Reimagining Origins of Life Research: Innovation and Synthesis via Experimentation, Instrumentation, and Data Analytics

Karyn L. Rogers, Rensselaer Polytechnic Institute
Phone: 518-276-2372, Email: rogerk5@rpi.edu

Co-Authors

Ulysse Pedreira-Segade (Rensselaer Polytechnic Institute), **Peter Fox** (Rensselaer Polytechnic Institute), **Jacob T. Shelley** (Rensselaer Polytechnic Institute), **Andrew Steele** (Carnegie Institute for Science), **Dustin Trail** (University of Rochester)

Co-Signers

Jeffrey Catalano (Washington University in St. Louis)
Aaron Goldman (Oberlin College)
Jun Korenaga (Yale University)
Ramanarayanan Krishnamurthy (Scripps Research Institute)
Susan Lang (University of South Carolina)
Timothy W. Lyons (University of California, Riverside)
Thomas M. McCollom (University of Colorado, Boulder)
Shweta Narkar (Rensselaer Polytechnic Institute)
Morgan F. Schaller (Rensselaer Polytechnic Institute)
Brenda Thomson (Rensselaer Polytechnic Institute)
E. Bruce Watson (Rensselaer Polytechnic Institute)
Loren Williams (Georgia Institute of Technology
Matthew van der Wielen (Rensselaer Polytechnic Institute)
Montwaun Young (Rensselaer Polytechnic Institute)

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Rationale**:** How life started on Earth remains one of the most elusive scientific questions ever posed. With recent advances in our mission capabilities we can cast an increasingly wide net to identify habitable exoplanets throughout the galaxy, and also make more robust observations of potential biosignatures on bodies closer to home (*e.g.*, Mars, Europa, Enceladus). Nonetheless, this compelling search for extraterrestrial life is hobbled by our limited understanding of how life started on our own planet. Identifying the specific planetary conditions and chemical pathways that fostered the emergence of terrestrial life would substantially inform, refine, and re-define our search for life elsewhere. Addressing this challenge is thus an essential objective for Astrobiology and Planetary Science to meet in the coming decade and beyond.

Goals, Challenges, and Opportunities:

More than a century ago, the Oparin-Haldane hypothesis for life's origins (Chang *et al.*, 1983) postulated that simple organic precursor molecules were produced from abiotic (geo)chemical reactions in various surface environments. Subsequent reactions and transformations produced more complex (*e.g.*, higher order) chemical species, eventually leading to proto-metabolic cycles and autocatalytic protocells. Decades of experiments and chemical models have probed these processes and brought a much more detailed understanding of many synthesis pathways. Furthermore, while the broad strokes of this hypothesis still stand, significant components have been added and removed. For example, as our understanding of Earth's early atmosphere evolved, the validity of the Miller-Bada amino acid synthesis mechanism has waned (c.f. references in Preiner *et al.*, 2020). Similarly, the discovery of deep sea hydrothermal systems and their ability to sustain chemosynthetic life via geochemical disequilibria has given rise to new theories for the location and nature of life's origin (Baross and Hoffman, 1985; Branscomb and Russell, 2018). These examples point to increasing consideration of how geologic conditions can both limit and foster prebiotic chemistry. While it is broadly true that geologic plausibility has come into sharper focus in prebiotic chemistry in the last decade (Sahai *et al*., 2016; Barge 2018), a synergistic view of prebiotic synthesis pathways co-evolving with the planetary system remains elusive. With innovations in interdisciplinarity (see below and Lyons *et al.*, 2020), this research community is poised to break free of this bottleneck, transition from siloed research avenues toward a consensus-driven approach, and transform the origins of life paradigm in the coming decade.

The chemical pathway that leads to life must encompass each of life's components: compartments, metabolic cycles, heritable characteristics, and catalytic function. Importantly, each of these components needs to be synthesized, transformed/complexified, and selected/enriched under realistic geological conditions. The main challenge within the origins of life (OoL) community is the discontinuity that exists across the various emergence pathways – in general, each of life's components is a specialty in itself and often pursued as such. For example, lipid synthesis is often considered separately from the evolution of proto-metabolic cycles. Even synthesis and complexification of any given component is often tackled separately (*e.g.*, the formation of nucleic acid monomers is largely considered separately from the polymerization of such monomers; Whitaker and Powner 2018, Becker *et al.,* 2019). The result has been myriad experimental conditions, optimized for each component of life, but with little integration of conditions and components across experiments. Many of these siloed research endeavors are the historical legacy of early partitioning within the community, often along disciplinary boundaries, but they also stem from the shear scope of the question being distributed across various scientific disciplines, including biochemistry, organic chemistry, and geology. Such multidisciplinarity often leads to mismatches in scientific language and culture (*e.g.*, deconstructionist and constructionist approaches), which further leads to disciplinary silos and away from integration.

