



The History and Philosophy of Origins-of-Life Studies: Orientations for the Future

Journal:	<i>Biological Reviews</i>
Manuscript ID	BRV-10-2017-0242
Manuscript Type:	Original Article
Date Submitted by the Author:	19-Oct-2017
Complete List of Authors:	<p>Mariscal, Carlos; University of Nevada, Reno (UNR), 1. Department of Philosophy, Ecology, Evolution, and Conservation Biology (EECB) Program, and Integrative Neuroscience Program</p> <p>Barahona, Ana; UNAM, 2. Department of Evolutionary Biology, School of Sciences</p> <p>Aubert-Kato, Nathanael; Ochanomizu University, Department of Information Sciences; Tokyo Kogyo Daigaku, Earth-Life Science Institute</p> <p>Aydinoglu, Arsev; Orta Dogu Teknik Universitesi, Design Factory; Blue Marble Space Institute of Science</p> <p>Bartlett, Stuart; Tokyo Kogyo Daigaku, Earth-Life Science Institute</p> <p>Cárdenas, María Luz; Aix Marseille University, CNRS, BIP, IMM</p> <p>Chandru, Kuhan; Tokyo Kogyo Daigaku, Earth-Life Science Institute</p> <p>Cleland, Carol; University of Colorado, Boulder</p> <p>Cocanougher, Benjamin; 9. Howard Hughes Medical Institute Janelia Research Campus; University of Cambridge, Department of Zoology</p> <p>Comfort, Nathaniel; Johns Hopkins University, Department of the History of Medicine</p> <p>Cornish-Bowden, Athel; Aix Marseille University, CNRS, BIP, IMM</p> <p>Deacon, Terrence; University of California, Berkeley, Department of Anthropology & Helen Wills Neuroscience Institute</p> <p>Froese, Tom; National Autonomous University of Mexico, 14. Institute for Applied Mathematics and Systems Research (IIMAS); National Autonomous University of Mexico, Centre for the Sciences of Complexity (C3)</p> <p>Giovannelli, Donato; Tokyo Kogyo Daigaku, Earth-Life Science Institute; Institute for Advanced Study, Interdisciplinary Studies; Rutgers University, Department of Marine and Coastal Science; YHouse, Inc.</p> <p>Hernlund, John; Tokyo Kogyo Daigaku, Earth-Life Science Institute</p> <p>Hut, Piet; Institute for Advanced Study, Interdisciplinary Studies; Tokyo Kogyo Daigaku, Earth-Life Science Institute; YHouse, Inc.</p> <p>Kimura, Jun; Osaka University, Department of Earth and Space Science</p> <p>Maurel, Marie-Christine; UMR 7205-ISYEB, CNRS-MNHN-UPMC</p> <p>Merino, Nancy; Tokyo Kogyo Daigaku, Earth-Life Science Institute; University of Southern California, Department of Earth Sciences</p> <p>Moreno, Alvaro; Universidad del Pais Vasco, 22. Department of Logic and Philosophy of Science, IAS-Research Centre for Life, Mind and Society</p> <p>Nakagawa, Mayuko; Tokyo Kogyo Daigaku, Earth-Life Science Institute</p> <p>Peretó, Juli; University of València-CSIC, 23. Department of Biochemistry and Molecular Biology and Institute for Integrative Systems Biology</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	I2SysBio Virgo, Nathaniel; Tokyo Kogyo Daigaku, Earth-Life Science Institute Witkowski, Olaf; Tokyo Kogyo Daigaku, Earth-Life Science Institute; Institute for Advanced Study, Interdisciplinary Studies Cleaves, Henderson; Tokyo Kogyo Daigaku, Earth-Life Science Institute; Institute for Advanced Study, Interdisciplinary Studies; Blue Marble Space Institute of Science; Georgia Institute of Technology, Center for Chemical Evolution
Keywords:	theories of life, LUCA, multidisciplinary science, prebiotic evolution, self- organization, artificial life, epistemology

The History and Philosophy of Origins-of-Life Studies: Orientations for the Future

Carlos Mariscal¹, Ana Barahona², Nathanael Aubert-Kato^{3,4}, Arsev Umur Aydinoglu^{5,6}, Stuart Bartlett³, María Luz Cárdenas⁷, Kuhan Chandru³, Carol Cleland⁸, Benjamin T. Cocanougher^{9,10}, Nathaniel Comfort¹¹, Athel Cornish-Bowden¹², Terrence Deacon¹³, Tom Froese^{14,15}, Donato Giovannelli^{3,16,17,18}, John Hernlund³, Piet Hut^{3, 16, 18}, Jun Kimura¹⁹, Marie-Christine Maurel²⁰, Nancy Merino^{3,21}, Alvaro Moreno²², Mayuko Nakagawa³, Juli Peretó²³, Nathaniel Virgo³, Olaf Witkowski^{3,16}, and H. James Cleaves II^{3,5,16,24*}

Affiliations

1. Department of Philosophy, Ecology, Evolution, and Conservation Biology (EECB) Program, and Integrative Neuroscience Program, University of Nevada, Reno (UNR). Reno, Nevada, USA. Email: *carlos@philbio.org*.
2. Department of Evolutionary Biology, School of Sciences, UNAM. Coyoacán 04510, CDMX, Mexico. *ana.barahona@ciencias.unam.mx*, 56224922
3. Earth-Life Science Institute, Tokyo Institute of Technology, Tokyo 152-8551, Japan
4. Department of Information Sciences, Ochanomizu University, Tokyo, Bunkyo-ku, Otsuka 2-1-1, 112-0012, Japan email: *naubertkato@is.ocha.ac.jp* tel +81 3-5978-5773
5. Blue Marble Space Institute of Science, Washington, DC 20011, United States
6. Design Factory, Middle East Technical University (METU), Ankara 06800, Turkey
7. Aix Marseille University, CNRS, BIP, IMM, Marseille, France, telephone + 33 491 16 41 38; email: *cardenas@imm.cnrs.fr*
8. Department of Philosophy, University of Colorado, Boulder
9. Howard Hughes Medical Institute Janelia Research Campus, Ashburn, VA 20147, United States
10. University of Cambridge, Department of Zoology, Cambridge, CB2 3EJ, United Kingdom, *btc23@cam.ac.uk*, tel: +1-859-481-1848
11. Department of the History of Medicine, Johns Hopkins University. *comfort@gmail.com*
12. Aix Marseille University, CNRS, BIP, IMM, Marseille, France, telephone + 33 491 16 41 38; email: *acornish@imm.cnrs.fr*
13. Department of Anthropology & Helen Wills Neuroscience Institute, University of California, Berkeley. Email: *deacon@berkeley.edu*
14. Institute for Applied Mathematics and Systems Research (IIMAS), National Autonomous University of Mexico (UNAM), Mexico City 04510, Mexico. Email: *t.froese@gmail.com*, Tel.: +52(1)56223617

15. Centre for the Sciences of Complexity (C3), National Autonomous University of Mexico (UNAM), Mexico City 04510, Mexico

16. Institute for Advanced Study, Princeton, NJ 08540, United States

17. Department of Marine and Coastal Science, Rutgers University, 71 Dudley Rd, New Brunswick 08901, New Jersey, USA. email: *giovannelli@marine.rutgers.edu* tel +1 (848) 932-3378

18. YHouse, Inc., New York, NY 10159, USA

19. Department of Earth and Space Science, Osaka University, Machikaneyama-Chou 1-1, Toyonaka City, Osaka 560-0043, Japan, *junkim@ess.sci.osaka-u.ac.jp*

20. UMR 7205-ISYEB, CNRS-MNHN-UPMC, 75005 Paris, France, *marie-christine.maurel@upmc.fr*, +33(0)6 84 33 57 91

21. Department of Earth Sciences, University of Southern California, Los Angeles 90089, California, USA. email: *nancymmer@usc.edu*

22. Department of Logic and Philosophy of Science, IAS-Research Centre for Life, Mind and Society, University of the Basque Country, Avenida de Tolosa 70, 20018 Donostia-San Sebastian, Spain. e-mail: *alvaro.moreno@ehu.es*

23. Department of Biochemistry and Molecular Biology, University of València and Institute for Integrative Systems Biology I²SysBio (University of València-CSIC), e-mail: *pereto@uv.es*, +34 963 543 666

24. Center for Chemical Evolution, Georgia Institute of Technology, Atlanta, GA 30332, United States

*To whom correspondence should be addressed. Email
henderson.cleaves@gmail.com, Tel. +1-858-366-3049

Abstract

In this review, we provide overview the central philosophical issues facing origins-of-life research, as well as the historical developments that have led to the multidisciplinary field of origins-of-life studies. We cover a range of perspectives on these topics, outlining the issues and developments in a way that can guide researchers and students from all fields.

With respect to philosophy, we provide brief summaries of debates with respect to (1) the nature (or definition) of life, whether there is one and how we should go about

1
2
3 research without an accepted theory of life, (2) the distinctions between synthetic,
4 historical, and universal projects in origins-of-life studies, (3) strategies for inferring the
5 origins of life, whether “bottom-up,” “top-down,” or otherwise, (4) whether metabolism or
6 replication originated first, (5) the early stages of prebiotic evolution and whether they
7 differed in kind or degree from current biology, (6) early organisms and populations, and
8 whether they differed in kind or degree from current biology, (7) the status of origins of
9 life as a science, and (8) the limitations of theoretical and practical tools for origins-of-life
10 research. Each of these debates influences the others. Although there are clusters of
11 researchers that agree on some answers to these issues, each of these debates is still
12 open.
13
14
15
16
17
18
19
20
21
22
23
24
25
26

27 With respect to history, we outline several independent paths that have led to
28 some of the approaches that are now prevalent in origins-of-life studies. These include
29 one path from early views of life through the scientific revolutions brought about by
30 Linnaeus (von Linné), Wöhler, Miller, and others. In this approach, new theories, tools,
31 and evidence guide new thoughts about the nature of life and its origin. We also
32 describe another family of paths, guided largely by a “circularity” approach to life, which
33 is guided by such thinkers as Maturana & Varela, Gánti, Rosen, and others. These
34 views echo ideas developed by Kant and Aristotle, though they do so using modern
35 science in ways that produce exciting avenues of investigation. By exploring the history
36 of these ideas, we can see how many of the issues that currently interest us have been
37 guided by the contexts in which the ideas were developed. The disciplinary
38 backgrounds of each of these scholars has influenced the questions they sought to
39 answer, the experiments they envisioned, and the kinds of data they collected.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

We conclude by encouraging scientists and scholars in the humanities and social sciences alike to explore ways in they can interact to provide a deeper understanding of the conceptual assumptions, structure, and history of origins-of-life research. This may be useful to help frame future research agendas and bring awareness to the multifaceted issues facing this challenging scientific question.

Keywords: theories of life, LUCA, multidisciplinary science, prebiotic evolution, self-organization, artificial life, epistemology

Contents

I. Introduction

II. Philosophical considerations with respect to the origins of life

2.1 The Nature of Life, and the Distinction Between Living and Non-Living Phenomena

2.2 What kind of origins are we seeking?

2.3 Top-Down / Bottom-Up

2.4 The Nature of the First Living Systems: Information first vs. Metabolism first

2.5 The Nature of the Processes Leading to LUCA

2.6 The Nature of Living Entities Prior to, and Including, LUCA

2.7 Communication Across Scientific Disciplines

2.8 Epistemological Limitations and Methods to Investigate the Origins of Life

III. Historical and Sociological considerations with respect to origins of life

3.1 Strand 1: From Chemistry to Molecular Biology

3.1.1 The Pre-Systematization of Biology Period

3.1.2 The Post-Systematization of Biology Period

3.1.3 The Chemistry Period

3.1.4 The Molecular-Biology Period

3.1.5 The Informatics Period

3.2 Strand 2: From Physics to Evolutionary Theory and Computation

3.2.1 Thermodynamics and dissipative structures

3.2.2 Self-organization: autopoiesis, metabolism-repair systems, the chemoton and related ideas

3.2.3 Replicators, Information and Evolution

3.2.4 Reaction networks, autocatalysis and the origin of heredity

3.2.5 “Tar,” Combinatorial Explosions and Alternative Chemistries

3.2.6 Artificial life and open-ended evolution

3.2.7 Summary and future challenges

IV Conclusions

Acknowledgements

References

I. Introduction

The origins of life is among the most fundamental and enduringly unexplained questions in science. There are many scenarios proposed for the origins of life on Earth, and the public may be surprised to learn just how little is understood about how life emerged. For practicing scientists, when deciding between radically distinct proposed models, it is unclear how to proceed. It can be difficult to agree on the object of inquiry, standards of evidence, or even what the disagreements are on various points of contention. To an extent, these problems are common to all sciences, but they face a new challenge in cutting-edge, multidisciplinary fields like the origins of life.

Scientists investigating the origins of life generally acknowledge the depth and complexity associated with the topic, which often requires input from many different scientific disciplines. Less recognized is the historical, sociological, and philosophical context surrounding the ways researchers in different disciplines work together to investigate this problem. The training for origins-of-life scientists may acknowledge, for

1
2
3 example, the difficulty of defining life without reflecting the complex history of those
4
5 debates in Western philosophy. Scientists may know of Charles Darwin's letter to his
6
7 friend Joseph Hooker, in which he conceived of life on Earth as starting in "some warm
8
9 little pond" (Darwin 1877, Peretó et al. 2009), but they may not realize that Darwin was
10
11 living in a time when many in the scientific community were steeped in the process of
12
13 rejecting the notions of spontaneous generation and vitalism, eliciting a difficult
14
15 conundrum for models of the natural emergence of life in an evolutionary context
16
17 (Farley 1977). They may be aware of the Miller–Urey experiment (Miller 1953), but have
18
19 little idea that Miller was motivated by reading Harold Urey, John Bernal, and Alexander
20
21 Oparin's works (Miller 1974). They may also lack the context with which to embed those
22
23 works, which came at a time in which Darwinism was being reconciled with Mendelian
24
25 genetics (in the West) and was often officially rejected outright in the Soviet Union
26
27 (DeJong-Lambert 2012). These facts nevertheless influence the disciplines, tools, and
28
29 methods that we still use today.
30
31
32
33
34
35

36
37 The study of the origins of life has a deep history, which has become increasingly
38
39 detailed over the last two centuries, in particular in the last 65 years. The history of a
40
41 scientific field influences what scientists consider to be interesting research programs,
42
43 reasonable evidence, and truth (Rudwick 1988, Golinski 1998). Each field establishes
44
45 its own null hypotheses and conceptions of parsimony, which may not be compatible
46
47 with other fields, and which may change over time.
48
49

50
51 As science is embedded in a global and temporal conversation, the study of
52
53 scientific debates is important because it allows observation and study of the epistemic
54
55 and social causes of scientific change and allows us to understand the nature of
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

science and its sociological relationships. This is perhaps most true with respect to sciences which overlap significantly with strongly held societal or political beliefs. The suppression of Mendelian genetics in the USSR by Lysenko (encouraged by Stalin) is an example of the dangers of allowing political considerations to determine what scientific problems are deemed useful, valid or relevant. Origins-of-life research is presently also at odds with many mainstream religious viewpoints worldwide, perhaps most notably in the United States (cf. Humes 2009).

There is ample scope for historical and philosophical work on origins-of-life studies to explore broad questions such as: (1) whether and to what extent origins-of-life concepts, hypotheses, and principles fit together logically, methodologically, theoretically, and empirically; (2) how and to what extent diverse empirical methods can provide evidence to support claims about origins, including traditional questions of explanation and confirmation; (3) what are the scope and limits of origins-of-life studies in relation to other sciences, including traditional questions about reduction and emergence (Griesemer 2008).

In this paper, we discuss some of the ways in which philosophers, historians, and other scholars in the natural and social sciences and humanities can inform and impact research about the origins of life. We begin by considering the conceptual issues in origins-of-life research, in which philosophers may play a fruitful role. We then consider historical and societal impacts on current origins-of-life research, and trace the historical development of two distinct threads of modern inquiry on the topic. Finally, we conclude with a call for breaking down disciplinary walls that are demonstrably harmful to scientific progress. We hope this will provide a roadmap for origins-of-life scientists

interested in the broader historical and philosophical basis of their work, as well as scholars in the humanities interested in exploring this exciting area.

II. Philosophical considerations with respect to the origins of life

In this section, we discuss some key philosophical issues in the origins of life. Out of dozens of philosophical and epistemological issues, eight are highlighted: (1) the nature (or perhaps the definition) of life, (2) what origins-of-life models aim to explain, (3) the strategies for inferring the origins of life, (4) the sequence of events by which life originated, (5) the processes by which life originated, (6) the nature of early living entities, (7) the status of the study of the origins of life as a science, and (8) the limitations of scientific tools in this field of research.

Compared to workers in more traditional areas of biology, scientists in the origins-of-life community tend to be more sensitive to the philosophical issues in their field, so some of these areas may seem familiar to practicing origins scientists. Some of these have been explored, but many areas remain contentious and underdeveloped. Given the increasing interest in the origins of life, more topics are likely to arise in the coming years.

2.1 The Nature of Life, and the Distinction Between Living and Non-Living Phenomena

How a non-living universe can give rise to a living universe is a deep question, not least because of the significant differences between living and non-living objects, but also because the emergence of life seems to have erased all evidence of any intermediate level of organization between complex physicochemical systems and the

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

simplest yet robust forms of life. Organizing all of these problems into a unified and successful research program requires a comprehension of the type of “biological” systems whose origins we are trying to understand. A progressive research program requires at least a rough outline of what is meant by a “minimal” form of life (Ruiz-Mirazo et al. 2004, Bich and Green 2017).

Many researchers explicitly assume that studying the origins of life requires a definition of life, a proposal which sounds straightforward, but may be problematic. It has been suggested that centuries of biological research have not significantly advanced this research program since Aristotle’s time, and the prospects for a generally accepted definition of life may be as remote as they have ever been (Cleland and Chyba 2007). For any definition of life, clever philosophers can pose apparent exceptions. It is possible that there is *no discoverable principle* capable of distinguishing life from non-life, and perhaps no defensible basis for assuming a clear, widely accepted dividing line between the two. If this is true, there are a number of potential alternative paths forward. Unfortunately, a large number of biochemists have shown no interest at all in the definition of life (Harold 2001, Szostak 2012). In contrast, this problem has been analyzed in the Artificial Life community for decades (e.g., Maturana & Varela 1980, Ruiz-Mirazo & Moreno 2004, Ruiz-Mirazo, Peretó & Moreno 2004, Bitbol & Luisi 2004).

The default path, which one may expect will lead to frustration, is to insist on a particular definition of life and debate it *ad nauseam*. Pragmatic approaches have been championed by researchers like Szostak (2012). This family of approaches takes the task of science as being divorced from philosophical definitions. These authors prefer

1
2
3 simple descriptors, general characteristics, operational definitions, or stipulative
4
5 definitions over precise formal definitions. This is a natural approach if one's goal is to
6
7 solve a defined problem rather than address the fundamental philosophical question.
8
9

10 Some may suggest skepticism or caution, urging continued research in the
11
12 hopes of discovering or creating an accepted second instance of life (Cleland & Chyba
13
14 2007, Cronin et al. 2006). Some authors challenge the entire project of seeking a
15
16 "definition" of life and instead suggest the goal is to develop a "theory" of life (Cleland &
17
18 Chyba 2007). Others argue that the fundamental need is to capture the aspects of life
19
20 that come closest to the *essence* of life (Cornish-Bowden & Cárdenas 2017). Others
21
22 argue that "life" means different things for the public than it does for scientists (and even
23
24 among different kinds of scientists), making a consensus more a matter of sociology
25
26 than scientific discovery (Machery 2012). The most extreme accounts are provided by
27
28 *eliminativists*, who maintain there is no objective category as "life," though they may still
29
30 accept pragmatic approaches to origins-of-life research (Descartes 1664/2010, Jabr
31
32 2013, Mariscal & Doolittle, In Press).
33
34
35
36
37

38 Another pragmatic approach, which cuts across biological theory efforts, is to
39
40 adopt a view of life from the perspective of a biosphere (Feinberg & Shapiro 1980,
41
42 Smith, In Press). From this point of view, rather than conceiving of organisms as living,
43
44 one might better view organisms as "alive" derivatively due to being part of a living
45
46 biosphere. It may be that the need for a definition of life is not as important as an
47
48 understanding of the series of planetary processes that can give rise to complexity and
49
50 life-like processes (Smith & Morowitz 2016). This may be a level of explanation most
51
52
53
54
55
56
57
58
59
60 scientists would feel too distant for the problem at hand.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Life is a multifarious phenomenon: it appears as individualized systems (e.g., single-celled wholly autotrophic organisms) as well as interwoven networks with deep historical connections (e.g., obligatorily symbiotic microbial communities with shared viruses and extensive horizontal gene transfer). Both dimensions are complementary and entangled. In other words, although the most striking characteristics of living systems appear essentially in all organisms, these necessarily form components of larger ecological webs and evolutionary processes. Philosophy in this domain serves the synthesis role, helping grasp the necessary stages of the transition from chemistry to biology, analyzing the fundamental problems associated with these transitions, and building a unifying conceptual framework to move scientific research forward. Philosophers may be concerned with issues like the emergence of functional organizations, of individuality and its self-reproduction; the origin of evolution and the unfolding of biological phenomenology; the appearance of genetic information, agency and regulation; or the origin of cooperation and symbiosis. A challenge of philosophical research is precisely to untangle the threads that tie these related, albeit conceptually different, issues together (Moreno 2016).

