a stronger bet for *hypothesis-driven* research.

Therefore, it is not so much a question of using artificial-intelligence methods to interpret or re-design multiple types of prebiotic molecular mixtures and reaction networks that ought to be broadly probed *in vitro*. Rather, a new generation of researchers must commit to working as strict "bottom-up" chemists (i.e., avoiding recurrent tricks such as the use of enzymes or other complex biomolecules) while making a special effort to think and project "top down" like proper biologists and try to put together specific combinations of functional components that should integrate those intermediate, minimally robust systems. This key, transdisciplinary task can be approached as a search for the natural pathway connecting organic chemistry with "life as we know it"[4] or from a wider, bio-synthetic motivation.[5] My guess is that many of these hypothesis-driven attempts will unfortunately fail. But a few will strike gold and refresh our hopes that humankind might one day grasp biogenesis and thereby a fundamental part of what has been going on, since a few thousand million years ago, at the surface of this peculiar planet.

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CATALYSIS

Reaction: Life Is Messy

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Some years ago, at a meeting during one of those periodic budget crises to which academic institutions are prone, an administrator raised a question about the advisability of continued support for "expensive" research in astrophysics and cosmology. "We have to keep supporting these fields," responded a (soft matter) physicist in the room; "they're the way we tackle our creation myth." The argument proved persuasive. Trying to understand the origin(s) of life represents a similar quest for chemists and biologists. Systems chemistry, taken here to comprise the study of how new functions emerge from networks of molecules and reactions, provides a valuable tool in seeking that goal.

A purely chemical approach, however, is not likely to yield the key to this most intriguing and challenging scientific puzzle. Life is messy. It's not like the systems most chemists study—where reagents are purified, conditions such as temperature, pressure, and humidity are under experimental control, experimental durations are shorter than grant cycles, external influences are avoided or minimized, and replicate experiments are feasible and reproducible. Systems chemistry might be a valuable tool, but it's not sufficient. Gradients, mechanical forces, external electromagnetic fields, phase separation, and various forms of transport—diffusion, convection, and osmosis—could all play crucial roles in addition to the chemistry. The appropriate question, in this writer's view, is not the historical one (i.e., how did life first arise on Earth?) but rather the more open-ended and potentially answerable one of establishing a set of sufficient conditions that could generate an "organism" that we would agree is "living." This requires establishing a set of criteria for what constitutes life, a non-trivial problem in itself and one that chemists are arguably less or at least no better equipped to answer than biologists, geologists, planetary scientists, computer scientists, or philosophers. "I know it when I see it" might not be a satisfactory principle with respect to life given that it could preclude recognizing forms of life very different from those currently known to us.

In 2016, the National Science Foundation (NSF) and National Aeronautics and Space Administration (NASA), recognizing the importance and the scope of the problem, convened an "Ideas Lab," a week-long workshop in which 29 scientists from a variety of disciplines, aided by four facilitators and six program officers, met "to interact and engage in free thinking on first principles, learn from one another, and create an integrated vision for future research projects."[1] The interdisciplinary teams that emerged from these discussions generated five research proposals that were awarded a total of nearly $9M by the two agencies. One such grant, dubbed the CESPOoL (Chemical Ecosystem Selection Paradigm for the Origins of Life) by its participants, includes chemists, biologists, physicists, an earth and planetary scientist, and a specialist in scientific animation from seven institutions. Its focus, both experimental and theoretical, is on using serial transfer experiments to impose *in vitro* selection for self-propagation ability on prebiotic soups interacting with mineral surfaces.[2] Incubating mineral grains in prebiotic soups and repeatedly diluting them with fresh soup and grains will enhance the abundance of any surface-associated, life-like interacting molecular ensembles (SLIMEs) that can propagate themselves from grain to grain faster than the rate of dilution. The hope is that screening multiple alternative minerals and organic soups will identify a combination that yields a SLIME, ideally one that has some capacity for evolutionary improvement in its rate of self-propagation.

A key idea in the CESPOoL project is that of an autocatalytic set, or more specifically a reflexively autocatalytic and food-generated set (RAF),[3] which is a collection of molecules and reactions wherein (1) some of the molecules (the "food set") are supplied by the environment, (2) all other molecules in the set can be produced from the food set or from other molecules in the set, and (3) every reaction in the set is catalyzed by one or more of the molecules in the set. The notion of an RAF is a generalization of the idea, introduced four decades ago by Eigen and Schuster, of a hypercycle,[4] which is a cycle of self-replicating macromolecules, e.g., RNAs linked such that each RNA encodes a ribozyme that catalyzes the replication of the next RNA and the last ribozyme catalyzes the replication of the first RNA so that the system forms an autocatalytic cycle. The sought-after SLIME would presumably represent an RAF in which key molecules in the set associate with a mineral surface, which would not only serve to retain the cooperating molecules in physical proximity but might also facilitate some of the required catalytic reactions. Mathematical models suggest that RAFs have a high probability of arising spontaneously in a well-chosen set of reactants.[5] RAFs are an example of the sort of emergent behavior envisioned in systems chemistry. Only after the loop of catalytic reactions is closed, where all molecules are kept close enough together to synthesize one another, can the ability of the network to self-propagate (make more of the same set of chemical species) emerge.

Although systems chemistry can offer important insights into how life might have arisen, major questions for which systems chemistry may or may not be a useful tool remain. The most obvious of these is which criteria will allow us to decide whether or not a system is alive, a question that has fascinated scientists and philosophers through the ages. Can life arise from building blocks very different from the nucleic acids and proteins that we are familiar with? Would we recognize such a life form if it existed? In temporally changing far-from-equilibrium environments such as those that existed on the prebiotic Earth, can appropriately constituted reaction networks harness periodic or stochastic fluctuations in external conditions to further their functional evolution? Is the chirality found in the amino acids and sugars of earthly life essential for all life? Whether or not we ultimately arrive at definitive answers to these questions or succeed in creating "life in the lab," it seems certain that our search will reveal new and important scientific principles and phenomena.

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