

CATALYSIS

Reaction: A New Genesis for Origins Research?

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I wonder whether the solution to the problem of understanding the origins of life lies not in recreating the chemistry that makes up current biology but rather in understanding the process through which life emerges from the “dead” or inorganic world. If you think about it, at the origin of life before the advent of cells, the wider ecosystem, and the products of biology, the world was devoid of complex molecules and systems created by Darwinian evolution. So how and where did life form in the first place? Was there a single genesis event? What is the probability of the origins of life? If there were two separate events, would they yield the same outcome? Answering any of these questions would arguably be one of the most profound achievements of modern science. We would be able to understand whether we are alone in the universe, figure out how far life might extend into our solar system, and determine what the future of life on Earth might look like.

From a simplistic point of view, if we assume that the newly formed planet

Earth was dead and the origin of life occurred on Earth, then it would be safe to assume (at least initially) that the wider environment controlled the emergence of life via chemical reactions (in seas, lakes, ponds, puddles, and vesicles). These reactions then produced molecules or polymers that could become evolvable, and biological systems emerged. Given that biology is “chemistry with history,” one of the greatest challenges facing today’s chemists is understanding how chemistry becomes historical. Today many researchers are turning their skills to exploring the origins-of-life problem, and with this, many new avenues are being explored. One important approach is the synthesis of “prebiotically plausible” molecules,¹ which uses target-driven organic chemistry to achieve incredible feats of synthesis under conditions that might be thought to be present on the early Earth. Although I think this is an exciting and fruitful endeavor, I wonder whether a process- or phenomenon-driven search might also help chemists break free from the historically constrained (and often revised) notion of which molecules and reactions are prebiotically plausible (opening up more avenues of research to expand the effort, funding, and excitement). Aiming for simple chemistry first rather than prebiotic plausibility might be the first step to relaxing the target-based reaction searches that dominate origins research today. This is because, rather than arguing for prebiotically plausible chemistry, we could start conceiving simple chemical systems that could withstand dilution, concentration, heat, light, etc. But more importantly, by abandoning the need for a single target, we will need to explore complex messy systems, and these might lead to another transition in origins research.

However, what if we went even further to replace a chemistry-first origin of

life with an evolution-first paradigm?² In our laboratory, we have been combining robotics that search formulations of simple model protocell droplets by using evolutionary algorithms to evolve droplets that lack any polymer genome (Figure 1). Could it be that matter, irrespective of the chemical details, will eventually become evolvable? How would that change the way that scientists explore the problem? I argue that this is the only way that a transition in complexity, and thus a universally agreed-upon signature of life, can be achieved. This might also be usable as a metric for locating new biosignatures on Earth and in the solar system, because all of the arguments around defining the characteristics of life get us into circular arguments without yielding insights that lead to a testable hypothesis. Some people argue that life does not exist discretely and that the “living state” is a planetary phenomenon. This approach is constrained further by those who have tried to define life, which mostly results in arguments that don’t correctly capture what life does (generates complex artifacts or biosignatures). Whatever your viewpoint, the key remaining question is, how can matter transition from the non-living to the living state? Recently, several researchers have declared that they are aiming to making new life in the lab. Some of them use biology as a template, but others (including us) are setting out to explore the real-time assembly of a new biology in the lab, on the fly. I think the key is to start with simple components to develop simple chemical systems that can become complex. But how can a target-free origin of life help us make progress? I argue that the development of molecular networks (that is, molecules that are linked by reactions that feed other reactions that produce by-products that feed the previous reactions) could be the route by which