Complementarily, historians can help us recover the social networks and investigative and theoretical pathways on which current and future thought on the origins of life are and will be built (Latour, 1987; Holmes, 2004). Perhaps most importantly, historical work can situate this rich, diverse body of scientific work in its shifting social and political contexts, thus helping frame research questions, consider ethical issues, teach upcoming generations of students, and communicate the meanings of this research to the broader public.

2.2 *What kind of origins are we seeking?*

In Scharf et al. (2015), some of us pointed out three overlapping explanatory projects relevant to the origins of life: those seeking explanations that are (1) necessary, (2) actual, or (3) merely possible.

First, explanations which were termed “universal” in Scharf et al. (2015) focus on *necessary* steps in the origins of life. Scientists seek such steps when they wish to understand universal processes in biology or the evolution of life itself. These are risky scientific conjectures, as universal claims are true only if the probability of an exception can be shown to be insignificant. This means that truly universal explanations ought to apply to any life we discover *or* create. Some of the present authors are skeptical of such claims, noting the difficulty in justifying inferences from a single example of life (Cleland & Copley 2005) (though see Section 3.2 for examples of how universal questions are investigated in practice.) The specificity of universal claims is still an open question, as are the rigidity, the level of description, and how such claims can be assessed.

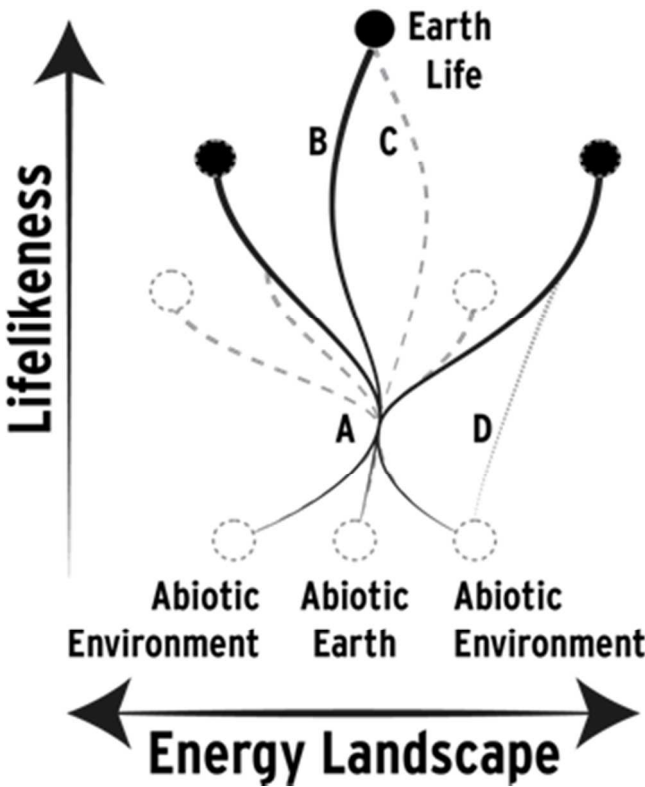


Figure 1. An illustration of paths from lifeless environments (dashed circles) to living worlds (black circles). Black lines mark paths actually taken somewhere in the Universe, dashed lines mark possible paths. Axes are unspecified metrics of “lifelikeness” (y) and an energy landscape through which precursors to life travel (x). A) universal explanations for the origins of life: steps that scientists think must be taken in any path from a lifeless world (bottom) to a living one (top); B) historical explanations, about the path life on Earth could have taken from a lifeless Earth to LUCA; C) synthetic explanations, which detail other possible paths life might have taken; D) synthetic explanations, which challenge universal explanations and detail how life may have been created under alternative scenarios. If there are few synthetic paths relative to universal paths, life on Earth would be highly convergent with life elsewhere, and *vice versa*. Adapted from Scharf et al. (2015). Scanning this possibility space is part of the difficulty of origins research.

1
2
3 The second type of explanation is historically-based and refers to the path life on
4 Earth could have taken from its inception (B in figure 1). These explanations are
5 contingent on knowledge of Earth history. To give accurate historical explanations,
6 prospective modelers or experimenters must keep up with geological models for the
7 early Earth, *e.g.*, the nature of the early oceans, the temperature of the environment, the
8 existence of energy sources, and so forth. As such models shift, so do the problems
9 and paradoxes origins-of-life researchers must solve. For example, there is some
10 disagreement about whether there was any dry land available on Earth for the origins of
11 life. A completely water-covered planet would offer support for origins models positioned
12 in deep-sea environments (see, for example, Russell et al. 2005), and at the same time,
13 undermine those that require intermittently dry conditions (*e.g.*, Nelson et al. 2001,
14 Maruyama et al. 2013, Damer & Deamer 2015). Historical explanations typically
15 assume that there was a single origin to life on Earth, although this may simply be
16 because this situation is currently indistinguishable from the scenario in which life
17 originated several times. Nevertheless, in the future, it may be possible to distinguish
18 the alternative possibilities of other origins having gone extinct or even having
19 hybridized with our own lineage (Gogarten-Boekels et al. 1995, see Figure 1). Some of
20 these points are also discussed by Cornish-Bowden and Cárdenas (2017).
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

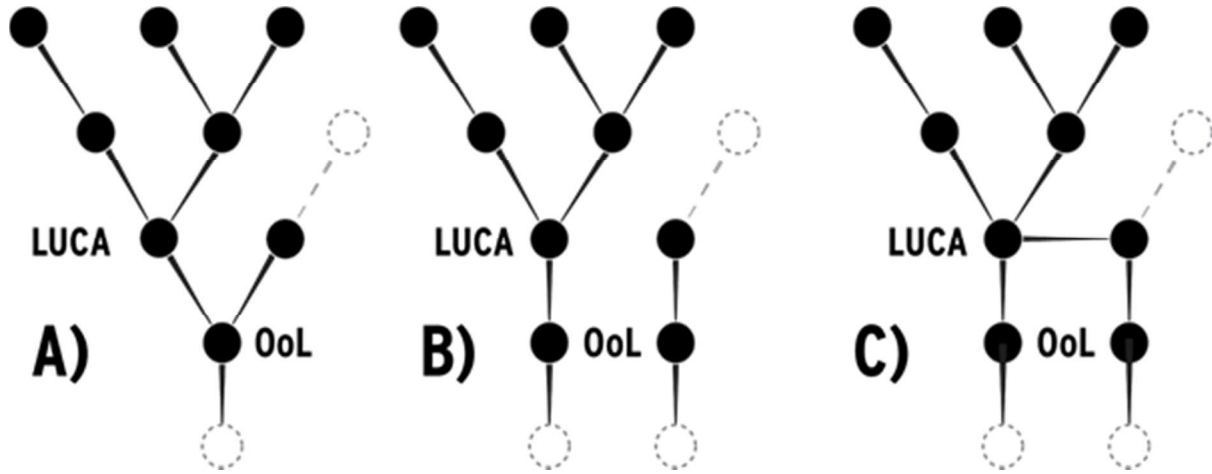


Figure 2. Three possibilities since the origin(s) of life (OoL) that are currently indistinguishable. Solid circles represent living taxa, dashed circles and lines represent non-living or extinct taxa, solid lines connect living taxa with their ancestors. A) All life on Earth shares a Last Universal Common Ancestor (LUCA). B) Life originated multiple times, but all other lineages have either gone extinct or are yet to be discovered (Cleland & Copley 2005, Davies & Lineweaver 2005). C) Life currently contains genes or other information from a second origin (or perhaps a distant relative), from which no descendants remain or have not yet been discovered. Adapted from Powell & Mariscal (2015).

Explanations of possibility, termed “synthetic explanations” by Scharf et al. (2015) are the least constrained kind of explanations. Synthetic explanations are somewhat analogous to existence proofs in mathematics: they show that something is possible by demonstrating it. Thus, synthetic explanations include experimental demonstrations of plausible prebiotic synthesis of biomolecules, the experimental construction of protocells, and many applications of synthetic biology as well as computational demonstrations of phenomena in evolution or self-organization. Typically, the value of synthetic approaches is not in directly answering questions about the

1
2
3 empirical world, since a demonstration that something is possible does not by itself
4
5 imply that it actually happened historically. Rather, their value is in showing that
6
7 something is possible that might have been thought impossible (Dray 1957), or that
8
9 something is difficult that might have been thought easy (or the converse), or simply in
10
11 making complex concepts easier to understand by exhibiting a concrete example.
12
13

14
15 Synthetic explanations are closely associated with questions about whether
16
17 alternative forms of life are possible. These include questions about alternative
18
19 chemistries (Bains 2004, Cleaves et al. 2015, Ilardo et al. 2015), alternative energy
20
21 sources (Schulze-Makuch & Irwin 2006), and alternative substrates (Langton 1998).
22
23 Opinions on these questions differ greatly within the community. Some, though not all,
24
25 approaches to such questions involve an assumption that the nature and origins of life
26
27 can be understood at a nonphysical, computational level of analysis. Whether this is so
28
29 has been a topic of debate. While modeling plays critical roles in origins studies
30
31 (Coveney et al. 2012), there is nevertheless some disagreement as to whether
32
33 sufficiently complex and descriptive computer simulations can tackle certain problems.
34
35 Critics point out that the material composition of a physical system is often crucial to its
36
37 causal capacity to perform a given function (e.g., Di Paolo et al, 2000; Silverman &
38
39 Bullock 2006). As an illustration, real-world glass filaments do not effectively conduct
40
41 electricity even though one can design a computer simulation of glass filaments that
42
43 conduct simulated electricity. Life may be like these other material things, its essence is
44
45 inseparable from its composition. A second worry concerns the *privileged level of*
46
47 *abstraction* implicit in such views, in which synthetic origins of “life” might count as
48
49 genuinely living only if being a living thing is merely a matter of exhibiting a set of
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

designated functional characteristics. But this is exactly the question: What *is* the appropriate level of abstraction for generalizing about life? Stripping away the material characteristics of life may presuppose an answer to the very question at issue, though Rosen (1991) argued otherwise: “I can epitomize a reductionist approach to organization in general, and to life in particular, as follows: *throw away the organization and keep the underlying matter*. The relational alternative to this says the exact opposite, namely: *throw away the matter and keep the underlying organization*.”

It should be noted, however, that this criticism does not apply to all computational approaches, most of which (e.g., Piedrafita et al. 2010) are not attempting to capture “life” *per se*, but rather to answer much more specific and limited questions. One can gain important insights into the nature and origins of life by abstracting from the physical and chemical characteristics of life and simulating them on a computer. But there is typically a trade-off between accuracy and generality, and accuracy is almost certainly a moving target which will be evaluated differently as the body of scientific knowledge expands. More accurate synthetic explanations, such as those from experimental evolution or synthetic biology, may add interesting details about particular scenarios for *life as we know it* (C in figure 1). Meanwhile, abstract functional computer models may yield broad insights about many kinds of *life as it could be*. One interesting note: synthetic origins-of-life explanations form a nice contrast with Universal explanations. Logic tells us that universal claims can be refuted with a single possible counter-example, so creative ways of evolving life can serve as tests to strong claims of universal biology (D in figure 1).

1
2
3 It is important to realize that at present origins-of-life researchers are engaged in
4
5 different research programs, which use different tools and accept different standards of
6
7 evidence. Much argument could be avoided if it were acknowledged within the origins-
8
9 of-life community that these research programs overlap and interact. For example, it is
10
11 irrelevant to challenge explicitly synthetic explanations by appealing to models of the
12
13 history of the Earth. While researchers in one camp may find alternative research
14
15 programs boring, impossible, or even irresponsible, it must be acknowledged that
16
17 standards of evidence are sometimes informed by unstated epistemic values. A
18
19 researcher valuing general explanations may be skeptical of relying on ever-changing
20
21 conceptions of conditions on the early Earth, while a researcher valuing accurate
22
23 explanations may worry about universal or synthetic explanations which appear
24
25 ungrounded by real-world examples. The philosophical literature on the various
26
27 epistemic values of science may be helpful in making sense of such fundamental
28
29 differences in scientific temperament (Kuhn 1962; Beatty 1997; Douglas 2016).
30
31
32
33
34
35
36
37
38
39

40 *2.3 Top-Down / Bottom-Up*

41
42 Another ambiguity with respect to the origins of life is the question of so-called
43
44 “top-down” and “bottom-up” approaches. Top-down approaches begin with
45
46 contemporary life on Earth and use the tools of comparative biology and systematics to
47
48 infer the nature of prior biological states, with the hope such extrapolations may carry all
49
50 the way back to life’s origins.
51
52

53
54 It is worth defining a few concepts here which at times cause confusion in such
55
56 discussions. Three terms in particular, the Last Universal Common Ancestor (*LUCA*),
57
58
59
60

the *progenote*, and the concept of the *protocell* often are sufficiently vague as to be used to represent a large number of hypothetical entities. *LUCA*, also known as the cenancestor, last common ancestor (LCA) or last universal ancestor (LUA), is generally conceived of as an inferred *population* of organisms from which all contemporary organisms on Earth are descended (but see section 2.6). The term *progenote* was coined by Woese and Fox (1977b) to represent the organism(s) which preceded *LUCA*, and which presumably had characteristics not found in *LUCA* and *vice versa*. The postulate of the progenote reflects recognition that the complexity of *LUCA* implies prior biological evolution (see section 2.5). The term *protocell*, finally, is sometimes used to refer to any cell-like assemblage which has some or all of the functions of a cell, shares some or none of the composition of a cell, and which may be either a hypothetical precursor to modern cells, a laboratory-synthesized (Maurer et al. 2011) or computer-simulated (Munteanu et al. 2007) tool for understanding early evolution, or simply something manufactured in the laboratory to simulate life. There is clearly room for finer definition of some of these concepts.

Top-down approaches often aim to infer the nature of *LUCA*, its contemporaries, and sometimes, the common ancestors of the genes present in either (e.g., Weiss et al. 2016, Giovannelli et al. 2017, Koonin 2016, Koonin et al. 2017, Williams et al. 2017, Martin et al. 2016, Tuller et al. 2010, Cornish-Bowden & Cárdenas 2017). Some of these approaches ignore the possibility that *LUCA* may have been significantly advanced in form and function from the first living entities. For example, Martin et al. (2016) consider *LUCA* to be close to the origin of life, conceptually overlapping with the progenote, and thus not significantly advanced, whereas others (Tuller et al. 2010,

Cornish-Bowden & Cárdenas 2017) think that it lived at the time of the bifurcation of the *Bacteria* and *Archaea* and resembled a modern bacterium, with various modern features, such as energy management by an ATP synthase working across a membrane. To date, there is little consensus as to what LUCA was phenomenologically, when it existed, and when life started, so there is potentially as much as a billion-years for the evolution which led to LUCA. While a billion years may be a somewhat comfortable time period for discussing microbial evolution post-LUCA, before LUCA the tempo of evolution could have been markedly different (as discussed in section 2.5).

There are at least three possibilities for the origins of life on Earth, as illustrated in Figure 2: (1) only one kind of life emerged on the early Earth, (2) alternative forms of life, differing from ours biochemically in important ways, emerged on the early Earth, and (3) modern Earth life is the result of the fusion of two or more separate origins, which may or may not have been considered fully living by present criteria. In all of these cases, some of the microbial descendants of LUCA's sister taxa, neighbors, or parents may still be with us today, invisible to current techniques used to explore the microbial world, a concept called the "shadow biosphere" (Cleland & Copley 2005, Davies & Lineweaver 2005). The efficacy of top-down approaches depends on whether A, B, or C is true as well as the extent to which past taxa have gone extinct.

There may have been earlier biological states on which biology depended to reach its present state, but which were subsequently discarded or outcompeted during the evolutionary development of the biosphere, a notion called "scaffolding" (Caporael, et al., 2013). As an example, it is generally held that RNA preceded DNA as an information storage molecule in living systems (Dworkin et al. 2003). This notion is

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

supported by several lines of evidence, including that DNA monomers are often biosynthesized from RNA monomers, the use of RNA primers in replication, the composition of key components of the translation apparatus, and more. A possibly relevant point is that collagen resembles a polymer of a tripeptide with glycine and proline as the first and second residues and many possibilities for the third: this tripeptide could have existed before there was any coding molecule (Cornish-Bowden 2016).

If scaffolding processes occurred in the lines of evidence we use to infer the nature of LUCA, then it is possible there might be little to be learned about the origins of life from studying modern biology, except in the most general sense. A considerable amount of evidence may have been erased as RNA shifted from an informational role to a subsidiary role. The assumption that all evolutionary adaptations have been preserved and carried forward is a potentially dangerous heuristic minimalism which may cloud evolutionary reconstructions. Much of what is currently believed about the trajectory of biological evolution hinges on unique, and potentially rare, mutational or environmentally determined “breakthrough” events, which would have been especially important early in the emergence of life.

Bottom-up approaches begin with known or inferred features of the early Earth and modern examples of chemistry, which have been studied over very short periods of time in laboratories (Orgel 1998a,b). These approaches infer the self-organization and evolution that might have led to the formation of life (Lazcano & Miller 1996). The field of prebiotic chemistry is central to bottom-up approaches. The purview of this field is to assess exactly what types of molecules could have been synthesized in the early solar

1
2
3 system, with the dual goals of trying to understand how the compounds life is composed
4
5 of could have been synthesized without the intervention of living things, and that
6
7 regardless of what life is composed of now, it should have started with whatever was
8
9 available. Bottom-up approaches require additional philosophical commitments, such as
10
11 what we seek to explain the origin of (whether a metabolism, membrane, or reproducer,
12
13 see section 2.4), as well as chemical assumptions, including the available molecules,
14
15 environmental parameters, interaction rates, and so on.
16
17
18

19
20 Top-down and bottom-up approaches do not necessarily conflict, but neither do
21
22 they necessarily coordinate. Bottom-up approaches, for example, can span the range of
23
24 the explanatory projects discussed in the previous section, while top-down approaches
25
26 are firmly historical in nature.
27
28
29
30
31
32

33 *2.4 The Nature of the First Living Systems: Information first vs. Metabolism first*

34

35 Since the time of Aristotle, two abstract functional characteristics of familiar Earth
36
37 life have been claimed to characterize all life, wherever and whenever it may be found
38
39 in the universe: (1) The capacity to self-organize and maintain self-organization for an
40
41 extended period against both internal and external perturbations and (2) the capacity to
42
43 reproduce and (since the time of Darwin) transmit to progeny adaptive characteristics.
44
45 According to Aristotle, “self-nutrition” (also known as metabolism) and “self-
46
47 reproduction” were basic to life, and he famously debated which one of the two was
48
49 most essential to life (Matthews 1996). Aristotle’s influence on the biological sciences is
50
51 alive and well today. Definitions of life almost invariably treat one of the two as logically
52
53 or scientifically more fundamental to life than the other. Metabolic (e.g., Oparin 1924),
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

thermodynamic (e.g., Kauffman 2000), and organizational (e.g., Maturana & Varela 1980, Rosen, 1991, Gánti 2003) definitions of life generally emphasize self-organization. Darwinian (e.g., Dawkins 1982), genetic (e.g., Joyce 1994), and information (e.g., Korzeniewski 2001) definitions of life, on the other hand, tend to emphasize reproduction. In this context, reproduction and replication should not be conflated: replication is perfect (or nearly perfect) reproduction. Organisms reproduce, genes replicate.

Models of the origins of life typically bifurcate along the same lines as definitions of life. Gene-first models of the origins of life (e.g. Gilbert 1986) parallel evolutionary-genetic definitions, and metabolism-first theories (e.g., Shapiro 2006) parallel metabolism-thermodynamic based definitions of life. The widespread view that a theory of the origins of life presupposes a definition of life was made explicit by Morowitz (1991, p. 4): “To ask how life originated, we are going to be forced into that intellectual maze of defining life.” Other views of life manage to treat both metabolism and reproduction as simply different forms of autocatalysis (Eschenmoser 2007, Pross 2012).

The widespread view that a theory of the origins of life must follow along the same lines as a definition of life is problematic (Cleland 2013). First, self-organization and reproduction may be little more than unreliable symptoms or signs of more fundamental but as yet undiscovered general properties of life. Analogous examples from the history of science are easy to find. Before the advent of the germ theory of disease, diseases such as tuberculosis and diabetes were identified in terms of overt symptoms, which resulted in the classification of what are now classified as the same

1
2
3 disease (resulting from the same underlying infectious agent) as different diseases, as
4
5 with consumption (characterized by a distinctive cough) and scrofula (characterized by
6
7 the swelling of the lymph nodes in the neck), which we now know are both caused by
8
9 the bacterium *Mycobacterium tuberculosis* (Herzog 1998). The reverse also happens:
10
11 diabetes is popularly regarded as one disease, but it exists in two types with distinct
12
13 pathogenic etiologies - lack of insulin production for type I versus insensitivity to insulin
14
15 by insulin receptors for type II.
16
17
18

19
20 Even supposing that the characteristics self-organization and reproduction are
21
22 basic to all life, why assume, with Aristotle, that one attribute is more fundamental to life
23
24 than the other? Numerous other models are possible. Many contemporary advocates of
25
26 the RNA World (e.g., Cech 1993, Lazcano 2010) contend that primitive autocatalytic
27
28 “metabolic” cycles may have been required to generate self-replicating collections of
29
30 RNA oligomers. Why postulate a double origin involving the emergence of first a
31
32 metabolic form of life which may have independently recurred several times *and then* a
33
34 genetic form of life (or *vice versa*)? However, a reproducing form would necessarily
35
36 remain inert until metabolic or environmental forces acted upon it. The emergence of a
37
38 proto-metabolic system may represent a complex, non-living system which is
39
40 nonetheless a necessary stage in the origins of life. Alternatively, the emergence of self-
41
42 or mutually-catalytic RNA oligomers disconnected to metabolic pathways for their
43
44 synthesis could similarly represent a necessary prebiotic stage in the emergence of life.
45
46 In other words, the origins of self-organization or reproduction *as we now know them*
47
48 may have been preceded by analogues or alternatives, suggesting that the question of
49
50 priority is at best underspecified. Nonetheless, the universality of metabolism across the
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

tree of life has logically been a strong guiding light in theories of the origin of life (Meléndez-Hevia et al. 2008).

