Collectively autocatalytic sets

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Voices

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The origins of life probably involved autocatalysis. Kauffman's 1986 description of collectively autocatalytic sets—self-replicating reaction networks—and related ideas have influenced efforts to study the properties of reaction networks that may have given rise to life. Here, researchers discuss the impact of collectively autocatalytic sets on the field.

Gonen Ashkenasy
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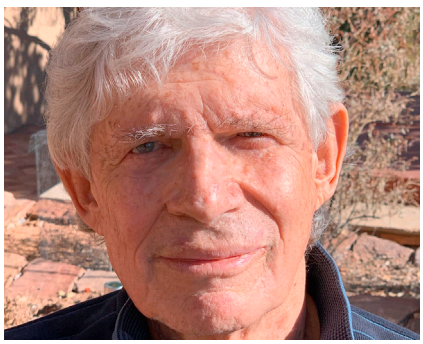
Increasing complexity in heterogeneous autocatalytic sets

Exploring the origin of life has borne several conceptual models that are capable of explaining self-organization and selective behavior in prebiotic networks. Among these models, the "collectively autocatalytic set" has stood out for its intuitive simplicity, implying that the emergence (or self-organization) of mutually catalyzed arrays of molecules, where the synthesis of each molecule is boosted by (at least) one catalytic pathway, is sufficient for their survival and selection in complex environments. Using a bottom-up approach, scientists studying systems chemistry have brought such models into reality by synthesizing autocatalytic networks of bio-related molecules, such as peptides and RNA. Intriguingly, in addition to general catalysis, as originally proposed by Kauffman, these synthetic networks are driven by specific (or fairly specific) template-directed reactions, which are crucial for their organization into subnetworks and other elaborate modules, including Boolean motifs. Recent work has highlighted the fact that merging together molecules from different families, such as nucleic acids and peptides, into heterogeneous autocatalytic sets forms richer environments, where the system structure, topology, and dynamics emerge from the synergetic interaction of the nucleic acid "digital" molecular information and the peptide "analog" aggregation. In the future, greater complexity could be induced in such synthetic autocatalytic networks by harnessing fueled, high-energy molecular assemblies or by running the reaction mixtures under continuous flow. Preliminary data reveal that flow conditions enhance selectivity to a remarkable extent, pushing weaker replicators to the brink of extinction—manifesting the ultimate selection in early chemical evolution and enabling the networks to exhibit intricate steady-state behavior, including multi-stability and oscillations.



Stuart Kauffman
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Our task now

I hope I may make a suggestion, or better, point to a big issue. It is true that some major researchers in the origin of life field have given up in despair. I was stunned to learn this. The field is badly fragmented. There is no overarching view around which many of us disparate workers can think to organize work. This is entirely unlike physics and CERN. But CERN and the physicists have the fundamental theory of particle physics. We do not know what our fundamental theory is. I think I may offer one a way to one: the evolving universe formed the stable atoms. These combined to make ever more complex molecules. These complex molecules were able to organize into complex reaction networks. At a critical diversity that, it happens, I discovered, a phase transition to collectively autocatalytic small molecule sets arose. Joana Xavier has demonstrated such sets in all 6,700 prokaryotes. It needs to be shown that these reproduce *in vitro*. If as a field, some number of us could coordinate around creating such small molecule collectively autocatalytic sets *de novo*, seeing how these might co-evolve to include lipids, peptides, and RNA, then seeing how these richer systems

might co-evolve to template replication and coding, we might find a pathway many of us could work on.

In short, the contributions in this Voices article may already give evidence for such a theme-pathway. It's just a suggestion, but it may bolster a new paradigm.

Doron Lancet
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Collectively autocatalytic sets connect chemistry to Darwinian evolution

It is consensual that life's emergence necessitates an early appearance of a self-copying chemical system. One scenario for that is "RNA-first," whereby life was seeded by a single polymeric self-replicating molecule. Another scheme, conceived by Stuart Kauffman, contends that life was set up by a supramolecular network that occasionally reaches catalytic closure, leading to self-reproduction of an *entire* "collectively autocatalytic set" (CAS). CAS is more life-like than RNA, revealing both the reproduction and metabolism "pillars" of life. A third pillar of life is compartmentalization. To add this element, we developed the Graded Autocatalysis Replication Domain (GARD) model, a chemical kinetic extension of CAS. Here, the small molecules are assumed to be highly diverse lipids, forming micellar and vesicular compartments. These have a measurable volume, hence defining concentrations and reaction rates, allowing computer simulations to foretell the network dynamics. This shows that while an assembly's growth and fission initially transits through random compositions, soon enough it reaches a reproducing composition ("composome"), which shows homeostatic (composition-preserving) growth, as happens in contemporary proliferating living cells.

