabolic processes of free-living prokaryotes. As a result, the first cell would have required a larger genome, thus increasing energy requirements—see Stephen J. Giovannoni et al., "Genetics: Genome Streamlining in a Cosmopolitan Oceanic Bacterium," *Science* 309, no. 5738 (2005): 1242–45, https://doi.org/10.1126/science.1114057. In addition, if enzymes or other processes were less efficient, the required energy output would have also increased.

26. Michael Lynch and Georgi K. Marinov, "The Bioenergetic Costs of a Gene," *Proceedings of the National Academy of Sciences of the United States of America* 112, no. 51 (December 22, 2015): 15690–95, https://doi.org/10.1073/pnas.1514974112.

27. Barry Herschy et al., "An Origin-of-Life Reactor to Simulate Alkaline Hydrothermal Vents," *Journal of Molecular Evolution* 79, no. 5–6 (December 27, 2014): 213–227, https://doi.org/10.1007/s00239-014-9658-4. The energy production corresponds to electrons in hydrogen gas reducing carbon dioxide to form formaldehyde.

28. The reactor simulation could generate, after an initial jump, approximately a 20 nanomolar (nM) increase in concentration of formaldehyde in 10 minutes within an approximately 1 liter vessel through the reduction of carbon dioxide. The entire process corresponds to two electrons, n=2, increasing in reduction potential, $E_r$, by less than 200 mV. The reduction potential can be converted to the free energy change for the production of one mole of formaldehyde using $\Delta G = nFE_r$. See Carl H. Hamann, A. Hamnett, and Wolf Vielstich,

*Electrochemistry* (Weinheim, Germany: Wiley-VCH, 2007), 78. The corresponding power generation density is on the order of 1 nW/g.

29. The final concentration of formaldehyde was less than 100 nM while the amount used in experiments to generate ribose is around .5 M (Herschy et al.). Processes such as thermophoresis could only concentrate organics by a factor of thousands under ideal conditions, which is far too small to assist any origin-of-life scenario. In addition, the measured formaldehyde might not have even resulted from the proton gradient. See J. Baz Jackson, "The 'Origin-of-Life Reactor' and Reduction of $CO_2$ by $H_2$ in Inorganic Precipitates," *J Mol Evol* 85, no. 1–2 (2017): 1–7, https://doi.org/10.1007/s00239-017-9805-9.
30. Peter Tompa and George D. Rose, "The Levinthal Paradox of the Interactome," *Protein Science* 20, no. 12 (2011): 2074–79, https://doi.org/10.1002/pro.747.
31. Norio Kitadai and Shigenori Maruyama, "Origins of Building Blocks of Life: A Review," *Geoscience Frontiers* 9, no. 4 (2018): 1117–53, https://doi.org/10.1016/j.gsf.2017.07.007.
32. The RNA world theory proposes that RNA chains known as ribozymes could play the role of primitive enzymes. However, ribozymes are only composed of four different nucleotides while proteins are composed of twenty different amino acids with a much larger variety of side chains. Therefore, ribozymes lack the capacity of proteins to drive a large diversity of reactions. Even if one ignored these limitations, the RNA world theory would face the same information challenges. See Stephen Meyer, *Signature in the Cell: DNA and the Evidence for Intelligent Design* (San Francisco: HarperOne, 2009): 294–321.
33. Hans Bisswanger, *Practical Enzymology* (Weinheim, Germany: Wiley-Blackwell, 2011), 1.
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