To further complicate discussion, metabolism and reproduction may be equivalent at some level of description (e.g., Eschenmoser & Kiskörek 1996, Pross 2012), and the distinction that fuels this binary controversy may in fact be a non-issue upon adopting this classification scheme. Moreover, in their focus on the molecular level chemical details both metabolism-first and reproduction-first theories have neglected another potentially essential aspect of the nature of life, namely its behavioral properties, which may have already played an adaptive role at its origins (Egbert & Di Paolo 2009, Hanczyc & Ikegami 2010, Froese et al. 2014).

The task of origins-of-life research is to produce a causal explanation for how life came to be. Whether one focuses on one factor of life and treats the other(s) as arriving later may depend on a choice of definitions or understanding of the relevant factors. This brings us to a central problem with tailoring a model of the origins of life closely on a definition of life: there may be little reason to suppose that one could extract a causal “recipe” for life (in general, or specifically with regard to life on Earth) from a description of the fundamental properties of life (even assuming that we know what they are) (Cleland 2013). It is not true in general that knowledge of the identifying properties of a material thing will reveal how it was produced. As an analogy, descriptions of quartz at the macromineralogical level (hardness, crystal habit, etc.) or the molecular level (SiO_2) both explain how to identify quartz. Neither, however, explains how quartz is produced under natural conditions. Geochemists have discovered that quartz crystallizes in magma and precipitates in hot springs, and there are possibly other ways in which it

forms under conditions very different from those found on Earth. Theories of the origins of life and definitions of life could cut across each other in that the origin may have occurred in one order, while the more fundamental feature of living creatures may have occurred in another. Under very different chemical and physical conditions (e.g., Earth compared with Saturn's moon Titan), there might be different causal pathways for achieving and linking self-organization and reproduction, some producing the building blocks for "metabolism" first and others producing the building blocks for "genes" first. The point is a lack of clarity about one's commitments to the nature of life can lead to theoretical confusions and ambiguities over what needs to be included in a model of the origins of life, and in fact, a commitment to a theory or definition of life may not even be entirely necessary for the sake of making progress in understanding steps in the emergence of life.

2.5 The Nature of the Evolution Before and at the Time of LUCA

There are numerous processes that operate in life today that contribute to biological evolution, e.g., lateral gene transfer, natural selection, drift, symbiosis, migration, and so forth (Baake & Gabriel 1999, Soucy et al. 2016). Even among these processes, there are diverse mechanisms by which they operate, reflecting a wide range of prevalence and importance throughout the tree of life. We understand the relative importance of these processes for some taxa (e.g., metazoa) much better than for others (e.g., proteoarchaeota). But while our understanding of these processes and their relative importance is incomplete, they are nevertheless relatively straightforward to investigate in many extant organisms. The situation is harder when making inferences to the past and much harder in the context of the origins of life.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

One philosophical worry that has received some attention is whether pre-LUCA evolution should be considered “Darwinian” in the way we typically think of evolution occurring for modern life (Goldenfeld & Woese 2007, Fry 2000, Malaterre 2015). Investigating this is both an empirical and philosophical question, requiring details about chemical and early biological evolution as well as a thorough account of what “Darwinian” evolution means. There is such a wide disagreement on both accounts that it may prove impossible to come to a consensus regarding the events of early evolution, much less as to whether the overall process may qualify as “Darwinian.” For some, “Darwinism” can only refer to the “Modern Synthesis” of Mendelian inheritance and natural selection. For others, it is a looser notion of heredity, variation, and differential fitness (Lewontin 1970). Most of evolutionary change is not Darwinian in either sense. Especially in the field of protein sequences, neutral evolution probably plays a much bigger role (Kimure, 1983). This is also supported by the long history of evolutionary thought before (Stott 2013) and after Darwin (Bowler 1992, Bowler 2013). Thus, it is possible that processes during the emergence of life were “evolutionary” without being “Darwinian,” though the details may matter greatly. According to Woese’s Progenote proposal (Woese 1998, Woese 2002), the map between organismal genotype and phenotype was originally imprecise, which meant that early life was dominated by lateral gene transfer that eventually slowed as the mapping “annealed.” Woese called this the “Darwinian Threshold.” From the perspective of cells, horizontal transfer violates assumptions of descent with modification, but from a selfish gene perspective, horizontal transfer and vertical inheritance are merely two ways of ensuring the

1
2
3 representation of the gene in the next generation. This notion is explained more fully in
4
5 the next section.
6

7
8 Many biologists currently disagree over whether evolutionary theory needs an
9
10 “extended” synthesis (Odling-Smee et al. 2003; Laland et al. 2014; Booth et al. 2016).
11
12 Central to this debate is whether features of biology such as epigenetic inheritance,
13
14 lateral gene transfer, or niche construction count as challenges to Darwinism. Perhaps,
15
16 as Booth et al. (2016) argue, the appropriate approach is to treat various processes
17
18 individually and point out that the evolution of some lineages could be explained
19
20 according to traditional Darwinian processes, while others may be better explained by
21
22 more recently discovered biological processes. Thus, a modest observation may be that
23
24 early evolution may have involved processes that were, to some degree, different than
25
26 contemporary evolutionary processes. For example, primitive cells may have lacked the
27
28 strong digital heredity we now see in the form of genes, though there was probably an
29
30 ancestor-descendant relationship that may allow for weakly efficacious Darwinian
31
32 processes. Whether one chooses to label such proto-biological processes as
33
34 “Darwinian” may depend on their perceived similarity to current processes. In any event,
35
36 some form of purely chemical (i.e., non-shape complementarity or information-based)
37
38 evolution may have preceded more familiar Darwinian ones (Meléndez-Hevia et al.
39
40 2008).
41
42
43
44
45
46
47
48
49
50
51

52 *2.6 The Nature of Living Entities Prior to, and Including, LUCA*

53

54 The current understanding of LUCA is hugely influenced by the pioneering work
55
56 of Carl Woese: Woese and Fox (1977a) are famous as the discoverers of a new branch
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

of organisms on the tree of life, the *Archaea*. Despite initial disagreement (Mayr 1998), Woese’s view is now widely accepted. Part of Woese’s original model attempted to address how three equally distinct domains could emerge from an abiotic Earth. This question becomes salient after Woese and Fox’s discovery of the domain Archaea (previously called Archaeobacteria), which they argued was as distinct from Bacteria as either was from Eukaryotes (Woese 1998, Woese et al. 1990).

The claim that life on Earth passed through a “Darwinian Threshold” (Woese 2002) is philosophically rich and depends on two assumptions: (1) life currently exhibits far less lateral transfer than was common in the origins of life and (2) a diffuse community exchanging genes is biologically plausible. The first assumption has been challenged by various authors (Doolittle 1999, Dagan and Martin 2006), although the debate continues as to the extent and importance of lateral gene transfer both in the past and presently (Kurland et al. 2003). The second assumption is vague, relying on genes being shuttled from one organism to another and being incorporated by one or both until all developed a coherent genotype/phenotype mapping that locked their respective gene complements into the three (or two, if one defines the split as prokaryotes vs. eukaryotes, or places the eukaryotes within the domain of the *Archaea*) major lineages. Such a view eschews our typical bioinformatics inferences that presume common origins coming in a single organism, effectively accepting universal common ancestry without accepting a common ancestor (Mariscal & Doolittle 2015).

There is also currently an active debate as to whether Fox and Woese underemphasized the importance of the *Archaea*, as new research strongly suggests the Eukaryotic domain branches within the Archaeal domain (Spang et al. 2015;

Raymann et al. 2015; Koonin 2015a; Koonin 2015b). Whatever the status of the two-domain vs. three-domain view of life, the emergence of any domain from any other high-level grouping remains a topic of considerable debate. Some researchers have doubts about how different membrane systems could have emerged from such biochemically radically different ancestors (Koonin 2009), but note that although it was long thought that lipids based on *sn*-glycerol 1-phosphate were confined to *Archaea*, some of the genes needed for such lipids are still retained in the Bacterium *Bacillus subtilis* (Guldán et al., 2008). Peretó et al. (2004) have provided a thorough analysis of this issue. Others have doubts about distinct origins for the proteins involved in DNA replication (Forterre 2002), while others believe there may have been many contemporaries to our ancestors that influenced their genomes but disappeared from the record (Fournier 2015), and thus many attempts at reconstruction of evolutionary pathways may be fundamentally flawed.

2.7 Communication Across Scientific Disciplines

One of the most interesting aspects of the field of origins of life is how many disciplines must work together to address the questions which are currently interesting (Griesemer 2008). One study of researchers funded by the NASA Astrobiology Institute (NAI) identified 170 separate Ph.D degree titles that could be clustered into 67 different sub-disciplines (Aydinoglu et al. 2015). NAI researchers, as well as those of the Earth-Life Science Institute and other institutions around the world, form a community whose research overlaps significantly with that of the origins-of-life community, including astronomy, astrophysics, atmospheric science, biochemistry, biology, chemistry, earth

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

science, environmental science, geosciences, marine sciences, and physics, to name but a few from the long list of Ph.D-granting departments.

Multidisciplinary endeavors, such as research into the origins of life, face special obstacles to defining themselves and organizing funding sources as multiple scientific communities must come together to determine the interesting research questions, shared standards of evidence, and methods to communicate across disciplinary boundaries (Eisenberg & Pellmar 2000, Medicine et al. 2005, Hilton & Cooke 2015). For historians and social scientists, origins-of-life studies provide an exciting opportunity to explore the social organization of research, the integration of empirical and theoretical results from many different backgrounds (biology, chemistry, geology, *etc.*), as well as the diversity of methods, theories, and principles which each field uses and how they can be meshed to be collectively productive. The involvement of philosophers and theologians in the discussions creates a rare opportunity for scholars to observe interactions between the humanities and sciences. A good example is represented by a paper by Carroll and Vicuña (2017).

The study of the origins of life is a genuinely *multidisciplinary* science, which is rapidly becoming *interdisciplinary*. Oceanography (Powell 2008), climate science (Shaman et al. 2013), cognitive science (Miller 2003), and astrobiology (Cockell 2002, Des Marais et al. 2003) are other examples of sciences at various stages along that path. In multidisciplinary science, the disciplinary elements retain their original identity as such fields represent an *ad hoc* mix of knowledge, information, and methods whereas interdisciplinarity requires a higher degree of integration to create a holistic view which generally results in the emergence of a new disciplinary community, a new

1
2
3 shared terminology and a new set of research questions, a communal understanding of
4 research problems, and sometimes even an organizational framework for collaboration
5
6 (Stokols et al. 2003, Medicine et al. 2005, Porter et al. 2007, Wagner et al. 2011). If the
7
8 origin of disciplines is analogous to the rise of organs in a multicellular organism, then
9
10 the origin of interdisciplinary science is analogous to the advent of a central nervous
11
12 system that regulates and coordinates the operation of the organs.
13
14
15
16

17
18 The fields of study we presently recognize as “traditional sciences” (which are
19
20 generally demarcations made only in the last few centuries) have been constructed so
21
22 as to be more conceptually unified based on their perceived investigation of
23
24 observationally discrete types of phenomena. Of course, it is a historical and
25
26 sociological question as to whether traditional sciences face the same issues of
27
28 interdisciplinary sciences, especially when considered over great temporal, cultural, or
29
30 geographic distances. It may turn out that some of the issues which present themselves
31
32 for multidisciplinary and interdisciplinary sciences are also manifested in “traditional
33
34 sciences,” so the difference may be merely one of degree and not kind.
35
36
37
38

39
40 Philosophical, historical, and sociological research into similar cases in which
41
42 dissimilar fields have needed to work together may yield insights into how origins-of-life
43
44 research may avoid the pitfalls which have plagued other multidisciplinary and
45
46 interdisciplinary endeavors. For example, the same term may be used by scientists with
47
48 different backgrounds in slightly different ways (“conceptual slippage”). This may lead to
49
50 a community that interacts in ways that are baroque and inconsistent from a
51
52 philosophical perspective. Such disagreements may help science progress, hinder it, or
53
54 simply waste researchers’ time. An alternative to conceptual slippage is a holistic
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

system designed by one researcher or research program, but this can be just as problematic when holistic systems come into conflict. We see this in debates about definitions of life, metabolism vs. reproduction first models, top-down vs. bottom-up models, and so on (see sections 2.1-2.6).

Multidisciplinary sciences may have a harder time finding stability (as measured by identification, funding, and institutional commitment) than interdisciplinary sciences. Multidisciplinary sciences may see their component sciences come and go in popularity, periodically favoring some holistic program, or proceed with unexamined tensions and never develop a common language or research program. The origins of life and astrobiology demand a reintegration of various fields of science that self-organized into discrete disciplines over the last 100–200 years. Further, they seem to demand integration of purpose of study in ways which have been systematically discarded over the same time period and start to ask questions which have been systematically discouraged in “normal science” in Kuhn’s sense (Kuhn 1962).

Another pitfall is the lack of shared standards of evidence (see section 2.8). Different disciplines use different methodologies, instruments, and techniques and thus, have different levels of acceptance for their findings. For instance, Benner *et al.* (2013) explained how chemistry, geology, biology, and physics operate and use models differently and as a result, had different standards of proof for discussing the claims of arsenic DNA made by researchers with insufficient knowledge and understanding of the differences in chemistry between phosphorus and arsenic (Wolfe-Simon et al. 2011). Similarly, a vigorous debate was created in the scientific community when it was argued that the ALH84001 meteorite contained evidence of past life on Mars (Dick & Strick

2005, Mesler & Cleaves 2015). While such tensions can have long-term detrimental effects on scientific communities, they can also serve to crystallize the terms of debate.

There have been some initiatives to develop more integrated approaches to origins-of-life research. In 1973, the International Society for the Study of the Origin of Life (see www.issol.org) was established to bring together the scientific thoughts behind the contributions of Oparin, Fox, Ponnampertuma, Miller, Urey and others, and the Society has held triennial conferences since. In a similar effort, the Origins of Life Gordon Research Conferences have been held every other year since 1982. In terms of organizational structure and financial support for researchers, the establishment of the NAI in 1996 (in part spurred by the ALH84001 controversy) was a milestone, though funding was mainly provided to scholars in the U.S. The NAI started its own conference (the Astrobiology Science Conference, AbSciCon) and workshops and has provided funding (approximately \$350 million to date) to interdisciplinary collaborative scientific research on the origins, evolution, and distribution of life in the universe. Partially as a result of these efforts, the number of peer-reviewed publications on the subject of origins of life has increased from about 50 to 400 per year between 1993 and 2011, and cross-disciplinary interaction has increased enormously among researchers from different disciplines as well (Taskin & Aydinoglu 2015, Aydinoglu et al. 2016, Aydinoglu & Taskin 2017). More recently, the ELSI Origins Network (EON) at the Earth-Life Science Institute with support from the John Templeton Foundation was launched to create a sustainable origins-of-life studies community by fostering its transformation from multidisciplinary to interdisciplinarity.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

However, some of the challenges for the sustainability of origins-of-life research still remain. When better-established disciplines compete to claim limited available funding, establishing new academic structures or organizational frameworks can meet with resistance. Securing resources (funding, jobs, and graduate students) becomes a challenge. This makes origins-of-life studies vulnerable to changes that happen over time, such as periodically favoring some holistic programs or research questions. Furthermore, lack of shared standards of evidence can cause tensions as explained above. Often, this will involve change in research priorities as various research programs wax and wane in popularity, and when new technologies, techniques, or theories emerge. In such cases, it may help to look to experts with an understanding of the change of multidisciplinary sciences over time.

2.8 Epistemological Limitations and Methods to Investigate the Origins of Life

The scientific enterprise begets tools to record features of matter and phenomena. The invention and development of tools that are needed to open investigations in new fields may open new avenues of inquiry and spur innovation and discovery. The invention of the polymerase chain reaction (PCR), for example, greatly sped up discovery in molecular biology. High-throughput sequencing, online genomic databases, and modern metagenomics have all helped expand the range of microorganisms available for detailed study, shining a light on the large number of presently unculturable organisms in a way not unlike when van Leeuwenhoek first opened the microscopic world to science. Theoretical tools also help guide research. We see this in grand ideas like Darwin’s theory of evolution by natural selection or the

1
2
3 Modern Synthesis that merged it with Mendelian genetics. New paradigms allow new
4
5 ideas to be explored and interpreted in new ways.
6
7

8 But while theoretical tools and scientific equipment open new areas to scientific
9
10 investigation, they also constrain others. The history of science is replete with examples
11
12 of insights authors failed to see until some new idea was developed. For example,
13
14 Herschel's discovery of Uranus required conceiving of the possibility of a new planet
15
16 unknown to previous astronomers (Schaffer 1981). New ideas or tools sometimes bury
17
18 entire fields as the displaced tools reveal themselves as too slow, imprecise, or simply
19
20 unpopular in comparison.
21
22
23

24 Scholars in the humanities interested in the development of the field of origins of
25
26 life would do well to keep in mind the scientific, technological, and social changes
27
28 ongoing elsewhere in the world throughout the relatively short existence of the field. A
29
30 study of these may explain much about this research area's development. With this in
31
32 mind, we turn to the development of the field across its relatively short history.
33
34
35
36
37

38 **III. Historical and Sociological considerations with respect to origins of life**

39

40
41 As in any scientific field of inquiry, one can trace the present state of the art via a
42
43 narrative constructed of various discoveries and publications, and their eventual
44
45 canonization or rejection in light of other concurrent discoveries. Very generally, this
46
47 development is linked to technological advances which allow for ever more
48
49 sophisticated measurements and descriptions of systems. The scientific body of
50
51 knowledge underlying these technological advancements is also subject to a similar
52
53 shifting temporal validation. That said, we can roughly split the history of origins-of-life
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

studies into two parallel strands. The first deals with the development of origins of life as a research topic within empirical fields, primarily chemistry, Earth science and biology, while the second traces the development of theoretical questions relating to the origins of life, crossing between the fields of physics, evolutionary theory and computer science. The less-documented history and landscape of the second is explored more extensively here. For the reader interested in the first, extensive surveys of contemporary chemical models for the origins of life can be found elsewhere (Orgel 1998a, b, Fry 2000, Luisi 2006, Cleaves 2012, Ruiz-Mirazo et al. 2013).

The first strand can be divided into several phases: (1) The pre-systematization of biology period, (2) the post-systematization of biology period, (3) the chemistry period, (4) the molecular biology period, and (5) the informatics period. Undoubtedly, other logical divisions could be proposed, and it is not necessarily true that the names of these periods completely define the course of the development of ideas during them. It is argued that the major transitions in these periods are changes in the background availability of data and the ease of its collection or generation as facilitated by increasingly sophisticated instrumentation or technique. Simply put, productive theory in this field has lagged significantly behind experiment and measurement, though increasingly, theory has become a driver of discovery in its own right.

3.1 Strand 1: From Chemistry to Molecular Biology

3.1.1 The Pre-Systematization of Biology Period

It can be argued that some of the most drastic changes in the structure of biological theory were driven by the remarkable surveys of biological phenomena

1
2
3 facilitated by the advent of global seafaring and trade encouraged during the Age of
4
5 Exploration and the expansion of European colonialism. Indeed, while previous thinking
6
7 on the organization of biology was largely produced by relatively localized thinkers (e.g.,
8
9 Aristotle), who had access to the biological diversity surrounding them observable by
10
11 the naked eye (or information collected anecdotally), the global voyages of seminal
12
13 theorists, such as Darwin and Wallace, contributed to their ability to construct general
14
15 comparative theories of evolution. Even in earlier times, the theories of Lamarck,
16
17 Goethe and others were highly dependent on fossils and remains returned to Europe by
18
19 colonial enterprises. It is intriguing to speculate that the next revolutions in models of the
20
21 universal aspects of biology may depend on exploration of far-flung solar system
22
23 environments.
24
25
26
27
28
29
30
31
32

33 3.1.2 The Post-Systematization of Biology Period

34
35 The construction of phylogenetic trees to establish kinship has a long history and
36
37 can probably, at least intellectually, be traced to the genealogical trees that were
38
39 already customary for humans to construct by virtue of the need to assure systematized
40
41 inheritance of owned goods and responsibility for child-rearing (Fox 1967).
42
43

44 The earliest attempts to aggregate organisms into systematic classification
45
46 schemes (e.g., von Linné et al. 1735/1964) relied on naked-eye observable similarities
47
48 between organisms. While there are numerous aspects of such classification schemes
49
50 which have since been discarded or superseded by molecular methods, this sort of
51
52 hierarchical classification and the history it implies lies at the heart of the biological
53
54 sciences.
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

In his evolutionary theory, Lamarck introduced a temporal dimension in the classical, widely-accepted concept of the “Great Chain of Being” derived from the ideas developed by Aristotle and Plato (Lovejoy 1936, Bowler 1989). According to this view, organisms climb to more complex and perfect organization, starting at the bottom of the ladder with the lowest forms of life. Lamarck proposed that the first rung was populated by simple organisms which originated by spontaneous generation, hence integrating the traditional belief of the possibility of life being suddenly generated from inanimate matter into an evolutionary framework (Farley 1977, Bowler 1989). For his part, Darwin, albeit having been reluctant to discuss the origins of life in public, never rejected the possibility of a kind of natural transition from pure chemistry to simple organisms (Peretó et al. 2009). His writing coincided with the Pasteur-Pouchet debate over whether the spontaneous generation of life was common (Farley & Geison 1974). The alternative, the Virchow maxim that living cells must always come from other living cells, pushed the origins question back to a hypothetical first origination event.