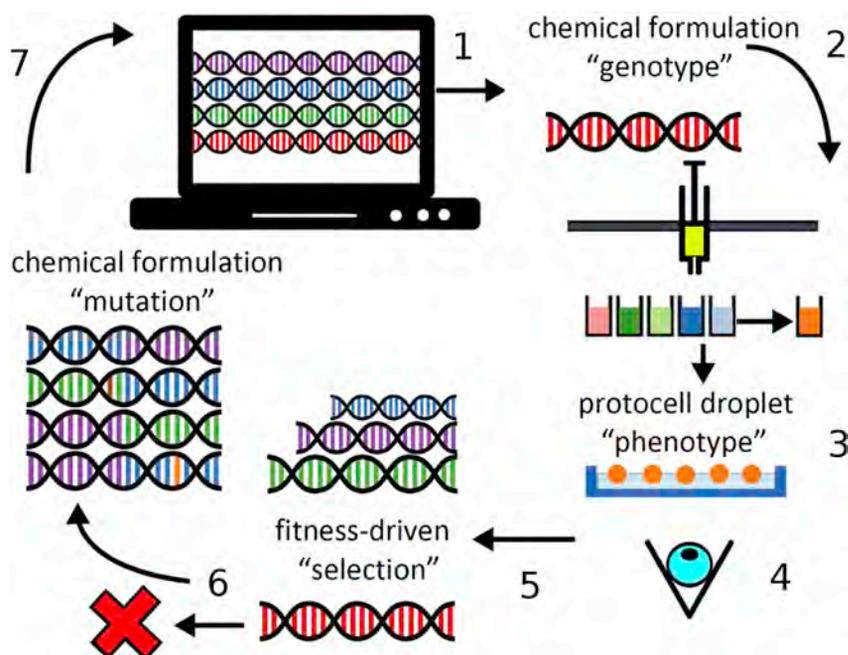


Figure 1. Scheme Showing the Robotically Assisted “Embodied” Evolutionary Process of the Protocells

In step 1, the formulations are selected from the computer database’s “genome,” and in step 2, the robotic process starts and the chemicals are mixed into a formulation ready for droplet formation. In step 3, the formulations are used for creating protocell droplets in a Petri dish. In step 4, image analysis is used for categorizing and quantifying protocell behavior, and in step 5, a fitness test is used for deciding which of the protocell assemblies “survive.” In step 6, the evolutionary process mates surviving individuals and introduces mutations. Finally in step 7, new offspring are produced, and the evolutionary program creates a new generation ready for step 1 to start again after the robot has cleaned the Petri dish.

evolvability arises. This means that the network of interacting molecules forms a primitive memory that functions in a manner similar to that of the genome found in modern biology. However, this “non-written” memory has a finite storage limit, which imposes a limitation on the number of available functions and hence the ability for the system to respond, adapt, and ultimately evolve in a range of different environments.

Taking this argument further, I suggest that the current state of biology can be explained only by a series of other biologies, each successively layered upon each other and each differing in the effective complexity, memory, and evolvability of the systems that define each biology. Ultimately, the reduction of biology to inorganic chemistry can

then effectively be measured in the complexity of each biology in terms of function, evolvability, and effective genome size. This suggestion is a departure from the all-or-nothing living world that characterizes the current targets (which are in my view unreasonable) given to the chemist to achieve. This means that we can take a new approach not only to the origins of life but also to producing an artificial life that starts the complexity ladder from simple to historical chemistry. By attempting this approach, we might be able to avoid the information catastrophe associated with the RNA-before-life world and replace this with a transition from one biology to another that adopts RNA. This information catastrophe occurs because the number of specified parameters allowing the synthesis of RNA precursors and functional

RNA systems vastly exceeds the available search space. This means that the chance that nature will randomly come up with the recipe for RNA formation is essentially zero given the vastness of chemical space and the absence of prior templates. However, it is quite conceivable that the ribosome could be produced by a prior life form, and thus the RNA world represents a stepping stone or bridge between the number of quite different life forms.