The absence of a common language or integration efforts across disciplines provides an exciting opportunity for transformation during the next decade. Cross-cutting experimental, instrumental, and data science innovations can be brought to bear on decades of disparate research avenues, overcome historical and disciplinary divisions, and set the OoL community on a new track towards integration and consensus. New data analysis methods can be applied to decades of prebiotic chemistry experiments with the potential to identify commonalities across experimental conditions and chemistries. Techniques that resided largely within the realm of experimental geochemistry can be adapted to more faithfully replicate early Earth environments and materials in prebiotic synthesis experiments, and innovations in analytical instrumentation, such as multimodality and miniaturization, allow for multiplexing and scaling of reactions so that a wide swath of environmental and experimental parameters can be accessed. Such innovations can lead to convergence of potentially several synthesis routes for each of life's components; identification of overlapping environmental conditions, and ultimately sequencing the prebiotic chemistry pathway within the context of evolving early Earth environments (Lyons *et al.*, 2020).

A case for Earth First Origins

To break free from historical and biological biases and well-worn paths, we suggest a new approach to searching for life's prebiotic origins. The Earth First Origins paradigm builds from the following tenet: *there is an inevitable co-evolution of early Earth and prebiotic chemistry.* This approach to prebiotic chemistry eschews directly targeting biomolecules based on modern biology and instead builds on the fundamental planetary processes that set the Earth system in motion. Global planetary evolution results in an array of localized environments, each with specific conditions, dynamics, and chemistries resulting from local water-rock-volatile interactions. The EFO paradigm suggests that ***"In order to know what chemistry occurred on early Earth, experimental and theoretical models that replicate dynamic Hadean environments are necessary. The chemistry that arises is, necessarily, the prebiotic chemistry that laid the foundation for life's emergence"*** (Rogers *et al*., 2019). There is no doubt that many of these environments were unproductive for prebiotic chemistry, producing either biologically-irrelevant species or no organic compounds at all. Others might have produced potential biomolecules whose selection or evolution was derailed as environmental conditions changed. ***"In one or more key cases, however, these dynamics, chemistries, and environments evolved synchronously, not by random events but rather ushered along by planetary processes, and led to the conditions conducive for life to emerge"*** (Rogers *et al*., 2019). EFO predicts a sequence of environmental conditions, enabled by evolving and adjacent geologic systems that foster life's emergence.

An Earth First Origins approach to prebiotic chemistry and life's origins requires an evolving feedback system (Fig. 1) among (i) progress in understanding specific and co-varying conditions in early Earth systems (Lyons *et al.*, 2020), (ii) faithful implementation

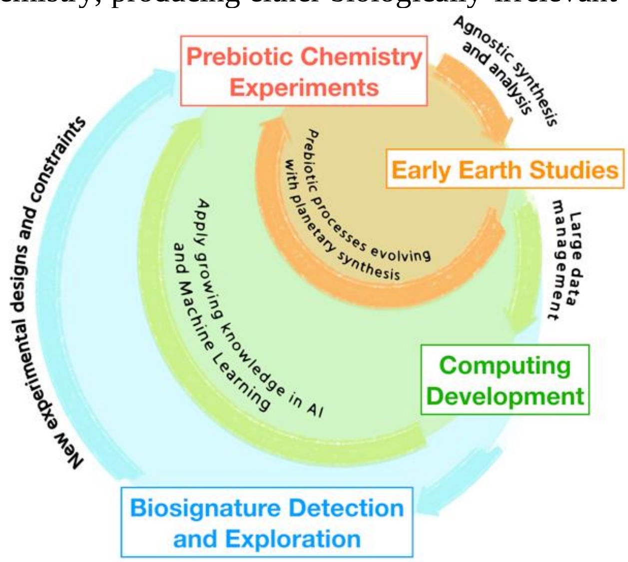

Fig. 1: Conceptual diagram of experimental, instrumental, and data science within the Earth First Origins Paradigm, and integration with planetary exploration and life detection. *Image credit: Meri Herrero Pérez*

of plausible early Earth conditions in prebiotic experiments via novel experimental devices, (iii) miniaturized and multimodal analytical platforms that can expand the scope, depth, and scale of experimental analyses; and (iv) the implementation of interdisciplinary virtual platforms that cross disciplinary language barriers through visualization, and apply machine learning to experimental results to generate predictive models that feed back into experimental design.