Several early scientists, including Haeckel, proclaimed that to be logically consistent an evolutionary scheme had to contemplate the appearance of the first organisms by natural mechanisms. He, and others of his period, postulated that there was no reason to assume an insurmountable barrier separating inert and living matter. The acceptance of this continuity, negated by vitalist scientists of the time, was essential for the first attempts to experimentally synthesize living forms.

The work of, among others, H. C. Bastian, J. Burke, A. L. Herrera, and S. Leduc can be retrospectively seen as sincere efforts to cross the frontier between the inanimate mineral world and the biological realm (Keller 2009, Strick 2009, Letelier et al.

2011, Barge et al. 2015, Cleaves et al. 2014, Campos 2015, Peretó 2016). The criticisms of vitalist scientists were reasonable based on their belief that non-material causes were involved in the functioning of life. Many materialist scientists, perhaps most prominently Jacques Loeb, qualified those early synthetic biology attempts as naive. Loeb's thinking embodied the transition from a colloidal chemistry view of the cell to a more chemically precise description based on the existence of macromolecules, such as proteins, and he was in a privileged position to proclaim the artificial synthesis of life as the ultimate goal of biology, although recognizing that his and his contemporaries' attempts were possibly premature (Deichmann 2009a, b, 2012). Present-day synthetic biologists share the same ambitions and incentives of the pioneers of one hundred years ago, and it is clear that a materialist approach remains seen as a prerequisite for developing a scientific approach to the origins of life (Fry 2000, 2006, Lazcano 2010).

3.1.3 The Chemistry Period

Friedrich Wöhler's demonstration of the abiotic synthesis of urea is often noted as a transition between pre-chemical and chemical conceptions of biology (Campaigne 1955). However, McKie (1944) described this as a chemical legend, saying that science does not advance in sudden leaps; in addition to McKie's comments, the "inorganic" ammonium cyanate that Wöhler used was of biological origin. Notable achievements in chemistry which have contributed to models for the origins of life include the elucidation of the structures of the biological molecules (including biopolymers) and their commonalities, the metabolic pathways which allow their synthesis and interconversion, as well as various other subtler inferences which can be scaffolded from this body of

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

knowledge. One could add to this the discovery of the cofactors, driven largely by medicinal observations of nutrient-deficiency diseases, and the development of the chemiosmotic theory (Mitchell 1961).

The development of experimental abiotic organic synthesis, later termed “prebiotic chemistry,” during the 19th and 20th centuries converged within a historical framework with the Oparin and Haldane proposals for the origins of life on Earth (Oparin 1924, Haldane 1929). Prebiotic chemistry emerged as the study of abiotic synthesis leading to the origins of life under plausible primitive conditions, taking into consideration the data reported by planetologists, cosmochemists, and geologists (Bada & Lazcano 2003). Several laboratories are presently engaged in a “systems chemistry” approach to prebiotic chemistry aiming to functionally integrate diverse complex subsystems, such as lipid vesicles and self-replicating ribozymes (de la Escosura et al. 2015).

3.1.4 The Molecular-Biology Period

It is now widely recognized that all known life on Earth shares a generally common set of biochemical attributes, for example the use of DNA as an information storage reservoir, the use of various RNA/protein-based biomolecular machines as a means for decoding this information, the use of an essentially common genetic code, and the use of protein enzymes to mediate the majority of biochemical transformations. These commonalities may contribute to a circular definition which constrains thinking on the topic, as with the exclusion of RNA as an information storage molecule, which implicitly excludes RNA viruses from the realm of the “living.” Importantly, the

1
2
3 identification of these well-defined chemical systems relied on the development of
4 analytical tools capable of assigning molecular identities to the agents of apparent
5 transformations (see section 2.8). For example, the realization that biological systems
6 are predominantly composed of, besides water, “protein” preceded the modern
7 chemical understanding of the mechanisms of protein biosynthesis. Likewise, the
8 discovery of DNA as an entity (Miescher 1871) long preceded its identification as the
9 principal carrier of genetic information (Avery et al., 1944, Hershey & Chase 1952),
10 which overlapped with the determination of its composition (Chargaff et al. 1952), and
11 preceded the elucidation of its double-helical structure as the basis of the biochemical
12 means of reproduction (Watson & Crick 1953; Judson 1979).
13
14
15
16
17
18
19
20
21
22
23
24
25
26

27 The discovery process surrounding the structure and function of DNA and the
28 central dogma of biology, which has been well-documented elsewhere, has provided a
29 “Rosetta Stone” for the understanding of biology. While this has offered a unifying
30 framework for understanding all known forms of life on Earth today, it has raised other
31 conceptual issues, such as how the apparent complexity of the interdependency of the
32 DNA–RNA–protein system arose, and whether this system is truly the first, first and
33 only, or only surviving system to have originated on Earth (Joyce et al. 1987, Dworkin et
34 al. 2003) (see section 2.3.)
35
36
37
38
39
40
41
42
43
44
45

46 Although during the development of molecular biology in the 20th century the
47 question of what is life was eclipsed by the description of life in physicochemical terms,
48 at present there is a renewed interest in the nature and origins of life in the context of
49 systems and synthetic biology (Morange 2009, 2013, 2016).
50
51
52
53
54
55
56
57
58
59
60

3.1.5 The Informatics Period

This last period, which continues today, is marked by a significant increase in the ability to collect large amounts of salient data quickly and cheaply, such that even the earliest-career students and scientists may add to the repository of information about the Tree of Life in remarkably short order. For example, whole-genome sequencing and the rapid decrease in the cost of DNA sequencing has led to an explosion in notions of species diversity on Earth (Mora et al. 2011, Locey & Lennon 2016, Hug et al. 2016). Other techniques have also allowed for remarkably detailed molecular-scale descriptions of complex chemical systems, which were in retrospect relatively poorly described (Schmitt-Kopplin et al. 2010). Lastly, we note that the impact of developments in computing power and resources, which are now common accessories to all modern scientific research, cannot be underestimated in the current period. It seems likely they will play an accelerated and accelerating role in the future of discoveries in this field.

It should be noted this brief history largely tracks thinking from the perspective of biology and chemistry. However, superposed on these discoveries has been the increasing realization that prebiotic chemistry occurred in a geological context and that the modern constructions of phylogenetics and geochemistry allow for some deconvolution of the interlinked effects biology has had on the evolution on Earth (Smith and Morowitz 2016). The composition, dynamics and evolution of the Earth have guided or at least prepared the playing field for biological evolution, and there is likely feedback between these two systems. The recognition of the tight coupling between the biosphere and geosphere can be traced to Vernadsky (McMenamin et al. 1998) and Henderson (1913), and in the context of the origin of life to Chamberlin and Chamberlin (1908), Oparin (1924) and Haldane (1929), among others. This remains a central thread

1
2
3 in origins-of-life research, and contributions from geochemistry and planetary science
4
5 cannot be underestimated.
6
7
8
9
10

11 12 *3.2 Strand 2: From Physics to Evolutionary Theory and Computation*

13
14 As well as being a history of empirical measurements, the history of origins-of-life
15
16 research is also a history of ideas. Here, in broad outline, the development of some of
17
18 the more important theoretical ideas in the field is presented. While the history sketched
19
20 in the previous section deals mainly with historical approaches to origins of life, this
21
22 history covers mostly universal and synthetic approaches (in the senses described in
23
24 section 2.2). Accordingly, the two histories cover largely disjoint sets of researchers,
25
26 and the integration of these two strands will be an important future challenge.
27
28
29

30
31 A common theme runs through many of the approaches below, termed here
32
33 “circularity.” This is the idea that some process or phenomenon is a cause of itself,
34
35 perhaps via a complex chain of intermediate causes (Rosen 1991, Letelier et al. 2011).
36
37 The many examples below should make clear that this need not be paradoxical, and
38
39 indeed, this idea is closely related to the concept of autocatalysis in chemistry, a
40
41 phenomenon for which there are already many known examples (e.g., Tjivikua et al.
42
43 1990, Soai et al. 1995). There is a particular challenge in integrating this notion of
44
45 circularity with that of open-ended evolution discussed below.
46
47
48

49
50 The history of theory in origins-of-life research is difficult to tell in a linear way
51
52 since so much of it was developed in parallel by different communities of researchers.
53
54 Accordingly, we organize it according to multiple sub-themes rather than temporally.
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

3.2.1 Thermodynamics and dissipative structures

This class of ideas largely has its origins in the work of Boltzmann (1886/1974). Although isolated physical systems approach a state of thermodynamic equilibrium, living organisms can, and must, maintain themselves out of equilibrium while pushing their environment closer towards equilibrium. This idea was popularized by Schrödinger (1944) who referred to “negative entropy” using the modern sign convention, and by Prigogine (1969), who observed that this applies not only to living organisms but to a host of purely physical phenomena (such as cyclonic storms), which he termed “dissipative structures.” This provides the first example of the notion of circularity: in a storm, kinetic energy leads to the extraction of work from a temperature gradient, which leads to the generation of more kinetic energy. Thus, storm systems “feed on negative energy” just as do living organisms. Building on Alan Turing’s early work on self-organization (Turing 1990), Nicolis and Prigogine developed the theory of chemical systems that can form dissipative structures, for example, in reaction-diffusion systems (Nicolis and Prigogine 1977). These have recently been reviewed by Goldbeter (2017), with particular emphasis on biological rhythms.

Dissipative structures can form spontaneously under the right conditions, for example, storm systems form in response to sufficiently strong temperature and moisture gradients. This observation has led other authors to suggest that the origins of life might be a similar phenomenon. That is, that life arose as a physical response to chemical gradients on the early Earth, allowing them to be dissipated more efficiently (Morowitz 1968, Schneider and Kay 1994; Virgo et al. 2014, Smith & Morowitz 2016).

This theoretical strand of research connects strongly with empirical research in geochemistry since a key component in any origins-of-life scenario is identifying a

1
2
3 source of usable energy to drive reactions. How thermodynamic driving forces could
4
5 drive organization in complex chemical reaction networks is explored further below.
6
7
8
9

10 11 3.2.2 Self-organization: autopoiesis, metabolism-repair systems, the chemoton and 12 related ideas 13

14 The term “self-organization” was coined by Kant (1790), in the context of defining
15
16 “natural purpose,” *i.e.*, the purposeful appearance of living systems. He characterized
17
18 this in terms of organisms being both the cause and effect of themselves and of their
19
20 offspring (Weber & Varela 2002; Letelier et al. 2011).
21
22
23

24 Since then, self-organization has become something of a catch-all term for
25
26 phenomena that appear organized without an obvious external cause. In fact, self-
27
28 organization is now recognized as a common and mundane feature of nature, rather
29
30 than a distinguishing feature of life. This includes dissipative structures but also other
31
32 physical phenomena, such as self-organized criticality (Bak et al. 1987) and pattern
33
34 formation in less physically-motivated systems, such as cellular automata (Wolfram
35
36 2002). Self-organizing phenomena have been seen as relevant to the origins of life, in
37
38 that they demonstrate that complex forms of order can emerge from simple systems
39
40 under the right conditions.
41
42
43
44

45 There are several distinct groups of people who have built upon, or recapitulated,
46
47 Kant’s basic idea to develop detailed theories about what it means to be a living
48
49 organism and about what this might inform about the origins of life. In particular, this has
50
51 produced the theories of *autopoiesis* (Maturana & Varela 1980), *metabolism-repair*
52
53 *systems* (Rosen 1991), and the *chemoton* (Gánti 2000), which were developed
54
55 independently but share several similarities.
56
57
58
59
60

Theory	Reference	Thermodynamically Open	Specific Catalyst	Catalytic Closure	Structural Closure
Hypercycle	Eigen & Schuster (1977)	Implicit	Yes	Yes	No
Autopoiesis	Maturana & Varela (1980)	Yes	No	No	Yes
Syser	White (1980), Ratner & Shamin (1980), Feistel (1983)	Implicit	Yes	Yes	No
Symbiosis	King (1982)	Unclear	Yes	Yes	No
Autocatalytic sets	Kaufmann (1986)	Implicit	Yes	Yes	No
(M,R) systems	Rosen (1991)	Yes	Yes	Yes	No
Chemoton	Gánti (2003)	Yes	No	No	Yes
RAF Sets	Hordijk & Steel (2004)	Yes	Yes	No	No
Autogen	Deacon (2012)	Yes	Yes	Yes	Yes

Table 1. A comparison of views of life as a form of “circularity.” Some of these are not discussed in the text, but references are provided for the interested reader.

Autopoiesis

The theory of autopoiesis (Maturana 1970, Maturana & Varela 1980, Maturana & Varela 1992) built upon the ideas of Ashby (1966) and others in the early cybernetics movement (Letelier et al. 2011, Froese & Stewart 2010), who sought an understanding of cognition and living systems in terms of dynamical systems theory and feedback loops. Maturana and Varela’s contribution was to characterize a living organism as a “network of processes of production (transformation and destruction) of components” (emphasis added). This definition, taken from (Maturana & Varela 1980) evolved over the course of the authors’ careers, but the basic idea of a self-producing network of processes remained similar. The first part of the definition sets out a particular version

1
2
3 of the idea of circularity, while the second asks that the network of processes not only
4 exist but also be spatially localized and that this spatial localization be the result of the
5 processes themselves rather than some external cause. Perhaps the most radical
6 aspect of this definition is that it doesn't say life *has* a network of processes but that life
7 *is* a network of processes. It is also worth noting that reproduction and evolution were
8 not seen as fundamental components of this approach: Maturana and Varela, in
9 common with Rosen, saw evolution as a separate process, built on top of the more
10 basic property of material self-production, and strove to avoid invoking evolution in their
11 definition of life. Rosen (1991) stated this explicitly: "To me it is easy to conceive of life,
12 and hence biology, without evolution. But not of evolution without life. Thus, evolution is
13 a corollary of the living."
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28

29 Maturana and Varela are silent on precisely what is meant by a "process" or a
30 "component" in their definition, opting for a more philosophical style of writing. For those
31 who favor precise language and examples, an excellent exploration of their key ideas
32 was published by Beer (2004). Perhaps, because of their writing style, Maturana and
33 Varela's ideas have been subject to different interpretations and developed in different
34 directions by multiple groups of researchers.
35
36
37
38
39
40
41
42

43 One particular split is between those who favor an "extended" view of
44 autopoiesis, in which the network might include processes that occur outside the
45 physical boundary of the organism (Di Paolo 2009, Virgo et al. 2011, Froese et al.
46 2012), opening up the possibility that interactions with the environment might have
47 played key roles even at the origins of life (Egbert et al. 2012; Froese et al. 2014), and
48 those who hold an internalist view, that the network of processes must exist entirely
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 within a surrounding membrane-like enclosure (Luisi 2006). Another ongoing debate
4
5 questions whether autopoiesis is sufficient to serve as a definition of life, or whether
6
7 additional concepts are needed, such as Di Paolo's (2005) concept of adaptivity.
8
9

10
11 *(M,R) Systems*

12 Rosen (1991) in his metabolism-repair systems, often called *(M,R)* systems, saw
13
14 living organisms as networks of processes "closed to efficient causation," a phrase
15
16 implying that all catalysts needed by an organism must be produced by the network of
17
18 processes itself and cannot be imported from the environment (apart, perhaps, from
19
20 metals). His papers and books are highly mathematical, and consequently even more
21
22 difficult to understand than those of Maturana and Varela, who, curiously, did not
23
24 consider catalysts at all. Attempts have been made to make Rosen's work more
25
26 intelligible to non-mathematicians (Cornish-Bowden *et al.* 2007, Letelier *et al.* 2011,
27
28 Cárdenas *et al.* 2017). Letelier, a former student of Maturana and Varela, was probably
29
30 the first to show the relationship between autopoiesis and metabolism-repair systems
31
32 (Letelier *et al.* 2003). Rosen's ideas are usually taken to consider single organisms, but
33
34 he himself saw them as relevant to webs of interactions between organisms (Cárdenas
35
36 *et al.* 2017).
37
38
39
40
41
42

43 *The Chemoton*

44 Gánti published almost all of his work in Hungarian, thus its influence was not
45
46 strongly felt in the West until Szathmáry translated it into English (Gánti 2000), and as a
47
48 result may warrant more precedence than it is often ascribed. His chemoton model is
49
50 more firmly based on chemistry than either autopoiesis or metabolism-repair systems.
51
52 He saw a living organism in terms of three interacting cycles: a metabolic cycle, an
53
54 information cycle to reproduce and transmit information to the next generation, and a
55
56
57
58
59
60

process to achieve structural closure. As with Maturana and Varela, he emphasized the importance of an enclosing membrane or other barrier, which Rosen did not consider (Cornish-Bowden 2015). Many scientists interested in the origin of life regard structural closure as essential, but this closure, although essential, may be provided by the environment in the form of lipid vesicles or pores in minerals. All of the theories discussed in this review are compared in Table 1.

As a chemist, Gánti was less concerned with philosophical issues about cognition and purpose, and more concerned with how a minimal instantiation of the chemoton could be materially produced. Perhaps Gánti's greatest insight was that although modern cells implement the key features of the chemoton using finely tuned catalysts and complex molecular machines (*i.e.*, proteins and nucleic acids), it should also be possible to implement them using stoichiometrically coupled reactions, though he did not explain how such reactions would have the necessary specificity to avoid competing side-reactions. This problem applies to all of the theories, but it is less severe with minimal models of metabolism-repair systems in which only a very small number of molecules need to have a high degree of specificity (Piedrafita et al. 2010). Thus, it is conceivable that the basic properties of metabolism, cellular individuality and evolution could all have arisen before the emergence of complex protein or ribozyme catalysts. This idea has been influential in work on reaction networks, as discussed below. Gánti envisioned an early organism quite different from modern organisms at the level of molecular mechanism, yet closely related in terms of its overall organizational structure.

These theories of autopoiesis, metabolism-repair systems, and the chemoton have left intellectual successors that are now central to origins-of-life research. Some of

these ideas are now embodied in the concept of the “protocell,” a general term for an encapsulated structure either mimicking a modern cell or somewhere along the evolutionary path leading to modern cells. The term has been used in the context of discussions of the origins of life since at least the 1960s (Bahadur 1966, Kampitz and Fox 1969), often to refer to concepts which might more precisely be termed colloids or coacervates now. The contemporary concept of a protocell (Rasmussen et al. 2008) clearly owes much to Maturana, Varela and Gánti’s thoughts on the topic. At present, the concept of a protocell usually refers to a membrane-enclosed compartment, inside which is either a “metabolic” set of autocatalytic reactions, or an information-copying replicator, or both. Production of the membrane by the reactions inside it is often conceptually optional, however, coupling all three processes in the manner of the chemoton is a key research goal of some current research programs. As stated above, the conceptual and temporal relationship between a protocell, the progenote and LUCA remains somewhat blurry.