If we can be released from the shackles of prebiotic plausibility, then our imaginations can run riot. If, as a phenomenon, life is about matter seeking a route to complexity, then how might this be achieved elsewhere in the cosmos?³ This is an incredibly hard and exciting question given that we currently have only one data point, but I argue that chemists can be center stage to seize this challenge. Laboratory experiments moving from target-driven synthesis of “single-point” molecules that exist in our current biology to systems of simple molecules that can generate complex artifacts could represent a whole new range of targets that could unite a generation of researchers. Such an effort would yield dividends relevant not only to origins questions but also to all of chemistry, biology, computational theory, physics, and nanoscience. To do this, we will have to be willing to move from the era of the molecule to that of the molecular network.⁴ By aiming to discover or synthesize a molecular network that can show complex behavior (multiple catalytic, mutually catalytic, or autocatalytic systems)⁵ from simple starting points, we will need to shift our focus from the many “origins” paradigms (RNA, peptide, lipid, and worlds) that are currently the focus of researchers exploring prebiotic chemistry to a more integrated approach. This is not an easy shift. A multidisciplinary effort that introduces machine learning, network

theory, -omics techniques, and automated workflows and also abandons the molecule in favor of complexity is called for. But if researchers working across the disciplines could make this leap, then we might be able to come up with origin-of-life models that explain the nature of modern biology. We might be able to target the synthesis of entirely new life forms in the laboratory much faster than the millions of years needed for the emergence of life on Earth.

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Reaction: Life, Origins, and the System

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In the April issue of *Chem*, Yitzhak Tor made an ardent plea for a paradigm shift away from “traditional” (i.e., post-Miller-Urey) approaches to abiogenesis research and prebiotic chemistry, particularly by embracing the systems view. His plea is, in my view, most timely and well founded. The time is certainly ripe for new ideas, new players, and new connections in the field of life origins.

As Prof. Tor points out, contemporary biological cells (and presumably the last universal common ancestor¹) are complex interconnected networks of chemical processes whose dynamic and periodic fluctuations constitute a far-from-equilibrium system. Therefore, by adopting a systems view of living, we are effectively changing our optic on the problem, and it is this change that I believe will ultimately prove to be of great value.

As chemists, when we look at biological life, we see chemicals of course! We see reactions between them—exchanges of energy from one part of the system to another and between the system and environment. We also see how the intricate and regulated mechanistic interplay between large molecular ensembles (DNA, RNA, and ribosomes) leads to the synthesis of new classes of large molecular assemblies (proteins), which subsequently have some functional value to the system itself. We ask how these molecules came to be, why these reactions occurred and not others, and how the complex interconnectedness of the system was built and regulated. These are valid questions, yet the traditional prebiotic chemistry tool in trying to answer such questions is reductionist, and such a method has a rather fine-grained optic. Adopting a systems approach allows for a more coarse-grained view of the problems.

In this new view of abiogenesis, Prof. Tor cites several seminal markers that pioneers such as Benner, Sutherland, Powner, Pross, Pascal, and many others have planted for our benefit. What happens when we widen the optics a little further? If we look at the system at the cellular level instead of the individual chemical processes and molecules, what is the system doing? Chemicals go in, and other chemicals go out; energy from the environment flows through the system and is transduced to molecular units of chemical energy currency (such as adenosine triphosphate in contemporary cells). The (cellular) system has motility within its environment to search for energy and chemical blocks for its own construction. The system grows and at some point divides and multiplies, and growth becomes associated more with a cellular ensemble than with the individual component systems. The system changes, and indeed, so too does the environment.

A focus on energy transduction, as flagged above, is one that provides several valuable insights in my view. Biological (cellular) systems are essentially complex chemical factories for the dissipation of energy from one form to another. They are, as Prigogine pointed out, examples of far-from-equilibrium arrangements whose thermodynamic properties are conducive to building complexity² through stochastic, spontaneous, self-organizing behavior. Prigogine called such arrangements dissipative systems, and they allow us to widen the optics of the systems view even further. Prigogine illustrates this himself by pointing out that dissipative systems are not solely the province of biology; they can also be found all around us in the form of rivers, volcanoes, civilizations, cities, weather patterns, our own planet, our solar system, galaxy clusters, and our universe itself. All such structures share a common drive toward transducing energy and using