Opportunities for Innovation and Transformation:

I – Synergies Across Disciplines: The last decade has seen a new focus among the OoL community to bring more realistic early Earth models to bear onto prebiotic chemistry experiments (*e.g.* Sahai *et al.*, 2016; Barge 2018). However, true interdisciplinary synergies require effort across the at-large communities, support from institutions to help cross disciplinary barriers, and new paradigms for approaching collaborations (Scharf *et al.*, 2015). Addressing this opportunity is NASA's Prebiotic Chemistry and Early Earth Environments RCN, which is *"striving to transform the origins of life community by breaking down language and ideological barriers and enhancing communication across the disciplinary divide between early Earth geoscientists and prebiotic chemists."* To initiate a truly synergistic relationship among disciplines requires experiments that target prebiotic synthesis pathways with direct and *a priori* consideration of early Earth environments. The Earth First Origins approach relies heavily on more robust and detailed models of both global and localized conditions, as well as their evolution during the Hadean and early Archean. Opportunities to expand our understanding of early Earth environments in ways that meaningfully impact the scope and direction of prebiotic chemistry, which are a central part of the Earth First Origins Paradigm, are discussed extensively in Lyons *et al.*, (2020).

II - Experimentation: Implementation of the Earth First Origins approach to prebiotic chemistry requires experimental facilities that can faithfully replicate the range of pressure-temperature-compositional-temporal conditions (PTXt) of early Earth environments in controlled settings. The full gamut of early Earth environments warrants initial consideration for abiotic synthesis potential. Predictive models based on machine learning algorithms applied to past results, together with pilot experimental studies, will produce more robust experimental facilities/approaches that replicate specific microenvironments and have the potential to explore the range of conditions and chemical processes that foster a successful prebiotic pathway. Such experimental facilities should target broad environmental categories, including deep sea hydrothermal systems, surface hot springs, evaporative surface pools, effluent channels, subsurface fluid flow (*e.g.*, groundwater, ocean crustal circulation, impact-generated subsurface flow), as well as exchange/interaction among such systems where it is geologically feasible. Therefore, systems that more faithfully replicate terran environments need to incorporate mineral, gas, and fluid phases, accommodate wide ranges of temperature, pressure, and incoming radiation, include thermal and chemical gradients, as well as dynamic variations among these. While many of these environmental parameters are not commonly implemented in more traditional prebiotic or organic synthesis experiments, they are more widespread in other fields, including geochemistry, geomicrobiology, and petrology. *The synergy between experimental needs of prebiotic chemists and the experimental capabilities of geoscientists have the added benefit of fostering much needed collaborations between these communities* (Lyons *et al.*, 2020). Therefore, flow-through and batch reactors, high pressure cells, or microfluidic chips should be adapted to the specifics of prebiotic chemistry. Even without new experimental facilities, experimentalists can implement more feasible conditions in existing experimental setups, by including more tractable, and key environmental parameters, like anoxic water, multi-phase mineral assemblages, and multi-component reaction solutions (Scharf *et al.*, 2015; Preiner *et al.*, 2020). For example, anoxic conditions are regularly implemented in microbiology, and two-phase (water/mineral) experiments are quite common in geochemistry. Finally, an explosion in microfluidic technologies could be applied to investigate water-rock reactions in any number of Hadean environments, and have the added benefit of being easily multiplexed and also enabling *in situ* chemical analyses.

The vast range of environmental conditions (e.g., variations in temperature, pH, redox state, fluid composition, etc.), geologic environments (fluid mixing, subsurface fluid flow, three-phase surface environments), and prebiotic targets (e.g., CO_2 reduction, monomer synthesis, polymerization, selection, etc.) that need to be probed with experiments brings into sharp focus the need to have both better informed and more efficient experimental designs, further opening opportunities for instrumentation and data science.