Autocatalytic Sets

A closely related concept is that of biological autonomy, developed in particular by Kauffman (2000) and Moreno and Mossio (2015). It builds on Maturana and Varela’s ideas of closure but more explicitly focuses on thermodynamic constraints and the specific chemical relations that can achieve them. Biological autonomy (which is itself an underspecified term: it is not clear to what degree of autonomy from the environment constitutes true autonomy, and there is likely no conception of an organism which can be completely disconnected from its environment as organisms are inherently throughput systems) was explicitly proposed as a necessary but insufficient condition

1
2
3 for life and as a possible intermediate step on the pathway from abiotic chemistry to
4
5 modern cellular life (Ruiz-Mirazo et al. 2004).
6
7

8 This concept was developed further by Kauffman (2004; Kauffman & Clayton
9
10 2009) to address the way that even the simplest organisms “act on their own behalf” in
11
12 his concept of “autonomous agency.” Kauffman emphasized that the self-preserving
13
14 and self-reproducing dynamics of living organisms required preserving a work cycle
15
16 capable of countering the incessant degradation imposed by the second law of
17
18 thermodynamics.
19
20
21
22
23

24 *Autogenesis*

25 Building on this, Deacon’s concept of “autogenesis” (e.g. Deacon 2012, 2015),
26
27 suggested that autonomous agency can be produced by the codependent linkage
28
29 between complementary types of self-organizing processes. In isolation, self-organizing,
30
31 self-replicating, autocatalytic, or self-assembling chemical processes are intrinsically
32
33 self-limiting. Their potential to persist is lost when they eventually exhaust substrates or
34
35 deplete local free energy. But codependent linkage between reciprocal catalytic
36
37 processes and self-assembling containment processes such that each process provides
38
39 the supportive and limiting boundary conditions for the other can prevent loss of the
40
41 synergy constraint linking these processes. Each thus limits the extent to which the
42
43 other can deplete the environmental conditions it depends on. As a whole, the system
44
45 effectively acts to repair damage, and if its components are more widely redistributed by
46
47 damage, localization of repair processes can result in reproduction. This does not fit into
48
49 either a metabolism-first or a replicator-first paradigm, though it is closer to the former
50
51
52
53
54
55
56
57
58
59
60

1
2
3 since it has been used to account for the subsequent evolution of a simple form of
4
5 molecular information (Deacon 2012, 2015, Deacon et al. 2014).
6
7
8
9

10
11
12 3.2.3 Replicators, Information and Evolution

13 Schrödinger (1944) predicted the existence of an “aperiodic crystal” to carry
14
15 hereditary information, characterizing this as “order from order,” as distinct from the
16
17 “order from disorder” that occurs with the formation of what are now termed dissipative
18
19 structures. For Schrödinger, life combined both of these sources of order.
20
21

22
23 Von Neumann had begun thinking about the instantiation of a “universal
24
25 constructor” already in the 1940’s, though his ideas were published posthumously only
26
27 two decades later (Von Neumann and Burks 1966). He suggested how a machine might
28
29 be constructed which was capable of constructing any object using coded instructions,
30
31 which could describe how to copy its own contents, effectively making a copy of itself.
32
33 This process is analogous to the biological processes of translation and replication,
34
35 although those molecular processes were not known at the time. Von Neumann’s
36
37 replicator is related to the concept of a *quine* in computer science, self-reference in
38
39 logic, and Gödel’s incompleteness theorems in mathematics.
40
41
42
43
44
45

46
47 *Quasispecies*

48 Theoretical developments in the origins of life had a close relationship with the
49
50 development of evolutionary theory in the 20th century, with a great deal of cross-
51
52 influence. A key development was Eigen’s quasispecies theory (Eigen & Schuster
53
54 1979). In the absence of highly evolved mutation repair mechanisms, one would expect
55
56 mutation rates to be far higher in primitive organisms than in modern biology. The result,
57
58
59
60

1
2
3 when mutation rates are high, is a much fuzzier kind of evolution, in which the steady
4
5 state is dominated not by the single fittest sequence but by a broad “cloud” of many
6
7 sequences, all constantly mutating among a set of accessible sequences. This cloud
8
9 can be conceived of as a “quasispecies.” Although formulated in the context of prebiotic
10
11 evolution, quasispecies theory was found to be useful in biology as well, particularly
12
13 when dealing with viral evolution, in which mutation rates can be very high. It has since
14
15 become a standard tool in the evolutionary theory toolbox (Domingo et al. 1985, Holland
16
17 et al. 1992, Eigen 1993, Domingo et al. 1997, Lauring & Andino 2010).

21
22 A key result of quasispecies theory is a phenomenon called the “error threshold.”
23
24 This says, in essence, that if the mutation rate is high then evolution might not converge
25
26 to the fittest peak because less fit mutants are produced at such a high rate that they
27
28 out-compete fitter sequences. This can take the form of a “sudden threshold,” where if
29
30 the mutation rate is above a critical value the fitness peak suddenly becomes
31
32 unobtainable (Nowak and Schuster 1989, Takeuchi and Hogeweg 2007 Nilsson and
33
34 Snoad 2000). Eigen's result showed that natural selection requires that organisms have
35
36 a high fidelity mechanism of heredity, making the origins problem more difficult than
37
38 might otherwise be assumed.
39
40
41
42

43
44 This reasoning leads to what Maynard-Smith and Szathmáry (1995) called
45
46 *Eigen's paradox* (Eigen 1971): to replicate a polymer with sufficiently high fidelity one
47
48 needs complex enzymes, but complex enzymes cannot evolve without sufficiently high
49
50 fidelity. This is no less of a problem for metabolism-first theories (or autopoiesis-first,
51
52 chemoton-first, etc.) than it is for replicator-first theories, since no matter the starting
53
54
55
56
57
58
59
60

point, systems must somehow end up with the modern biological mechanisms, or some equivalent, which one way or another solve this problem.

Hypercycles

To resolve this paradox, Eigen and Schuster (1978) proposed the hypercycle model, a conceptual evolving system in which multiple short sequences exist, each coding for an enzyme (or, in more modern formulations, a catalyst) that is not capable of replicating every possible sequence with high fidelity, but which is able to selectively catalyze the replication of one of the other sequences. These sequences form a cycle, each catalyzing the replication of the next.

However, while the hypercycle may solve Eigen’s paradox in principle, it is open to a different problem, as pointed out by Nee and Maynard Smith (1990). This is the problem of “parasites.” A sequence can mutate such that it no longer catalyzes replication of the next sequence in the cycle but still benefits from being replicated by the previous one. If this happens there is no immediate selective pressure against the mutant sequence and so such “parasitic” sequences can take over the hypercycle, causing its overall self-replication to cease. The chemoton suffers from the same problem, as indeed does autopoiesis, as McMullin (2004) observed when attempting to model it *in silico*.

One solution proposed for this problem, by Maynard Smith and Szathmry (1997), is compartmentalization. The idea here is that the hypercycle chemistry could be contained in many separate compartments (e.g., vesicles), which need not all contain exactly the same set of sequences. In this case, if the hypercycle in one particular vesicle is taken over by parasites, it will be at a selective disadvantage compared to those vesicles that are parasite-free. This can be seen as a form of group selection at

1
2
3 the molecular level. Maynard Smith and Szathmáry (1997) saw this as the first of their
4 identified “major transitions in evolution.” This set of ideas, alongside those connected
5 to autopoiesis and the chemoton, have reinforced the idea of the protocell as a key
6 concept in origins of life (Rasmussen 2009).
7
8
9
10
11

12
13 Origins-of-life and evolutionary theory also have connections at later stages in
14 the evolution of life, for example, in the form of a model of the evolution of the genetic
15 code and the transition from a mode of evolution dominated by horizontal gene transfer
16 to one dominated by vertical descent (Vetsigian et al. 2006).
17
18
19
20
21
22
23
24
25

26 3.2.4 Reaction networks, autocatalysis and the origin of heredity

27 Living cells consist of both a system for storing, translating, and copying genetic
28 information and a network of metabolic reactions that produce informational molecules.
29 These are so tightly integrated into the same self-producing network of processes that it
30 is hard to imagine either existing in its modern form without the other. Historically, both
31 the empirical and the theoretical sides of the field have been split into two camps,
32 known as “replicator first” and “metabolism first.” While the former group has focused
33 attention on the possibility that evolution could occur among heteropolymers in the
34 absence of enzymes as discussed in section 3.2.3 above, the latter are more focused
35 on how chemistry resembling metabolism might arise in the absence of heteropolymers.
36 While these have often been posed as diametrically opposed hypotheses, there is now
37 a great deal of cross-communication between the two communities of researchers,
38 along with a growing realization that this might not be the strictly either-or question it
39 originally seemed.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

It should be noted that "metabolism first" denotes a very broad spectrum of approaches, in part because the term "metabolism" has different meanings to different researchers. To some, it refers specifically to small-molecule reactions that resemble extant biochemical pathways (e.g., the reductive tricarboxylic acid cycle), whereas to others, it has come to denote the entire network of processes that constitutes an individual, as per the concepts of autopoiesis and metabolism-repair systems discussed above. Thus the first group is more concerned with how specific reaction mechanisms could be catalyzed prebiotically, whereas the latter are more interested in what could lead to the emergence of a self-maintaining reaction network, all the better if it enables open-ended evolution, regardless of what chemical substrates it uses.

A key concept for both groups is *autocatalysis*. One example is the so-called "formose reaction," in which a small amount of glycolaldehyde (GA) is added to, or spontaneously forms, in a solution of formaldehyde under appropriate conditions (Butlerow 1861, Breslow 1959). GA, a simple two-carbon sugar, engages with formaldehyde, a simple one carbon compound, to produce a cycle of reactions that both add additional formaldehyde molecules or other aldehydes and ketones produced by the reaction, and split the products up into smaller molecules. The result is that more GA is produced, along with a variety of other sugars. Each GA molecule is causally responsible for the production of more GA, via a network of several reactions. This can be seen as a very simple kind of circularity.

Morowitz (1968) and then Wächtershäuser (1988) proposed that autocatalytic cycles resembling the reductive tricarboxylic acid (rTCA) cycle (which had recently been proposed as perhaps the most ancient biological carbon-fixation pathway) could be

1
2
3 catalyzed by minerals on the early Earth. Similar ideas have also been proposed by
4
5 Russell and colleagues (2005). Morowitz stressed that this would be a natural result of
6
7 energy gradients on the early Earth, *i.e.*, that autocatalytic cycles are close relatives of
8
9 dissipative structures, but occurring in the domain of chemistry rather than physics. This
10
11 idea had already been spelled out in some detail by King (1980), though not in a
12
13 geochemical context (see also Virgo et al. 2016). Wächtershäuser's model stressed the
14
15 importance of mineral surfaces in these processes, in particular of minerals that could
16
17 reasonably be expected to be present in submarine hydrothermal environments which
18
19 had recently been discovered, found to host ecosystems at least in part disconnected
20
21 from solar energy, and proposed as sites for the origins of life (Corliss et al. 1981).
22
23
24
25
26

27 Cycles of intermediates, essential in the chemoton, are also essential for seeing
28
29 the flaw in the traditional distinction between enzymes and metabolites. The distinction
30
31 breaks down when it is recognized not only that all enzymes *are* metabolites, because
32
33 they are synthesized within an organism, but also that all the metabolites in a cycle are
34
35 also catalysts, because they are regenerated by the cycles in which they are used
36
37 (Cornish-Bowden & Cárdenas 2007, 2008). Thus, such cycles may have played
38
39 important roles in the origins of life.
40
41
42

43 The notion of autocatalytic metabolic reaction networks, particularly in instances
44
45 in which they were explicitly described, was quickly criticized on the grounds that under
46
47 “reasonable prebiotic conditions” (a criticism generally levied by chemists to point to
48
49 instances where chemistry *in silico* or on paper is unlikely to translate meaningfully to
50
51 real-world chemistry) there would also be side reactions that remove intermediates from
52
53 such cycles, producing products that do not contribute to the self-production and
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

possibly making them too “leaky” to self-propagate. Taking the example of the rTCA cycle, which has at least eight enzymatically-controlled steps depending on how one does the accounting, each step must proceed in high enough yields in order for the cycle to self-reproduce (Orgel 2008, King 1982). The self-reproduction of this cycle remains, to date, experimentally unvalidated. While this yield/cycle completion problem is conceptually related to the problem of parasites in hypercycles, it is a fundamentally different problem in methodologically subtle but important ways (Szathmáry 2013). These criticisms highlight significant experimental and conceptual hurdles which must be overcome for these explanations to have strong explanatory value in this field. Besides the few proposed examples which seek to link modern biochemical pathways with geochemistry, and which have met with hard criticism, there are undoubtedly many ways how mutually catalytic chemistry *could* be engendered which need not have parallels or surviving parallels in modern biochemistry. The emergence of the field of systems chemistry (Nitschke 2009, von Kiedrowski et al. 2010) and the quick realization of its potential importance to origins questions (Ruiz-Mirazo et al. 2013) highlights the hopes scientists have that such approaches may be fruitful.

Another approach to autocatalysis is that of Kauffman (1993), who proposed a prebiotic scenario in which peptides (or some other polymer, such as RNA) would be able to selectively catalyze ligation and cleavage of other specific peptides (or ribozymes). In his model, for every such reaction, there is a probability that it is catalyzed by any other polymer present in the system. He showed mathematically that this model has a phase transition. According to his analysis, at certain threshold values of system component diversity and probabilities of catalysis, very large autocatalytic

sets may form, in which a large number of species all catalyze the production of at least one other member of the set and which are also catalyzed by at least one other member of the set. Friston (2013) has proposed a model that resembles Kauffman's in some respects and reaches the similar conclusion that "biological self-organization is not as remarkable as one might think." However, it is not clear whether Kauffman's model provides a realistic model of peptide catalysis with respect to energetics or specificity. The indication that phase transition behavior may be displayed by such sets is nevertheless potentially important for origins research, as it suggests that under at least some theoretically possible conditions, it can be *easier* to create a large, complicated system whose many parts play loose functional roles than it is to create a smaller system with a minimum of functional parts (which is perhaps more similar to the present actualized biological state of affairs). This suggests the possibility that the origins of life might not have been simple but instead might have passed through stages which were more complex than they might otherwise seemingly have needed to be, and consequently, approaches to understanding the origins of life which seek to draw short and straight lines between modern biology and prebiotic chemistry may be misguided. A serious problem with Kauffman's model is that although it explains how large systems can arise from simple properties of molecules, it does not explain why uncontrolled growth should not continue forever, until all that is left is tar (see Section 3.2.5).

A key challenge for metabolism-first approaches (and indeed all approaches) is to explain the emergence of heredity. If information-carrying polymers are the result of evolution, then it is crucial to understand the nature of evolution prior to their emergence and the reasons for their emergence. One concept that has been proposed for this is

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

compositional heredity, the idea that if early life was comprised of molecular aggregates or coacervate-like assemblies that reproduced by simple fission, with their offspring having a similar composition to their parents, which might provide “enough” heredity for more complex mechanisms to evolve (Segré et al. 2000). Whether hereditary information can be passed on by system dynamics, diffuse structural information, or only covalently-bonded linear polymers remains a contentious issue, and regardless of which combination of these is correct, more work is needed in order to understand why, in present life, more sophisticated heredity mechanisms potentially emerge as a result.

A more abstract approach to the emergence of complex autocatalytic systems was pioneered by Fontana and Buss (1994), who defined an "artificial chemistry" in which simple computer programs (e.g., lambda calculus expressions) play the role of molecules. In their model, when two programs react, their “product” is determined by running one program with the other as an input. This was not intended as a realistic model of chemistry but as a way to conceptually probe how complex self-maintaining structures can emerge. A key result was that the system converged onto compositions that were collectively autocatalytic (or self-maintaining in their terminology), as well as being “closed,” meaning that they contained only a small subset of all possible molecules. Nevertheless, the mechanisms involved in self-maintenance could be quite complex. These concepts were generalized by Dittrich & Di Fenizio (2007) into "chemical organization theory," which can be applied to more realistic models and real chemical systems. Artificial chemistry has become an active research topic (Banzhaf & Yamamoto 2015) and now includes approaches such as that of Benkö *et al.* (2003a,b; 2004; 2005) and Andersen *et al.* (2013; 2014), that are attempting to more closely

1
2
3 approximate the details of prebiotic chemical systems, such that they can be compared
4
5 against experimental measurements. There is already a rich body of computational
6
7 work which can potentially be screened for applicability to real world chemistry. The
8
9 cross-pollination of experimental and computational chemistry approaches to the
10
11 question of origins may be ripe for new discoveries.
12
13
14
15
16
17
18

19 3.2.5 “Tar,” Combinatorial Explosions and Alternative Chemistries

20 Modern researchers often use the terms “abiotic chemistry” and “prebiotic
21
22 chemistry” almost interchangeably. To the extent that a useful distinction is to be had,
23
24 “abiotic” refers to any chemistry which occurs without biological mediation (*e.g.*, the
25
26 chemistry which occurs in meteorites, should it be proven they played no role in the
27
28 origins of life, or the photochemical transformations of smog), while “prebiotic” chemistry
29
30 describes abiotic chemistry that is purported to be important for the origins of life.
31
32 Prebiotic chemistry may include the study of compounds not present in contemporary
33
34 biochemistry (see for example (Cafferty and Hud 2015, and Chandru et al. 2016). While
35
36 views entertained before and during the 19th century might have allowed the possibility
37
38 that life could arise independently from biologically-derived precursors, which is distinct
39
40 from the notion that “imperfect” organisms may arise from more able ones, and from the
41
42 notion that non-living sets of molecules not present in contemporary biology may
43
44 actualize living states, it is now generally held that this is extremely unlikely and that
45
46 there was some special set of attributes of environment and/or chemistry which allowed
47
48 life to arise.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

A distinction between environmental biological and abiological organic chemistry was rarely deemed methodologically important until the Miller-Urey experiment (Miller 1953). By that time, serious doubts as to whether biology was the *only* way organic molecules could be formed had already been raised, and quashed (Campaigne 1955), and synthetic organic chemistry as a field was already extremely mature. Nevertheless, explicit investigation into the mechanisms by which completely abiological processes could produce organic chemical novelty, let alone chemical novelty with unusual properties, such as autocatalysis, are sparse in the literature before that time (e.g., Garrison et al. 1951). It is not clear when they were first investigated with the question of origins, as opposed to the mechanisms by which already biological organisms carried out transformations (Löb 1913). The Miller-Urey experiment at the very least presented a clear methodological distinction between processes which were guided or unguided by human researchers (and implicitly to what extent this was philosophically tractable).

Since the Miller-Urey experiment, it has been evident that prebiotic chemistry can produce diverse sets of products and generally may do so under the set of assumptions of what constitutes reasonable prebiotic conditions. While these often include the building blocks of modern biochemistry they also include a great deal of other molecules, and the overlap may be largely coincidental as the processes of production are distinct for the sake of the question at hand. Other purported prebiotic chemistries (which are often validated by the overlap of their products with the compounds isolable from carbonaceous meteorites) include HCN polymerization (Ferris et al. 1978), the formose reaction (Decker et al. 1982), Maillard chemistry (Baynes 2005) and Fischer–Tropsch-type chemistry (Anders et al. 1973). This diversity of products results from

1
2
3 “combinatorial explosions”: a small number of reactive components can be put together
4
5 in an exponentially increasing number of ways (Schuster 2000). These complex
6
7 mixtures of products have often been referred to as “tar” or “asphalt” (Benner et al.
8
9 2012) because they are often darkly colored, viscous and composed of many
10
11 compounds, in contrast to what synthetic organic chemists generally seek as products,
12
13 *i.e.*, simple mixtures from which single desired compounds can be easily isolated.
14
15

16
17 Many researchers have approached this problem by attempting to constrain the
18
19 chemistry so that only one or a few specific products are generated. Indeed, it is
20
21 possible that there is some set of reactions and reaction conditions which might *only*
22
23 produce modern biochemicals and do so in high yield, no matter how implausible.
24
25 Planets offer large surface areas, and large amounts of time are available, so who is to
26
27 say which set of conditions is impossible? It may be equally possible that this molecular
28
29 diversity is not a problem to be avoided but instead played an essential role in the
30
31 emergence of life. Investigating this possibility requires not only further development of
32
33 artificial chemistry models but also new experimental techniques (see for example
34
35 Andersen et al. 2013).
36
37
38
39

40
41 A related question is why life is made of the particular set of building blocks that it
42
43 is. Various computational works (Meringer et al. 2013, Cleaves et al. 2015, Ilardo et al.
44
45 2015, Zubarev et al. 2015) have shown that there are many more possible amino acids,
46
47 intermediary metabolites or nucleosides than those used by life, and moreover, that the
48
49 set used by life appears to be adapted to provide “optimal” coverage of the space of
50
51 properties that such building blocks would be expected to have. Given the huge
52
53 diversity of possible prebiotic molecules, it seems conceivable that the earliest
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ancestors of life were not made of the same chemical building blocks as modern life at all. If this idea is entertained, it would mean there are a very large number of chemical systems which require exploration to fully understand why life is constructed the way it is, and optimization and contingency deserve greater scrutiny than the simple products of abiotic chemistry.

3.2.6 Artificial life and open-ended evolution

In the late 20th century, it became feasible to simulate evolution computationally. It has become increasingly fashionable to implement the basic features of replication with heritable variation in fitness, and observe their effects *in silico*. This line of research began in earnest with Booker et al.'s (1989) genetic algorithm. This quickly gave rise to a number of early works in the field that became known as "Artificial Life." Artificial Life, or more briefly ALife, does not refer exclusively to *in silico* evolutionary simulation study. Artificial Life refers more to a broad community of researchers and a loose set of common interests than to any particular methodology or agreed upon set of assumptions.

These early works included Tom Ray's Tierra (<http://life.ou.edu/tierra/>), in which self-replicating programs compete and "evolve"; Langton's "loops" (Langton 1984), a self-replicating cellular automaton far simpler than von Neumann's original concept; and Karl Sims' *Creatures* (Sims 1994), a three dimensional physical simulation in which creatures made of cuboid blocks "evolve" surprisingly complex behaviors. Simulations of these kinds are now regularly used by evolutionary biologists.

1
2
3 Evolutionary simulations are useful because they provide practical, time-
4 compressed, manipulable explorations of evolutionary dynamics. However, perhaps the
5 greatest insight from *in silico* modeling of evolution is a negative one: *in silico* evolution
6 seems to easily hit limits in terms of complexity. It is straightforward to set up an
7 evolutionary simulation that produces complex or surprising solutions to a problem, but
8 at some point, it saturates, failing to produce further innovations. A famous early
9 example is Ray's "Tierra," in which an initial self-replicating program evolves to become
10 parasitic on other programs but further innovations do not occur after that. In contrast,
11 biology has continued to produce innovations for several billion years and shows no
12 sign of stopping. This capacity for (apparently) unbounded innovation has become
13 known as "open-ended evolution," and the problem of fully understanding and
14 reproducing it in simulations is a major current goal of ALife research (Taylor et al.
15 2016). The framing of the problem is still in flux, with some groups seeking a numerical
16 measure of complexity (Bedau & Packard, 1991, Bedau et al. 2000) while others seek
17 an explanation for more qualitative changes along the lines of Maynard Smith and
18 Szathm ry's major transitions (Maynard Smith & Szathm ry 1995).

19
20 This is important for origins-of-life research for similar reasons to Eigen's results
21 regarding the hypercycle. Whatever form early evolution took, it must have had
22 sufficient capacity for innovation to be able to reach the complexity of a modern cell.
23 The fact that this has not yet been recapitulated in simulations reinforces the notion that
24 they lack some fundamental understanding of what prerequisites permit this. For this
25 reason, there is now substantial interest in the role of open-endedness in the origins of
26 life (Ruiz-Mirazo et al. 2008, Gleiser et al. 2012, Adams et al. 2017a, b) including open-

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ended evolvability as part of a definition of life. However, others, following Maturana and Varela (1980) and Rosen (1991), regard evolvability as a corollary of life, not a prerequisite (Cárdenas *et al.*, 2017, Cornish-Bowden and Cárdenas, 2017).

A related topic is the evolution of evolvability, *i.e.*, the study of how the mechanisms of evolution are themselves subject to natural selection. Insights from simulations have played a key role in the development of this idea (Dawkins 1989, Altenberg 1994). A significant insight is that the variety of phenotypic changes that can be achieved by mutation is strongly dependent on the “genotype-phenotype map” (Wagner & Altenberg 1996), *i.e.*, the biological mechanisms for reading and interpreting the genome.

3.2.7 Summary and future challenges

In summarizing theoretical and modeling approaches to the origins of life, we draw attention to two common themes. The first is the notion of “circularity,” that is that components of living systems are both causes and effects of themselves (Maturana 1970; Rosen 1991). “Circularity,” rather than a more technical term such as “closure to efficient circular causation” or “operational closure,” emphasizes that this basic idea is a common theme across many approaches to understanding the origins of life. The second is open-endedness, or the notion that life is not constant over time but always has the capacity for innovation or increasing complexity. These two themes are to some extent in tension: circularity suggests constancy over time while open-endedness suggests change. Resolving this tension is an interesting challenge for future work.

1
2
3 However, for most accounts, the circularity applies to a particular individual, and it is not
4
5 an individual that evolves, but a population.
6
7

8 Perhaps a much greater challenge is in integrating these synthetic and universal
9
10 approaches with historical approaches. A full answer to the problem of the origins of life
11
12 would include understanding how these properties of circularity and open-endedness
13
14 arose in the geochemical context of the early Earth, what role they played in the
15
16 transition from chemistry to biology and the evolution of modern life, and indeed, what
17
18 roles they continue to play.
19
20

21
22 How can the evidence from geology, chemistry, and biology be brought to bear
23
24 on these questions? Conversely, how should insights from theory inform research in
25
26 evolution and prebiotic chemistry? Integration of these approaches will undoubtedly
27
28 open new perspectives on the question, but a full understanding of how this can be
29
30 done can only come from greater communication and mutual understanding between
31
32 the researchers involved.
33
34
35
36
37

38 **IV Conclusions**

39
40 The origins of life on Earth is one of the most important, most difficult
41
42 unanswered questions in science. There are several ways of approaching its study, and
43
44 the relative importance of these have changed over time. The scientific community
45
46 agrees that both the approach and putative answer will likely draw on insights which will
47
48 be multidisciplinary in nature.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

In this paper, we described historical and philosophical issues in the study of the origins of life, which we argue may help guide research as much as careful study of biochemistry or evolution. Philosophical issues included:

(1) the nature of life, where we outlined several approaches that serve as alternatives to the traditional quest for a definition of life.

(2) the explanatory project of origins-of-life research, in which we argued universal (true for origins everywhere), historical (descriptions of life’s origin on Earth), and synthetic (possible ways of originating life) research programs overlap, are all interesting scientifically, but are not equivalent or directly transferable.

(3) the research strategies for origins-of-life research, typically thought of as either top-down (inferring from current life to LUCA) or bottom-up (starting from non-life and working out how to get life started), which face different epistemological problems and require distinct philosophical commitments.

(4) the metabolism-first vs. reproduction-first debate, which we challenged as presuming too much about the nature of life.

(5) the nature of evolution prior to LUCA, which was certainly different from contemporary evolution, although we questioned whether the difference was greater than some of the vastly diverse processes we see in life today.

(6) the nature of entities prior to LUCA, which are sometimes thought of as loose communities, though whether such communities can serve as ancestral requires rethinking the nature of ancestors;

(7) the challenges of origins-of-life which are common to multidisciplinary sciences: competing research programs, diverse standards of evidence, and communicating across disciplinary divisions.

(8) the development of new theories or tools, which offer opportunities for new avenues of research, but may also constrain others.

We also discussed two complementary approaches toward writing the history of origins-of-life science, each of which spans great swaths of time and several revolutionary changes in the theories, tools, and practices of scientists interested in this area. Those two strands were:

(1) From chemistry to molecular biology, tracing the paradigmatic changes made by *international travel* to develop comparative views of biology, *systematizing biology* as a historical science in which similarities of taxa were due to descent with modification, *chemistry* as a guiding force in exploring particular ways biotic polymers could form from their abiotically-produced parts, *molecular biology* and its focus on genetic material, and *informatics*, in which new technologies make the production of data vastly simpler than its interpretation.

(2) The second strand was from the theoretical questions relating to the origins of life, crossing between the fields of physics, evolutionary theory and computer science. Here the vastly different approaches led by thermodynamics, self-organization, replicators, reaction networks, and artificial life have led to distinct research programs that reveal intriguing features of life and perhaps even its nature or origin.

The history of a field and its philosophical commitments shape how we conceive of the problem as well as what would be acceptable as a solution. The ways the

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

understanding of the questions being asked are historically situated, and the ways research programs are loaded with philosophical commitments, many of which are not shared by all researchers in the relevant fields, can induce disagreements. Addressing and acknowledging these disagreements and their histories can go a long way toward resolving debates in this field.

Acknowledgements

The authors wish to thank the Earth-Life Science Institute Origins Network (EON) at the Tokyo Institute of Technology for hosting the meeting History and Philosophy of Origins Research Workshop that took place on August 2016 in Tokyo, Japan, which this publication is based. This project/publication was supported by the ELSI Origins Network (EON), which is supported by a grant from the John Templeton Foundation. The opinions expressed in this publication are those of the authors and do not necessarily reflect the views of the John Templeton Foundation. T.F.’s work on this article was supported by an ELSI Origins Network (EON) Long-Term Visitor Award and by an UNAM-DGAPA-PAPIIT project (IA104717).

References

- Adams, A. & Walker, S. I. (2017). Real-world open-ended evolution: A league of legends adventure. *International Journal of Design & Nature and Ecodynamics* **12**, 458-469.
- Adams, A., Zenil, H., Davies, P.C.W. & Walker, S.I. (2017). Formal definitions of unbounded evolution and innovation reveal universal mechanisms for Open-ended evolution in dynamical systems. *Scientific Reports* **7**, 997.
- Altenberg, L. (1994) The evolution of evolvability in genetic programming." *Advances in Genetic Programming* **3**, 47-74.
- Anders, E., Hayatsu, R. & Studier, M. H. (1973). Organic compounds in meteorites. *Science* **182**, 781-790.
- Andersen, J. L., Andersen, T., Flamm, C., Hanczyc, M. M., Merkle, D. & Stadler P. F. (2013). Navigating the chemical space of HCN polymerization and hydrolysis: guiding graph grammars by mass spectrometry data. *Entropy* **15**, 4066-4083.
- Andersen, J. L., Flamm, C., Merkle, D., & Stadler, P. F. (2013). Inferring chemical reaction patterns using rule composition in graph grammars. *Journal of Systems Chemistry*, **4**, 4.
- Andersen, J. L., Flamm, C., Merkle, D., & Stadler, P. F. (2014). Generic strategies for chemical space exploration. *International Journal of Computational Biology and Drug Design* **7**, 225-258.
- Ashby, W. R. (1966). *Design for a Brain: The Origin of Adaptive Behaviour*. Chapman and Hall, London.
- Avery, O.T., MacLeod, C. M. & McCarty, M. (1944). Studies on the chemical nature of the substance inducing transformation of pneumococcal types: induction of transformation by a desoxyribonucleic acid fraction isolated from *Pneumococcus* Type III . *Journal of Experimental Medicine* **79**, 137–158.
- Aydinoglu, A. U., Allard, S. & C. Mitchell. (2015). Measuring diversity in disciplinary collaboration in research teams: An ecological Perspective. *Research Evaluation* **25**, 18-36.
- Aydinoglu, A. U., Mitchell, C. & Allard, S. (2016). Measuring diversity in disciplinary collaboration in research teams: An ecological perspective. *Research Evaluation* doi: 10.1093/reseval/rvv028.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Aydinoglu, A. U. & Taskin, Z. (2017). Origins of life research: A Bibliometric Approach. *Origins of Life and Evolutions of Biospheres* doi: 10.1007/s11084-017-9543-4.

Baake, E. & Gabriel, W. (1999). Biological Evolution through Mutation, Selection, and Drift: an Introductory Review. *Annual Reviews of Computational Physics* **7**, 203-264.

Bada, J. L. & Lazcano, A. (2003). Prebiotic soup - Revisiting the Miller experiment. *Science* **300**, 745-746.

Bahadur, K. (1966). *Synthesis of Jeewanu: The Protocell*. Ram Narain Lal Beni Prasad. Uttar Pradesh, India.

Bains, W. (2004). Many chemistries could be used to build living systems. *Astrobiology* **4**, 137-167.

Bak, P., Tang, C. & Wiesenfeld, K. (1987). Self-organized criticality: An explanation of the 1/f noise. *Physical Review Letters* **59**, 381-384.

Banzhaf, W. & Yamamoto, L. (2015). *Artificial Chemistries*. MIT Press. Cambridge.

Barge, L. M., S. S. Cardoso, J. H. Cartwright, G. J. Cooper, L. Cronin, A. De Wit, I. J. Doloboff, B. Escribano, R. E. Goldstein & F. Haudin (2015). From chemical gardens to chemobionics. *Chemical Reviews* **115**, 8652-8703.

Baynes, J. W. (2005). *The Maillard reaction : chemistry at the interface of nutrition, aging, and disease*. New York Academy of Sciences, New York.

Beatty, J. (1997). Why do biologists argue like they do?. *Philosophy of Science* **64**, S432-S443.

Bedau, M. A., McCaskill, J. S., Packard, N. H., Rasmussen, S., Adami, C., Green, D. G., & Ray, T. S. (2000). Open problems in artificial life. *Artificial Life* **6**, 363–376.

Bedau, M. A., & Packard, N. H. (1991). Measurement of evolutionary activity, teleology, and life. In *Artificial Life II*. Santa Fe Institute Studies in the Sciences of Complexity, Vol. X, (Redwood City, CA: Addison-Wesley, 1992), pp. 431-461.

Beer, R. D. (2004). Autopoiesis and cognition in the game of life. *Artificial Life* **10**, 309-326.

- Benner, S. A., Bains, W. & Seager, S. (2013). Models and standards of proof in cross-disciplinary science: The case of arsenic DNA. *Astrobiology* **13**, 510-513.
- Benner, S. A., Kim, H.-J. & Carrigan, M. A. (2012). Asphalt, Water, and the Prebiotic Synthesis of Ribose, Ribonucleosides, and RNA. *Accounts of Chemical Research* **45**, 2025-2034.
- Benkő, G., Flamm, C., & Stadler, P. F. (2003). Generic properties of chemical networks: artificial chemistry based on graph rewriting. In *Advances in Artificial Life, ECAL*, Dortmund, Germany, 10-19.
- Benkő, G., Flamm, C., & Stadler, P. F. (2003). A graph-based toy model of chemistry. *Journal of Chemical Information and Computer Sciences*, 43(4), 1085-1093.
- Benkő, G., Flamm, C., & Stadler, P. F. (2004). Multi-phase artificial chemistry. The Logic of Artificial Life: Abstracting and Synthesizing the Principles of Living Systems, 1, 10-20.
- Benkő, G., Flamm, C., & Stadler, P. (2005). Explicit collision simulation of chemical reactions in a graph based artificial chemistry. *Advances in Artificial Life*, 725-733.
- Bich, L. & Green, S. (2017). Is defining life pointless? Operational definitions at the frontiers of Biology. *Synthese*. 1-28.
- Bitbol, M. & Luisi, L. (2004). Autopoiesis with or without cognition: defining life at its edge. *J. R. Soc. Interface* **1**, 99–107.
- Boltzmann, L. (1886/1974). The second law of thermodynamics. In *Theoretical Physics and Philosophical Problems*. Edited by McGuinness, B. F. (ed. Springer), p. 24.
- Booker, L. B., Goldberg, D. E. & Holland, J. H. (1989). Classifier systems and genetic algorithms. *Artificial intelligence* **40**, 235-282.
- Booth, A. Mariscal, C. & Ford, W. (2016). The Modern Synthesis in the light of microbial genomics. *Annual Review of Microbiology*. **70**, 279-297.
- Bowler, P. J. (1989). *Evolution: the History of an Idea*. University of California Press, Berkeley.
- Bowler, P. J. (1992). *The Eclipse of Darwinism: Anti-Darwinian Evolution Theories in the Decades Around 1900*. Johns Hopkins University Press, Baltimore.

Bowler, P. J. (2013). *Darwin Deleted: Imagining a World Without Darwin*. University of Chicago Press, Chicago.

Breslow, R. (1959). On the mechanism of the formose reaction. *Tetrahedron Letters* **21**, 22-26.

Boutlerow, A. (1861). Formation synthétique d'une substance sucrée. *C. R. Acad. Sci* **53**, 145–147.

Cafferty, B. J. & Hud, N. V. (2015). Was a Pyrimidine-Pyrimidine base pair the ancestor of Watson-Crick base pairs? Insights from a systematic approach to the origin of RNA. *Israel Journal of Chemistry* **55**, 891-905.

Campaigne, E. (1955). Wohler and the overthrow of vitalism. *Journal of Chemical Education* **32**, 403.

Campos, L. A. (2015). *Radium and the Secret of Life*. University of Chicago Press, Chicago.

Caporael, L. R., Griesemer, J. R. & Wimsatt, W. C. (Editors) (2013) Developing Scaffolds in Evolution, Culture, and Cognition. (Vienna Series in Theoretical Biology), MIT Press.

Cárdenas, M. L., Benomar, S. & Cornish-Bowden, A. (2017). Rosennean complexity and its relevance to ecology. *Ecological Complexity*, in press.

Carroll, W. E. & Vicuña, R. (2017). God, nature and the origins of life. *Science & Christian Belief* **29**, 37–41.

Cech, T. R. (1993). The efficiency and versatility of catalytic RNA: implications for an RNA world. *Gene* **135**, 33–36.

Chamberlin, T. & Chamberlin, R. (1908). Early terrestrial conditions that may have favored organic synthesis. *Science* **28**, 897-911.

Chandru, K., Gilbert, A., Butch, C., Aono, M. & Cleaves II, H.J. (2016). The abiotic chemistry of thiolated acetate derivatives and the origin of life. *Scientific reports* **6**, 29883.

Chargaff, E., Lipshitz, R. & Green, C. (1952). Composition of the desoxypentose nucleic acids of four genera of sea-urchin. *Journal of Biological Chemistry* **195**, 155-160.

Cleaves, H. J. (2012). Prebiotic chemistry: What we now, what we don't. *Evolution: Education and Outreach* **5**, 342-360.

Cleaves, H. J., Lazcano, A. Mateos, I. L. Negrón-Mendoza, A. Peretó, J., & Silva, E. (2014). *Herrera's 'Plasmogenia' and Other Collected Works: Early Writings on the Experimental Study of the Origin of Life*. Springer, New York.

Cleaves, H. J., Meringer, M. & Goodwin, J. (2015). 227 Views of RNA: Is RNA unique in its chemical isomer space? *Astrobiology* **15**, 538-558.

Cleland, C. E. (2013). Common cause explanation and the search for a smoking gun. *Geological Society of America Special Papers* **502**, 1-9.

Cleland, C. E. & Chyba, C. F. (2007). *Planets and Life: The Emerging Science of Astrobiology*. Cambridge University Press, Cambridge.

Cleland, C. E. & Copley, S. D. (2005). The possibility of alternative microbial life on Earth. *International Journal of Astrobiology* **4**, 165-173.

Cockell, C. (2002). Astrobiology—a new opportunity for interdisciplinary thinking. *Space Policy* **18**, 263-266.

Corliss, J., Baross, J. & Hoffman, S. (1981). A hypothesis concerning the relationship between submarine hot springs and the origin of life on Earth. *Oceanologica Acta* **4**, 59-69.

Cornish-Bowden, A. (2015) Tibor Gánti and Robert Rosen: contrasting approaches to the same problem. *Journal of Theoretical Biology* **381**, 6–10.

Cornish-Bowden, A. (2016) *Biochemical Evolution*. Garland Press, New York.

Cornish-Bowden, A. & Cárdenas, M. L. (2007). Organizational invariance in (M,R) systems. *Chemistry and Biodiversity* **4**, 2396–2406.

Cornish-Bowden, A. & Cárdenas, M. L. (2008). Self-organization at the origin of life. *Journal of Theoretical Biology* **252**, 379–387.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Cornish-Bowden, A. & Cárdenas, M. L. (2017). Life before LUCA. *Journal of Theoretical Biology* **434**, 68-73.

Cornish-Bowden, A., Cárdenas, M. L., Letelier, J.C. & Soto-Andrade, J. (2007). Beyond reductionism: metabolic circularity as a guiding vision for a real biology of systems. *Proteomics* **7**, 839-845.

Coveney, P. V., Swadling, J. B., Wattis, J. A. D. & Greenwell, H. C. (2012). Theory, modeling and simulation in origins of life studies. *Chemical Society Reviews* **41**, 5430-5446.

Cronin, L., Krasnogor, N., Davis, B. G., Alexander, C., Robertson, N., Steinke, J. H. & Siepmann, P. (2006) The imitation game—a computational chemical approach to recognizing life. *Nature biotechnology* **24**, 1203-1206.

Dagan, T. & Martin, W. (2006). The tree of one percent. *Genome Biology* **7**, 118.

Damer, B. & Deamer, D. (2015). Coupled phases and combinatorial selection in fluctuating hydrothermal pools: A scenario to guide experimental approaches to the origin of cellular life. *Life* **5**, 872-887.

Darwin, F. (1877). *The Life and Letters of Charles Darwin, Including an Autobiographical Chapter*. Murray, London.

Davies, P. C. & Lineweaver, C. H. (2005). Finding a second sample of life on Earth. *Astrobiology* **5**, 154-163.

Dawkins, R. (1982). Universal Darwinism. In *Evolution from Molecules to Men* (ed. D.S. Bendall), pp. 403-425. Cambridge University Press, Cambridge, UK.

Dawkins R (1989) in *Artificial Life: The Proceedings of an Interdisciplinary Workshop on the Synthesis and Simulation of Living Systems*, ed. Langton C.G. (Addison–Wesley, Reading, MA), 6, 201–220.

De la Escosura, A., Briones, C. & Ruiz-Mirazo, K. (2015). The systems perspective at the crossroads between chemistry and biology. *Journal of theoretical biology* **381**, 11-22.

Deacon, T. W. (2011). *Incomplete Nature: How Mind Emerged from Matter*. W. W. Norton, New York.

1
2
3 Deacon, T. (2015) Steps to a science of biosemiotics. *Green Letters* **19**, 293-311.

4
5
6 Deacon, T., Srivastava, A. & Bacigalupi, J. (2014). The transition from constraint to
7 regulation at the origin of life. *Frontiers in Bioscience* **19**, 945-957.

8
9
10 Decker, P., Schweer, H. & Pohlmann, R. (1982). Bioids: X. Identification of formose
11 sugars, presumable prebiotic metabolites, using capillary gas chromatography/gas
12 chromatography—mass spectrometry of *n*-butoxime trifluoroacetates on OV-225. *Journal*
13 *of Chromatography A* **244**, 281-291.

14
15
16
17 Deichmann, U. (2009). Chemistry and the engineering of life around 1900: Research
18 and reflections by Jacques Loeb. *Biological Theory* **4**, 323-332.

19
20
21 Deichmann, U. (2009b). "Molecular" versus "Colloidal": controversies in biology and
22 biochemistry, 1900-1940. *Bull Hist Chem* **32**, 105-118.

23
24
25 Deichmann, U. (2012). Crystals, colloids, or molecules?: early controversies about the
26 origin of life and synthetic life. *Perspectives in biology and medicine* **55**, 521-542.

27
28
29 DeJong-Lambert, W. (2012). *The Cold War Politics of Genetic Research: An*
30 *Introduction to the Lysenko Affair*. Springer, Netherlands.

31
32
33 Descartes, R. (1664/2010). Treatise on Man. In: *The Nature of Life: Classical and*
34 *Contemporary Perspectives from Philosophy and Science*. Edited by M. A. Bedau &
35 C.E. Cleland. New York, N.Y.: Cambridge University Press, p. 15-20. 9-14. (Original
36 translation published in 1985 by J. Cottingham, R. Stoothoff, and D. Murdoch,
37 Cambridge University Press. Original work published in 1664).