III - Instrumentation: One of the more significant analytical challenges to an Earth First Origins approach to prebiotic chemistry is that realistic early Earth environments aren't idealized conditions and such prebiotic experiments will inevitably contain a messy combination of organic and inorganic compounds in different phases. To best tackle this task, multiple analytical techniques that are capable of providing orthogonal information (often termed 'multimodal' analyses) are necessary to properly characterize the array of complex experiments that will result in the production of a combinatorial explosion that requires non-targeted analysis strategies (Colón-Santos *et al.*, 2019). Unfortunately, each chemical analysis approach often requires unique instrumentation and sample preparation procedures that are time consuming and limit sample throughput. To properly cope with the large number and overall complexity of samples from an agnostic Earth First Origins approach, the chemical analysis approaches should be 1) highly selective, 2) sensitive to a broad range of analyte concentrations, 3) non- or minimally-destructive, and 4) performed in parallel (*i.e.* at the same time). It would also be highly advantageous to devise parallelized analysis methods that can be performed inline with the experiments. Parallel, multimodal chemical analysis minimizes sample volumes, improves throughput, and offers the ability to determine correlations between diverse species and phases. For instance, molecular mass spectrometry, Raman spectroscopy, and elemental analysis can be integrated inline to determine product identity, the local chemical environment of organic compounds, and co-localization with elemental/mineral species. The role and importance of micro- and nano-domains can be better understood if spatial information is preserved during the analysis, so-called multimodal chemical imaging. These analytical methods can be performed with sufficient time resolution to yield insights into reaction pathways, kinetics, and chemical dynamics. This combination of *in situ* and bulk analyses is essential to accurately deduce the context and dynamics of any prebiotic system.

Finally, recent technological advances have led to high quality chemical instrumentation in compact portable or transportable packages for nearly every analytical approach. Use of miniature, portable instruments for a parallel, multimodal analysis platform makes it possible to obtain multidimensional measurements at any laboratory or site. Development and assessment of integrated multimodal chemical analysis systems would greatly benefit planetary science and the search of extraterrestrial life or precursors for life. Since both programs require compact and portable devices, instrument development projects should be geared for both Earth-based prebiotic chemistry experiments and the search for the presence of extant/extinct life elsewhere.

IV - Data and Analytics: The origins of life community has become increasingly multidisciplinary and prolific in recent decades. As such, the influx of models, experiments, and analyses that investigate both early Earth conditions as well as prebiotic pathways are ripe for synergy and synthesis. Therein lies the opportunity for this community to be transformed by incorporating *data science*, which is the *4th paradigm of science* (Hey *et al.* 2009; note the first three: 1st: observation/experiment, 2nd: theory, 3rd: computation). Far beyond fancy ingest and graphing of big data, multicomponent application of data science can (i) overcome cross-disciplinary language barriers; (ii) enable data curation that allows for global comparisons across experiments/ parameters/outcomes; and (iii) integrate environmental models with machine learning and exploratory-driven (and hypothesis-generating; Ma *et al.* 2017) visualizations, thus formulating predictions for new, more likely-to-succeed prebiotic experiments. The challenges that currently stifle integration between prebiotic chemistry experiments and early Earth environmental parameters include discontinuities in multi-modal, multi-scalar, high-dimensional, and sparse and heterogeneous data – and also differing vocabularies.

Implementation of a data science paradigm can be facilitated with virtual laboratories (Szalay 2001), which are central analysis, data curation, modeling and visualization platforms. Applied to the OoL field, such virtual laboratories could (i) enable scientists to run part or all of their data analysis/analytics pipeline, on not only their datasets but others; (ii) mine the literature and extant (previously dark) databases for experimental parameters/outcomes so that AI/machine learning (*e.g.* Barbastathis *et al.*, 2019) can identify relations and trends that are missed while looking only at static data; (iii) combine geochemical and geophysical models, with known constraints from early Earth environments, to serve as a clearinghouse for experimental plausibility; and (iv) integrate these models with *ab initio*/molecular dynamic simulations, structure generation methods, and novel visualization tools to explore complex reaction networks and target the most promising experimental space (Cleaves *et al.*, 2019; Meisner *et al.* 2019). Such virtual services are underpinned by data infrastructure: big data analysis to ingest and process prebiotic experiments, including the large sets of data generated by in-line multimodal chemical analyses, which also need better databases, and data structures (*e.g.* graph-based), and stronger policies for the open sharing and exchange of data. The explicit modeling of the semantics related to instruments, experiments, measurements, locations and science vocabularies, as well as important inter-relations and data integration provides a pathway for scientific insights and provides a unifying solution for an otherwise fragmented research community. Deeper and close partnerships with data scientists will be essential for the OoL community in the coming decade. A greater focus on computational and data science analysis of OoL problems will enable researchers to bridge the gap between prebiotic chemistry and early evolutionary history (a field that already relies heavily on computational analysis and data mining). This goal will become a real possibility in the next decade and may finally yield a historic account of the origin of life as it occurred on Earth.