38
39
40
41 Des Marais, D. J., Allamandola, L. J., Benner, S. A., Boss, A. P., Deamer, D.,
42 Falkowski, P. G., Farmer, J. D., Hedges, S. B., Jakosky, B. M., Knoll, A. H., Liskowsky,
43 D. R., Meadows, V. S., Meyer, M. A., Pilcher, C. B., Nealson, K. H., Spormann, A. M.,
44 Trent, J. D., Turner, W. W., Woolf, N. J. & Yorke, H. W. (2003). The NASA astrobiology
45 roadmap. *Astrobiology* **3**, 219-235.

46
47
48
49 Dick, S. J. & Strick, J. E. (2005). *The Living Universe: NASA and the Development of*
50 *Astrobiology*. Rutgers University Press, New Jersey.

51
52
53 Di Paolo, E. A. (2005). Autopoiesis, adaptivity, teleology, agency. *Phenomenology and*
54 *the cognitive sciences* **4**(4), 429-452.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Di Paolo, E. A. (2009). Extended life. *Topoi* **28**, 9-21.

Di Paolo, E, A., Noble, J. & Bullock, S. (2000). Simulation models as opaque thought experiments. In *Proceedings of Artificial Life VII: The Seventh International Conference on the Simulation and Synthesis of Living Systems*. (ed. MIT press). pp. 497-506. MIT, Cambridge, Mass.

Dittrich, P. & Di Fenizio, P. S. (2007). Chemical organisation theory. *Bulletin of mathematical biology* **69** **4**, 1199-1231.

Domingo, E., & Holland, J. J. (1997). RNA virus mutations and fitness for survival. *Annual Reviews in Microbiology* **51**, 151-178.

Domingo, E., Martínez-Salas, E., Sobrino, F., de la Torre, J. C., Portela, A., Ortín, J. & VandePol, S. (1985). The quasispecies (extremely heterogeneous) nature of viral RNA genome populations: biological relevance—a review. *Gene* **40**, 1-8.

Doolittle, W. F. (1999). Phylogenetic classification and the universal tree. *Science* **284**, 2124-2128.

Douglas, H. (2016). Values in Science. In *Oxford Handbook of Philosophy of Science*. (ed. Oxford University Press), pp. 609-630.

Dray, W. (1957). *Laws and Explanation in History*. Oxford University Press, Oxford, UK.

Dworkin, J. P., Lazcano, A. & Miller, S. L. (2003). The roads to and from the RNA world. *J Theor Biol* **222**, 127-134.

Egbert, M. D., Barandiaran, X., & Di Paolo, E. A. (2012). Behavioral metabolism: The adaptive and evolutionary potential of metabolism-based chemotaxis. *Artificial Life* **18**, 1-25.

Egbert, M. D. & Di Paolo, E. (2009). Integrating autopoiesis and behavior: An exploration in computational chemo-ethology. *Adaptive Behavior* **17**, 387-401.

Eigen, M. (1971). Selforganization of matter and the evolution of biological macromolecules. *Naturwissenschaften* **58**, 465-523.

Eigen, M. (1993). Viral quasispecies. *Scientific American* **269**(1), 42-49.

Eigen, M. & Schuster, P. (1978). The hypercycle. *Naturwissenschaften* **65**, 7-41.

- 1
2
3 Eigen, M. & Schuster, P. (1979). *The Hypercycle. A Principle of Natural Self-*
4 *Organization*. Springer-Verlag, Berlin.
- 5
6
7 Eisenberg, L. & Pellmar, T. C. (2000). *Bridging Disciplines in the Brain, Behavioral, and*
8 *Clinical Sciences*. National Academies Press, Washington D.C.
- 9
10
11 Eschenmoser, A. (2007). On a hypothetical generational relationship between HCN and
12 constituents of the reductive citric acid cycle. *Chemistry & biodiversity* **4**, 554-573.
- 13
14
15 Eschenmoser, A. & Kisakürek, M. V. (1996). Chemistry and the Origin of Life. *Helvetica*
16 *Chimica Acta* **79**, 124.
- 17
18
19 Farley, J. (1977). *The Spontaneous Generation Controversy From Descartes to Oparin*.
20 The Johns Hopkins University Press, Baltimore.
- 21
22
23 Farley, J., & Geison, G. L. (1974). Science, politics and spontaneous generation in
24 nineteenth century France: The Pasteur-Pouchet debate. *Bulletin of the History of*
25 *Medicine*, 48(2), 161.
- 26
27
28 Feinberg, G. & Shapiro, R. (1980). *Life Beyond Earth: The Intelligent Earthling's Guide*
29 *to Life in the Universe*. W. Morrow Quill Paperbacks, New York.
- 30
31
32 Feistel, R. (1983). On the evolution of biological macromolecules. III. Precellular
33 organization . *Studia Biophysica* **93**, 113–120.
- 34
35
36 Ferris, J. P., Joshi, P. C., Edelson, E. H. & Lawless, J. G. (1978). HCN: A plausible
37 source of purines, pyrimidines and amino acids on the primitive earth. *Journal of*
38 *Molecular Evolution* **11**, 293-311.
- 39
40
41 Fontana, W. & Buss, L. W. (1994). What would be conserved if "the tape were played
42 twice ?". *Proceedings of the National Academy of Sciences*. **91**, 757-761.
- 43
44
45 Forterre, P. (2002). The origin of DNA genomes and DNA replication proteins. *Current*
46 *Opinion in Microbiology*. **5**, 525-532.
- 47
48
49 Fournier, G. P., Andam, C. P., & Gogarten, J. P (2015). Ancient horizontal gene transfer
50 and the last common ancestors. *BMC Evolutionary Biology* **15**, 70.
- 51
52
53 Fox, R. (1967). *Kinship and Marriage: An Anthropological Perspective*. Cambridge
54 University Press, Cambridge.
- 55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Franklin M. H. (2001). *The Way of the Cell: Molecules, Organisms, and the Order of Life*. Oxford University Press, Oxford.

Friston, K. (2013). Life as we know it. *Journal of the Royal Society Interface* **10**, 20130475.

Froese, T., Ikegami, T. & Virgo, N. (2012). The behavior-based hypercycle: From parasitic reaction to symbiotic behavior. In C. Adami, D. M. Bryson, C. Ofria, & R. T. Pennock (ed. *Artificial Life 13: Proceedings of the Thirteenth International Conference on the Simulation and Synthesis of Living Systems*), pp. 457-464. The MIT Press, Cambridge.

Froese, T. & Stewart, J. (2010). Life after Ashby: Ultrastability and the autopoietic foundations of biological individuality. *Cybernetics & Human Knowing* **17**, 83-106.

Froese, T., Virgo, N. & Ikegami, T. (2014). Motility at the origin of life: Its characterization and a model. *Artificial Life* **20**, 55-76.

Fry, I. (2000). *Emergence of Life on Earth: A Historical and Scientific Overview*. Rutgers University Press, New Jersey.

Fry, I. (2006). The origins of research into the origins of life. *Endeavour* **30**, 24-28.

Gánti, T. (2000). Levels of life and death. (2003): *The Principles of Life*. Oxford University Press, Oxford, 1-10.

Gánti, T.(2003). *The Principles of Life*. Oxford University Press, Oxford and New York.

Garrison, W. M., Morrison, D., Hamilton, J., Benson, A. & Calvin, M. (1951). Reduction of carbon dioxide in aqueous solutions by ionizing radiation. *Science* **114**, 416–418.

Gilbert, W. (1986). Origin of life: the RNA world. *Nature* **319**, 6055.

Giovannelli, D., Sievert, S. M., Hügler, M., Markert, S. Becher, D. Schweder, T. & Vetriani, C. (2017). Insight into the evolution of microbial metabolism from the deep-branching bacterium, *Thermovibrio ammonificans*. *eLife*, **6**, e18990.

Gleiser, M., B. Nelson and S.I. Walker (2012) Chiral Polymerization in Open Systems From Chiral-Selective Reaction Rates. *Origins of Life and Evolution of the Biosphere* **42**, 333-346.

- Gogarten-Boekels, M., Hilario, E., & Gogarten, J. P. (1995). The effects of heavy meteorite bombardment on the early evolution—the emergence of the three domains of life. *Origins of Life and Evolution of the Biosphere* **25**, 251-264.
- Goldbeter, A. (2007) Dissipative structures and biological rhythms. *Chaos* **27**, 10462.
- Goldenfeld, N. & Woese, C. (2007). Biology's next revolution. *Nature* **445**, 369-369.
- Golinski, J. (1998). *Making Knowledge Natural: Constructivism and the History of Science*. Cambridge University Press, Cambridge.
- Griesemer, J. (2008). Origins of Life Studies. *The Oxford Handbook for Philosophy of Biology*. (ed. Oxford University Press), 263-299. Oxford University, New York.
- Guldan, H., Sterner, R. & Babinger, P. (2008) Identification and characterization of a bacterial glycerol-1-phosphate dehydrogenase: Ni²⁺-dependent AraM from *Bacillus subtilis*. *Biochemistry* **47**, 7376–7384.
- Haldane, J. B. S. (1929). The origin of life. *The Rationalist Annual* **148**, 3-10.
- Hanczyc, M. M. & Ikegami, T. (2010). Chemical basis for minimal cognition. *Artificial Life* **16**, 233-243.
- Harold, F. M. (2001). *The way of the cell: molecules, organisms, and the order of life*. Oxford University Press, Oxford, UK.
- Henderson, L. J. (1913). *The Fitness of the environment*. Macmillan, Basingstoke.
- Hershey, A.D. & Chase, M. (1952). Independent functions of viral protein and nucleic acid in growth of bacteriophage. *Journal of General Physiology* **36**, 39–56.
- Herzog, H. (1998). History of Tuberculosis. *Respiration* **65**, 5-15.
- Hilton, M. L. & Cooke, N. J. (2015). *Enhancing the Effectiveness of Team Science*. National Academies Press, Washington D.C.
- Holland, J. J. D., De La Torre, J. C., & Steinhauer, D. A. (1992). RNA virus populations as quasispecies. In *Genetic Diversity of RNA Viruses* (pp. 1-20). Springer, Berlin Heidelberg.

Holmes, F. L. (2004). *Investigative Pathways : Patterns and Stages in the Careers of Experimental Scientists*. Yale University Press, New Haven.

Hordijk, W., Steel, M. & Kauffman, S. (2012). The Structure of Autocatalytic Sets: Evolvability, Enablement, and Emergence. *Acta Biotheoretica* **60**, 379–392

Hug, L.A., Baker, B.J., Anantharaman, K., Brown, C.T., Probst, A.J., Castelle, C.J., Butterfield, C.N., HERNSDORF, A.W., Amano, Y., Ise, K. and Suzuki, Y. (2016). A new view of the tree of life. *Nature Microbiology*, **1**, p.16048. doi:10.1038/nmicrobiol.2016.48.

Humes, E. (2009) *Monkey Girl: Evolution, Education, Religion, and the Battle for America's Soul*. Harper Collins, New York.

Ilardo, M., Meringer, M., Freeland, S., Rasulev, B. & Cleaves II, H. J. (2015). Extraordinarily Adaptive Properties of the Genetically Encoded Amino Acids. *Scientific reports* **5**, 9414.

Jabr, F. (2013). Why Life Does Not Really Exist. *Scientific American* <http://blogs.scientificamerican.com/brainwaves/2013/12/02/why-life-does-not-really-exist/>, accessed: May 29, 2014.

Joyce, G. F., Deamer, D. W. & Fleischaker, G. (1994). *Origins of Life: The Central Concepts*. Jones and Bartlett, Boston.

Joyce, G. F., Schwartz, A. W., Miller, S. L. & Orgel, L. E. (1987). The case for an ancestral genetic system involving simple analogues of the nucleotides. *Proceedings of the National Academy of Sciences USA* **84**, 4398-4402.

Judson, H. F. (1979). *The Eighth Day of Creation: Makers of the Revolution in Biology*. New York: Simon and Schuster, New York.

Kampitz, G. & Fox, S. W. (1969). The condensation of the adenylates of the amino acids common to protein. *Proc Natl Acad Sci U S A* **62**, 399-406.

Kant, I. (1790). *Critique of Judgment*. Hafner Press, Royal Oak.

Kauffman, S. A. (1993). *The Origins of Order: Self-organization and Selection in Evolution*. Oxford University Press, New York.

Kauffman, S. A. (2000). *Investigations*. Oxford University Press, New York.

- Kauffman, S. A. (2004). Autonomous agents. In *Science and ultimate reality: Quantum theory, cosmology and complexity*. (ed. Cambridge University Press), pp. 654-666. Templeton Foundation, Philadelphia and London.
- Kauffman, S. A. & Clayton, P. (2009). On emergence, agency, and organization. *Biol Philos* **21**, 501-521.
- Keller, E. F. (2009). *Making Sense of Life: Explaining Biological Development with Models, Metaphors, and Machines*. Harvard University Press, Cambridge.
- Kimura, M. (1983). *The Neutral Theory of Molecular Evolution*. Cambridge University Press, Cambridge.
- King, G. (1980). Evolution of the coenzymes. *Biosystems* **13**, 23-45.
- King, G. (1982) Recycling, reproduction, and life's origins. *BioSystems* **15**, 89–97.
- Koonin, E. V. (2009). On the origin of cells and viruses. *Annals of the New York Academy of Sciences* **1178**, 47-64.
- Koonin, E. V. (2015a). Origin of eukaryotes from within archaea, archaeal eukaryome and bursts of gene gain: eukaryogenesis just made easier? *Philosophical Transactions of the Royal Society B*. **370**, 20140333.
- Koonin, E. V. (2015b). Archaeal ancestors of eukaryotes: not so elusive any more. *BMC Biology* **13**, 84.
- Koonin, E. V. (2016). Horizontal gene transfer: essentiality and evolvability in prokaryotes, and roles in evolutionary transitions. *F1000 Research* **5**:F1000 Faculty Rev-1805.
- Koonin, E. V., Makarova, K. S. & Wolf, Y. I. (2017). Evolutionary Genomics of Defense Systems in Archaea and Bacteria. *Annual Review of Microbiology* **71**, 233-261.
- Korzeniewski, B. (2001). Cybernetic formulation of the definition of life. *Journal of Theoretical Biology*, **209**, 275-286.
- Kuhn, T. S. (1962). *The Structure of Scientific Revolutions*, University of Chicago Press, Chicago.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Kurland, C. G., Canback, B., & Berg, O. G. (2003). Horizontal gene transfer: a critical view. *Proceedings of the National Academy of Sciences* **100**, 9658-9662.

Langton, C. G. (1984). Self-reproduction in cellular automata. *Physica D: Nonlinear Phenomena* **10**, 1-2, 135-144.

Langton, C. G. (1998). A new definition of artificial life.
<http://www.chairetmetal.com/cm03/intro.htm>

Laland, K., Uller, T., Feldman, M., Sterelny, K., Müller, G. B., Moczek, A., Jablonka, E., Odling-Smee, J., Wray, G. A., Hoekstra, H. E., Futuyma, D. J., Lenski, R. E., Mackay, T. F., Schluter, D. & Strassmann, J. E. (2014). Does evolutionary theory need a rethink? *Nature* **514**, 161-164.

Latour, B. (1987). *Science in Action*. Harvard University Press, Cambridge.

Lauring, A. S., & Andino, R. (2010). Quasispecies theory and the behavior of RNA viruses. *PLoS pathogens* **6**, e1001005.

Lazcano, A. (2010). Historical Development of Origins Research. *Cold Spring Harb Perspectives in Biology* **2**, a002089.

Lazcano, A. & Miller, S. L. (1996). The origin and early evolution of life: prebiotic chemistry, the pre-RNA world, and time. *Cell* **85**, 793-798.

Letelier, J.-C., Cárdenas, M.L. & Cornish-Bowden, A.(2011). From L'Homme Machine to metabolic closure: steps towards understanding life. *Journal of Theoretical Biology* **286**, 100–113.

Letelier, J.-C., Marín, G. & Mpodozis, J. (2003). Autopoietic and (M,R) systems. *Journal of Theoretical Biology* **222**, 261–272.

Lewontin, R. (1970). The Units of Selection. *Annual Review of Ecology and Systematics* **1**, 1-18.

Löb, W. (1913). Über das Verhalten des Formamids unter der Wirkung der stillen Entlandung. Ein Beitrag zur Frage der Stickstoff-Assimilation. *Berichte der deutschen chemischen Gesellschaft* **46**, 684-697.

Locey, K. J. & Lennon, J. T. (2016). Scaling laws predict global microbial diversity. *Proceedings of the National Academy of Sciences* **113**, 5970–5975.

Lovejoy, A. O. (1936). *The Great Chain of Being: A Study of the History of an Idea*. Harvard University Press, Cambridge Mass.

Luisi, P. L. (2006). *The Emergence of Life: From Chemical Origins to Synthetic Biology*. Cambridge University Press, Cambridge.

Machery, E. (2012). Why I stopped worrying about the definition of life... and why you should as well. *Synthese* **185**, 145–164.

Malaterre, C. (2015). Chemical evolution and life. *BIO Web of Conferences* **4**, 00002.

Mariscal, C. & Doolittle, W. F. (2015). Eukaryotes first: how could that be?. *Phil. Trans. R. Soc. B* **370**, 20140322.

Mariscal, C., Doolittle, W. F. Life and Life Only: A Radical Alternative to Life Definitionism. *Synthese*, in press.

Martin, W. F., Weiss, M. C., Neukirchen, S., Nelson-Sathi, S. & Sousa, F. L. (2016). Physiology, phylogeny, and LUCA. *Microb. Cell* **3**, 582–587.

Maruyama, S., Ikoma, M., Genda, H., Hirose, K., Yokoyama, T. & Santosh, M. (2013). The naked planet Earth: Most essential pre-requisite for the origin and evolution of life. *Geoscience Frontiers* **4**, 141–165.

Matthews, G.B. (1996). Aristotle on Life. In *The Philosophy of Artificial Life*, (ed. Boden, M.A.) pp. 305–313. Oxford University Press, Oxford.

Maturana, H. (1970). *Biology of cognition Report 9 Biological Computing Laboratory*. University of Illinois, Urbana-Champaign.

Maturana, H. R. & Varela, F. J. (1980). *Autopoiesis and Cognition: the Realisation of the Living*. D. Reidel Pub. Co., London.

Maturana, H. R. & Varela, F. J. (1992). *The tree of knowledge: the biological roots of human understanding*. Shambhala, Boston.

Maurer, S. E., DeClue, M. S., Albertsen, A. N., Dörr, M., Kuiper, D. S., Ziock, H., Rasmussen, S., Boncella, J. M. & Monnard, P. (2011). Interactions between catalysts and amphiphilic structures and their implications for a protocell model. *ChemPhysChem* **12**, 828-835.

Maynard Smith, J. & Szathmary, E. (1995). *The Major Transitions in Evolution*. Oxford University Press. Oxford.

Mayr, E. (1998). Two empires or three?. *Proceedings of the National Academy of Sciences* **95**, 9720-9723.

McKie, D. (1944). Wöhler's "Synthetic" urea and the rejection of vitalism: a chemical legend. *Nature* **153**, 608-610.

McMenamin, M. A. S., Margulis, L., Vernadsky, V. I., Ceruti, M., Golubic, R., Guerrero, R., Ikeda, N., Ikesawa, N., Krumbein, W.E., Lapo, A., Lazcano, A., Suzuki, D., Tickell, C., Walter, M. & Westbroek, P. (1998). *The Biosphere*. Springer, New York.

McMullin, B. (2004). Thirty years of computational autopoiesis: a review. *Artificial Life* **10**, 277-295.

Medicine, I., Engineering, N. A., Sciences, N. A., Committee on Science, E. P. P., Research C. F. I. (2005). *Facilitating Interdisciplinary Research*. National Academies Press, Washington.

Meléndez-Hevia, E., Montero-Gómez, N. & Montero, F. (2008). From prebiotic chemistry to cellular metabolism — the chemical evolution of metabolism before Darwinian natural selection. *Journal of Theoretical Biology* **252**, 505-519.

Meringer, M., Cleaves, H. J. & Freeland, S. J. (2013). Beyond terrestrial biology: Charting the chemical universe of α -amino acid structures. *Journal of Chemical Information and Modeling* **53**, 2851-2862.

Mesler, B. & Cleaves, H.J. (2015). *A Brief History of Creation: Science and the Search for the Origin of Life*. W. W. Norton Incorporated, New York.

Miescher, J. F. (1871). Ueber die chemische Zusammensetzung der Eiterzellen. *Medisch-chemische Untersuchungen* **4**, 441-460

1
2
3 Miller, G. A. (2003). The cognitive revolution: a historical perspective. *Trends in*
4 *cognitive sciences* **7**, 141-144.

5
6
7 Miller, S. L. (1953). A production of amino acids under possible primitive Earth
8 conditions. *Science* **117**, 528-529.

9
10
11 Miller, S. L. (1974). The first laboratory synthesis of organic compounds under primitive
12 conditions. In *The Heritage of Copernicus: Theories "more pleasing to the mind"* (ed.
13 MIT Press), pp. 228-224. Cambridge, Mass., and London.

14
15
16 Mitchell, P. (1961). Coupling of Phosphorylation to Electron and Hydrogen Transfer by a
17 Chemi-Osmotic type of Mechanism. *Nature* **191**, 144-148.