Implications for Planetary Science

The search for life's origins on this planet has been hampered by a narrow view of life as we know it. The experiments and analytical approaches outlined above have the possibility to further enable a paradigm shift in our search for habitable bodies elsewhere. To develop a strategy for the detection of non-terran life, a set of robust criteria for life detection that forms a testable hypothesis must be identified and require a combination of multiple lines of evidence produced by geophysics, geology, planetary science, geochemistry, biology (*e.g.* Steele *et al.*, 2016; Pearce *et al.*, 2018; Alleon and Summons, 2019; Chan *et al.*, 2019; Sapers *et al.*, 2019; Stewart *et al.*, 2019; Bowman *et al.*, 2020; Brasser *et al.*, 2020). Steele *et al.*, (2016), states *"the simplest form of extraterrestrial life detection with minimal assumptions on the nature of the organism or a potential "alien biochemistry" to be detected, is to understand the possible abiotic organic chemical reactions, given the context of the samples and look for perturbations to that physiochemical system. Life* *assists in the detection process in that it is competition-driven to select a relatively small number of the many known organic chemicals produced by abiotic processes. Therefore, anomalous deviations from predicted abiological yields of organic chemicals under given conditions may be the easiest life detection protocol."* This philosophy for life detection requires, among other things, an understanding of possible abiotic chemistries produced in abiotic environments (including early Earth conditions) and the preservation/diagenesis of that signal with time. Therefore, the search for the reactions that led to the origin of life on Earth also represent our most robust search strategy for finding life elsewhere.

Furthermore, life detection elsewhere depends critically on accessing potential habitable zones, gaining a clear understanding of the geological context of potential measurements, and most importantly, applying a multimodal analytical approach to *in situ* biosignature detection. As such, the research trajectory we describe above facilitates technological innovations that have direct applicability to future life detection missions. For example, miniaturized and multimodal analytical instruments that require minimal sample volumes can be matured into flight-ready instruments and expand the breadth of chemical space and reaction context that is detectable. Furthermore, when considering life detection on subsurface ocean worlds, high pressure devices developed for prebiotic chemistry can be re-purposed for sampling of extraterrestrial oceans. Therefore, technological innovations developed within the prebiotic chemistry and early Earth research community will directly inform, refine, and enhance our search for life elsewhere. This includes missions to Enceladus, Europa, and Mars, where even a non-life signal would provide a critical result in our search for the reasons abiotic chemistry was able to transition through prebiotic to biotic chemistry on Earth. Though apparently separate, the scientific endeavors of understanding the origin of life on Earth and the search for life elsewhere are completely intertwined, with each feeding the observations, instrument development, data acquisition and interpretation, that is essential to the other.

Summary of Recommendations

The Origins of Life community often has been set apart from other aspects of NASA Astrobiology, Planetary Science, and Mission objectives. Furthermore, within the community, disciplinary divisions often set apart geoscientists from prebiotic and organic chemists. At the cusp of the next decade of Planetary Science and Astrobiology, a new paradigm is possible, where OoL research is fully complementary to and intertwined with the search for life elsewhere, contributing to our understanding of life detection, dynamic planetary habitability, and the early evolution of life. ***Integration within the community, and expanding inclusion of geoscientists, along with cross-cutting innovation in experimental, instrumental and data analysis techniques, positions this field to be a key part of the NASA Planetary Science and Astrobiology portfolio, including mission-based exploration for life elsewhere.*** To capitalize on this opportunity, we make the following recommendations to NASA:

- *NASA should continue to target and grow cross-disciplinary research in OoL, both through institutions like PCE3, as well as via funding models that target robust collaborations between Earth scientists and prebiotic chemists; novel and agnostic approaches that circumvent historical biases; and early Earth research that directly impacts OoL.*
- *NASA should build cross-cutting programs for novel instrument development that bridge origins of life, planetary science and exploration, and Earth sciences.*
- *NASA should acknowledge that the search for life and the search for terrestrial life's origins are linked, and make efforts to bring the mission, prebiotic chemistry and early Earth environment communities together.*

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