18
19
20 Mora, C., Tittensor, D. P., Adl, S., Simpson, A. G. B. & Worm B. (2011). How Many
21 Species Are There on Earth and in the Ocean?. *PLoS Biology* **9**, e1001127.

22
23
24 Morange, M. (2009). *Life explained*. Yale University Press, Connecticut.

25
26
27 Morange, M. (2013). *Histoire de la biologie moléculaire*. La Découverte, Paris.

28
29
30 Morange, M. (2016). *Une histoire de la biologie (inédit)*. Points, Paris.

31
32
33 Moreno, A. (2016). Some conceptual issues in the transition from chemistry to biology .
34 *History and Philosophy of the Life Sciences* **38**, 1-16.

35
36
37 Moreno, A. & Mossio, M. (2015). *Introduction. Biological Autonomy. A Philosophical and*
38 *Theoretical Enquiry*. Springer, Netherlands.

39
40
41 Morowitz, H. J. (1968) Energy flow in biology: biological organization as a problem in
42 thermal physics, 2nd Edition. Academic Press, New York and London.

43
44
45 Morowitz, H. J. (1991) *The Thermodynamics of Pizza*. Rutgers University Press,
46 Brownstown.

47
48
49 Munteanu, A., Stephan-Otto, Attolini C., Rasmussen, S., Ziock, H. & Solé, R. V. (2007).
50 Generic Darwinian selection in catalytic protocell assemblies. *Philosophical*
51 *Transactions of the Royal Society of London B: Biological Sciences* **362**, 1847-1855.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Nelson, K. E., M., Robertson, P., Levy, M. & Miller, S. L. (2001). Concentration by evaporation and the prebiotic synthesis of cytosine. *Origins of Life Evol Biosphere* **31**, 221-229.

Nee, S., & Maynard Smith, J. (1990). The evolutionary biology of molecular parasites. *Parasitology* **100**, S5-S18.

Nicolis, G. & Prigogine, I. (1977). *Self-organization in nonequilibrium systems*. Wiley, New York.

Nilsson, M., & Snoad, N. (2000). Error thresholds for quasispecies on dynamic fitness landscapes. *Physical Review Letters*, **84**, 191.

Nitschke, J. R. (2009). Systems chemistry: Molecular networks come of age. *Nature* **462**, 736-738.

Nowak, M., & Schuster, P. (1989). Error thresholds of replication in finite populations mutation frequencies and the onset of Muller's ratchet. *Journal of theoretical Biology* **137**, 375-395.

Odling-Smee, F. J., Laland, K. N. & Feldman, M. W. (2003). *Niche Construction: The Neglected Process in Evolution*. Princeton University Press, Princeton.

Oparin, A. I. (1924). *The Origin of Life*. Izd. Moskovshii Rabochil, Moscow,

Orgel, L. E. (1998a). The origin of life - a review of facts and speculations. *Trends in Biochemical Sciences* **23**, 491-495.

Orgel, L. E. (1998b). The origin of life - How long did it take?. *Origins of Life and Evolution of the Biosphere* **28**, 91-96.

Orgel, L. E. (2008). The implausibility of metabolic cycles on the prebiotic Earth. *PLoS Biol* **6**, e18.

Peretó, J. (2016). Erasing Borders: A Brief Chronicle of Early Synthetic Biology. *Journal of molecular evolution* **83**, 176-183.

Peretó, J., Bada J. L. & Lazcano, A. (2009). Charles Darwin and the Origin of Life. *Origins of Life and Evolution of Biospheres* **39**, 395-406.

Peretó, J., López-García, P. & Moreira, D. (2004). Ancestral lipid biosynthesis and early membrane evolution. *Trends in Biochemical Sciences* **29**, 469-477.

Piedrafita, G., Montero, F., Morán, F., Cárdenas, M. L. & Cornish-Bowden, A. (2010). A simple self-maintaining metabolic system: robustness, autocatalysis, bistability. *PloS Computational Biology* **6**, e1000872.

Porter, A. L., Cohen, A. S. , Roessner J. D. & Perreault, M. (2007). Measuring researcher interdisciplinarity. *Scientometrics* **72**,117-147.

Powell, T. M. (2008). The rise of interdisciplinary oceanography. *Oceanography* **21**, 54-57.

Powell, R. & Mariscal C. (2015). Convergent evolution as natural experiment: the tape of life reconsidered. *Interface focus* **5**,1-13.

Prigogine, I. (1969). Structure, dissipation and life. *Theoretical physics and biology*, 23-52.

Pross, A. (2012). *What is Life? How Chemistry becomes Biology*, Oxford University Press, Oxford.

Rasmussen, S. (2009). *Protocells: Bridging Nonliving and Living Matter*. MIT Press, Cambridge, Mass.

Rasmussen, S., Bedau, M. A., Chen,L., Deamer,D., Krakauer,D. C., Packard, N. H. & Stadler, P. F. (2008). *Protocells: Bridging Nonliving and Living Matter*. MIT Press, Cambridge, Mass.

Ratner, V. A. & Shamin, V.(1980). *Mathematical Models of Evolutionary Genetics*. ICG, Novosibirsk.

Raymann, K., Brochier-Armanet, C. & Gribaldo, S. (2015). The two-domain tree of life is linked to a new root for the Archaea. *Proceedings of the National Academy of Sciences* **112**, 6670-6675.

Rosen, R. (1991) *Life itself*. Columbia University Press, New York.

Rudwick, M. J. S. (1988). *The Great Devonian Controversy: The Shaping of Scientific Knowledge Among Gentlemanly Specialists*. University of Chicago Press, Chicago and London.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Ruiz-Mirazo, K., Briones, C. & de la Escosura, A. (2013). Prebiotic systems chemistry: new perspectives for the origins of life. *Chemical Reviews* **114**, 285-366.

Ruiz-Mirazo, K. & Moreno, A. (2004). Basic autonomy as a fundamental step in the synthesis of life. *Artificial Life* **10**, 235-259.

Ruiz-Mirazo, K., Peretó, J. & Moreno, A. (2004). A universal definition of life: autonomy and open-ended evolution. *Origin of Life and Evolution of Biospheres* **34**, 323–346.

Ruiz-Mirazo, K., Umerez, J. & Moreno, A. (2008). Enabling conditions for 'open-ended evolution'. *Biology & Philosophy* **23**, 67-85.

Russell, M. J., Hall, A. J., Boyce, A. J. & Fallick, A. E. (2005). 100th anniversary special paper: On hydrothermal convection systems and the emergence of life. *Economic Geology* **100**, 419-438.

Schaffer, S. (1981). Uranus and the Establishment of Herschel's Astronomy. *Journal for the History of Astronomy* **12**, 11-26.

Scharf, C., Virgo, N., Cleaves, H. J., Aono, M., Aubert-Kato, N., Aydinoglu, A., Barahona, A., Barge, L. M., Benner, S. A., Biehl, M., Brasser, R., Butch, C. J., Chandru, K., Cronin, L., Sebastian, D., Jakob, F., Hernlund, J., Hut, P., Ikegami, T., Jun, K., Kobayashi, K., Mariscal, C., McGlynn, S., Menard, B., Packard, N., Pascal, R., Pereto, J., Rajamani, S., Sinapayen, L., Smith, E., Switzer, C., Takai, K., Tian, F., Ueno, Y., Voytek, M., Witkowski, O. & HIKARU, Y. (2015). A strategy for origins of life research. *Astrobiology* **15**, 1031–1042.

Schmitt-Kopplin, P., Gabelica, Z., Gougeon, R. D., Fekete, A., Kanawati, B., Harir, M. Gebefuegi, I., Eckel, G. & Hertkorn, N. (2010). High molecular diversity of extraterrestrial organic matter in Murchison meteorite revealed 40 years after its fall. *Proceedings of the National Academy of Sciences* **107**, 2763-2768.

Schneider, E D. & Kay, J. J. (1994). Life as a manifestation of the second law of thermodynamics. *Mathematical and computer modelling* **19**, 25-48.

Schrödinger, E. (1944). *What is Life?: The Physical Aspect of the Living Cell*, The University Press, Cambridge.

Schulze-Makuch, D. & Irwin, L. N. (2006). The prospect of alien life in exotic forms on other worlds. *Naturwissenschaften* **93**, 155-172.

Schuster, P. (2000). Taming combinatorial explosion. *Proceedings of the National Academy of Sciences* **97**, 7678-7680.

Segré, D., Ben-Eli, D. & Lancet, D. (2000). Compositional genomes: prebiotic information transfer in mutually catalytic noncovalent assemblies. *Proceedings of the National Academy of Sciences* **97**, 4112-4117.

Shaman, J., Solomon, S., Colwell, R. R., & Field, C. B. (2013). Fostering advances in interdisciplinary climate science. *Proceedings of the National Academy of Sciences* **110**, 3653-3656.

Shapiro, R. (2006). Small molecule interactions were central to the origin of life. *Q. Rev. Biol.* **81**, 105-125.

Silverman, E. & Bullock, S. (2004). Empiricism in artificial life. In *Proceedings of the Ninth International Conference on Artificial Life*. (ed. MIT Press), pp. 534-539. MIT Cambridge, Mass.

Sims, K. (1994). Evolving 3D morphology and behavior by competition. *Artificial life* **1**, 353-372.

Smith, K. What is Life? *Biological Theory*, in press.

Smith, E. & Morowitz, H. J. (2016) *The Origin and Nature of Life on Earth: The Emergence of the Fourth Geosphere*. Cambridge University Press, Cambridge.

Soai, K., Shibata, T., Morioka, H. & Choji, K. (1995). Asymmetric autocatalysis and amplification of enantiomeric excess of a chiral molecule. *Nature* **378**, 767-768.

Soucy, S. M., Huang, J. & Gogarten, J. P. (2016). Horizontal gene transfer: building the web of life. *Nature Reviews Genetics* **16**, 472-482.

Spang, A., Saw, J. H., Jorgensen, S. L., Zaremba-Niedzwiedzka, K., Martijn, J., Lind, A.E., van Eijk, R., Schleper, C., Guy, L. & Ettema, T. J. G. (2015). Complex archaea that bridge the gap between prokaryotes and eukaryotes. *Nature* **521**, 173-179.

Stokols, D., Fuqua, J., Gress, J., Harvey, R., Phillips, K., Baezconde-Garbanati, L., Unger, J., Palmer, P., Clark, M. A. & Colby, S. M. (2003). Evaluating transdisciplinary science. *Nicotine & Tobacco Research* **5**, S21-S39.

Stott, R. (2013). *Darwin's Ghosts: In Search of the First Evolutionists*, Bloomsbury, London.

Strick, J. E. (2009). *Sparks of life: Darwinism and the Victorian debates over spontaneous generation*, Harvard University Press, Cambridge Mass. and London.

Szathmáry, E. (2013). On the propagation of a conceptual error concerning hypercycles and cooperation. *Journal of Systems Chemistry* **4**,1-4.

Szostak, J. W. (2012). Attempts to define life do not help to understand the origin of life. *Journal of Biomolecular Structure and Dynamics* **29**, 599-600.

Takeuchi, N. & Hogeweg, P. (2007). Error-threshold exists in fitness landscapes with lethal mutants. *BMC Evolutionary Biology* **7**, 15.

Taskin, Z. & Aydinoglu, A. U. (2015). Collaborative multidisciplinary astrobiology research: A bibliometric study of the NASA Astrobiology Institute. *Scientometrics* doi: 10.1007/s11192-015-1576-8.

Taylor, T., Bedau, M., Channon, A., Ackley, D., Banzhaf, W., Beslon, G., Dolson, E., Froese, T., Hickinbotham, S., Ikegami, T., McMullin, B., Packard, N., Rasmussen, S., Virgo, N., Agmon, E., Clark, E., McGregor, S., Ofria, C., Ropella, G., Spector, L., Stanley, K. O., Stanton, A., Timperley, C., Vostinar, A. & Wiser M. (2016). Open-Ended Evolution: Perspectives from the OEE workshop in York. *Artificial Life* **22**, 408-423.

Tjivikua, T., Ballester, P., Rebek, J. (1990) A self-replicating system. *J Am Chem Soc* **112**, 1249–1250.

Tuller, T., Birin, H., Gophna, U., Kupiec, M., Ruppín, E. (2010). Reconstructing ancestral gene content by coevolution. *Genome Res* **20**, 122–132.

Turing, A. M. (1990). The chemical basis of morphogenesis. *Bulletin of mathematical biology* **52**, 153-197.

Varela, F. (1979). *Principles of Biological Autonomy*. Elsevier North Holland, New York.

Varela, F. G., Maturana, H. R. & Uribe, R. (1974). Autopoiesis: The organization of living systems, its characterization and a model. *BioSystems* **5**, 187-196.

- Vetsigian, K., Woese, C. & Goldenfeld, N. (2006). Collective evolution and the genetic code. *Proceedings of the National Academy of Sciences* **103**, 10696-10701.
- Virgo, N., Egbert, M. D. & Froese, T. (2011). The role of the spatial boundary in autopoiesis. In *Advances in Artificial Life: Darwin Meets von Neumann. 10th European Conference, ECAL 2009*. (ed. Springer), pp. 234-241. Berlin.
- Virgo, N., Ikegami, T., & McGregor, S. (2016). Complex autocatalysis in simple chemistries. *Artificial life*, **22**: 138-152.
- Virgo, N., McGregor, S., & Ikegami, T. (2014). Self-organising autocatalysis. *Artificial Life*, **14**.
- von Kiedrowski, G., Otto, S. & Herdewijn, P. (2010). Welcome Home, Systems Chemists!. *Journal of Systems Chemistry* **1**, 1.
- von Linné (Linnaeus), C. (1735/1964). *Systema Naturae*, Facsimile of the First edition, Edited by Engel-Ledeboer, M. S. J. & Engel, H. Nieuwkoop, B. de Graaf.
- Von Neumann, J., & Burks, A. W. (1966). Theory of Self-reproducing Automata. *IEEE Transactions on Neural Networks* **5**, 3-14.
- Wächtershäuser, G. (1988). Before enzymes and templates: theory of surface metabolism. *Microbiological Reviews* **52**, 452-484.
- Wagner, G. P. & Altenberg, L. (1996). Perspective: complex adaptations and the evolution of evolvability. *Evolution* **50**, 967-976.
- Wagner, C. S., Roessner, J. D., Bobb, K., Klein, J. T., Boyack, K. W., Keyton, J., Rafols, I. & Börner K. (2011). Approaches to understanding and measuring interdisciplinary scientific research (IDR): A review of the literature. *Journal of informetrics* **5**, 14-26.
- Watson, J.D. & Crick, F.H.C. (1953). Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid. *Nature* **171**, 737-738.
- Weber, A. & Varela, F.V. (2002). Life after Kant: Natural purposes and the autopoietic foundations of biological individuality. *Phenomenology and the cognitive sciences* **1**, 97-125.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Weiss, M. C., Sousa, F. L., Mrnjavac, N., Neukirchen, S., Roettger, M., Nelson-Sathi, S. & Martin, W. F. (2016). The physiology and habitat of the last universal common ancestor. *Nature Microbiology* **1**, 1-8.

White, D. H. (1980). A theory for the origin of a self-replicating chemical system. I: natural selection of the autogen from short, random oligomers. *Journal of Molecular Evolution* **16**, 121–147.

Williams, T. A., Szöllősi, G. J., Spang, A., Fostere, P. G., Heaps, S. E., Boussau, B., Ettema, T. J. G. & Embley, T. M. (2017). Integrative modeling of gene and genome evolution roots the archaeal tree of life. *Proceedings of the National Academy of Sciences* **114**, E4602–E4611.

Woese, C. R. (1998). The universal ancestor. *Proceedings of the National Academy of Sciences* **95**, 6854-6859.

Woese, C. R. (2002). On the evolution of cells. *Proceedings of the National Academy of Sciences of the United States of America* **99**, 8742-8747.

Woese, C. R. & Fox, G. E. (1977a). Phylogenetic structure of the prokaryotic domain: the primary kingdoms. *Proceedings of the National Academy of Sciences* **74**, 5088-5090.

Woese, C. R. & Fox, G. E. (1977b). The concept of cellular evolution. *Journal of Molecular Evolution* **10**, 1–6.

Woese, C. R., Kandler, O. & Wheelis, M.L. (1990). Towards a natural system of organisms: proposal for the domains Archaea, Bacteria, and Eucarya. *Proceedings of the National Academy of Sciences* **87**, 4576-4579.

Wolfe-Simon, F., Blum, J. S., Kulp, T. R., Gordon, G. W., Hoefft, S. E., Pett-Ridge, J., Stolz, J. F., Webb, S. M., Weber, P. K. & Davies, P. C. (2011). A bacterium that can grow by using arsenic instead of phosphorus. *Science* **332**, 1163-1166.

Wolfram, S.(2002). *A New Kind of Science*. Wolfram Media, Champaign.

Wong, J. (2005). Coevolution theory of the genetic code at age thirty. *BioEssays* **27**, 416-425.

Zubarev, D. Y., Rappoport, D. & Aspuru-Guzik A. (2015). Uncertainty of Prebiotic Scenarios: The Case of the Non-Enzymatic Reverse Tricarboxylic Acid Cycle. *Scientific Reports* **5**,1-7.

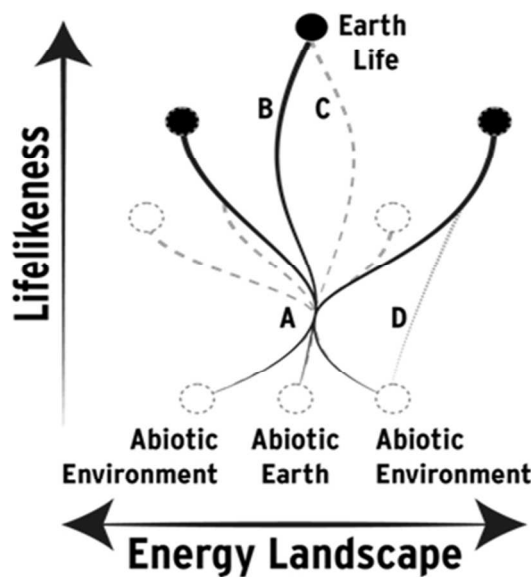


Figure 1. An illustration of paths from lifeless environments (dashed circles) to living worlds (black circles). Black lines mark paths actually taken somewhere in the Universe, dashed lines mark possible paths. Axes are unspecified metrics of “lifelikeness” (y) and an energy landscape through which precursors to life travel (x). A) universal explanations for the origins of life: steps that scientists think must be taken in any path from a lifeless world (bottom) to a living one (top); B) historical explanations, about the path life on Earth could have taken from a lifeless Earth to LUCA; C) synthetic explanations, which detail other possible paths life might have taken; D) synthetic explanations, which challenge universal explanations and detail how life may have been created under alternative scenarios. If there are few synthetic paths relative to universal paths, life on Earth would be highly convergent with life elsewhere, and vice versa. Adapted from Scharf et al. (2015). Scanning this possibility space is part of the difficulty of origins research.

254x190mm (96 x 96 DPI)

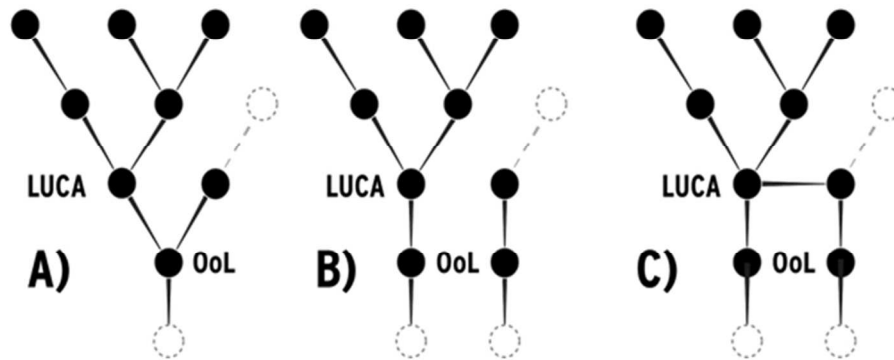


Figure 2. Three possibilities since the origin(s) of life (OoL) that are currently indistinguishable. Solid circles represent living taxa, dashed circles and lines represent non-living or extinct taxa, solid lines connect living taxa with their ancestors. A) All life on Earth shares a Last Universal Common Ancestor (LUCA). B) Life originated multiple times, but all other lineages have either gone extinct or are yet to be discovered (Cleland & Copley 2005, Davies & Lineweaver 2005). C) Life currently contains genes or other information from a second origin (or perhaps a distant relative), from which no descendants remain or have not yet been discovered. Adapted from Powell & Mariscal (2015).

254x190mm (96 x 96 DPI)

Theory	Reference	Thermodynamically Open	Specific Catalyst	Catalytic Closure	Structural Closure
Hypercycle	Eigen & Schuster (1977)	Implicit	Yes	Yes	No
Autopoiesis	Maturana & Varela (1980)	Yes	No	No	Yes
Syser	White (1980), Ratner & Shamin (1980), Feistel (1983)	Implicit	Yes	Yes	No
Symbiosis	King (1982)	Unclear	Yes	Yes	No
Autocatalytic sets	Kaufmann (1986)	Implicit	Yes	Yes	No
(M,R) systems	Rosen (1991)	Yes	Yes	Yes	No
Chemoton	Gánti (2003)	Yes	No	No	Yes
RAF Sets	Hordijk & Steel (2004)	Yes	Yes	No	No
Autogen	Deacon (2012)	Yes	Yes	Yes	Yes