GARD simulations also reject criticism that reaching a reproducing CAS network requires an improbably large molecular repertoire. GARD simulations show that reproducing composomes emerge not from an enlargening of the molecular repertoire, but when a small dynamically preferred repertoire is "distilled." Further, we recently proved that this reproducing assembly state constitutes an attractor, which in the field of dynamical systems is a state toward which a system tends to evolve. Thus, a state of reproduction is attained unexpectedly fast (see https://www.cell.com/cell-reports-physical-science/fulltext/S2666-3864(23)00152-2). All that, along with recent accumulating experimental evidence, shows that CAS's standing in the study of selection and evolution is highly fortified.

Sijbren Otto
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The search for network-level autocatalysis has just begun

Autocatalysis is a fascinating phenomenon as it funnels material from the environment into more autocatalysts. Hence, autocatalytic systems attract matter to them, which has made them appealing in the context of the question of the origin of life. Autocatalysis is relatively well-studied for individual molecules. Yet theoretical work by Kauffman, Steel, and Hordijk suggests that reaction networks can also become autocatalytic. Indeed, several cycles found in the metabolic networks of cells exhibit this type of autocatalysis (albeit not autonomously, given that enzymes are needed for catalyzing the individual reactions). It has been argued that autocatalytic sub-networks are almost inevitable when a reaction network of any kind gets sufficiently large. This would suggest that it must be possible to identify such autocatalytic sets also outside metabolic networks. Yet, except for the formose reaction, virtually no examples exist where autocatalysis takes place only at the network level. Why are such experimental manifestations so rare? It could be that theory overestimates their abundance. But it could also be that scientists have not yet looked hard enough. Indeed, I argue that more efforts are needed to settle this ambiguity. This calls for an approach where reaction networks are created, starting from simple starting materials (similar to the iconic Urey-Miller experiments), but now not focusing on chemical structure, and instead on the emergence of specific

behavior: network-level autocatalysis. Such experiments are far from easy to conduct. First, it is not obvious what starting materials and conditions would maximize the probability of autocatalysis emerging. Second, it is not obvious how to detect the onset of autocatalysis. However, since the days of Urey and Miller, our analytical capabilities have moved on and the time has come to start a serious systematic search for experimental manifestations of autocatalytic sets.

Kepa Ruiz-Mirazo
University of the Basque Country (Department of Philosophy and Biofisika Institute—CSIC, UPV/EHU)

Autocatalysis: A wild card for (proto)-biology, from reductionism to emergence

Although not exclusively present in the living domain and not proved strictly necessary for the latter, autocatalysis is commonly interpreted in biology as a powerful natural driving force, implemented through a variety of physical-chemical mechanisms, that operates at the core of the metabolic organization of all cellular organisms and, therefore, is also key to understanding their potential for growth, reproduction, and evolution. However, the relationship between life and the autocatalytic behavior of some of its components is far from trivial, because they always come coupled, *in vivo*, with other fundamental molecular transformation processes. It is, indeed, the combination of autocatalytic and negative feedback loops/motifs that leads, *in vitro*, to complex spatial and temporal patterns of self-organization.

Given those premises, the idea that autocatalysis played a critical role in abiogenesis is compelling, like many authors in the origins-of-life camp have defended. Yet, depending on the theoretical background of the proponent and the type of approach followed, the idea has taken different shapes and meanings over the years. Both fragments of the term, the "auto" (typically assumed to be a single molecular species that contributes to its own synthesis, but sometimes also referring to a collection of different molecules involved in a seed-dependent reaction cycle, a densely inter-connected network of precursor catalysts, or even a supramolecular structure whose physical formation enhances the chemical production of its building blocks) as well as the "catalysis" (i.e., the triggering mechanisms, which have been demonstrated as remarkably diverse), contribute to the ambiguity. This is an ambiguity that I consider fruitful, though, because the experimental research pathways where the different proposals have found support have often provided new insights for the field, giving room to a really wide suite of strategies, ranging from the most reductionist (still pursuing the "Holy Grail" of molecular self-replication) to the systems-oriented minds (hoping to catch, in a more heterogeneous material setting, the emergence of "Kantian wholes").

Sergey Semenov
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An autocatalytic alternative that implies complexity

Autocatalytic sets have been an attractive alternative to the "information-polymer-first" hypothesis since their introduction by Kauffman. It offers a solution to the improbability of the formation of self-replicating RNA. Simply put, forming many short cross-catalytic molecules is statistically more likely than forming one highly efficient self-replicator. Despite its attractiveness from a theoretical perspective, experimental work on autocatalytic sets has faced significant challenges. The major challenge is the need for independent autocatalytic cores to utilize Darwinian-like mechanisms of evolution and complexification. This problem can be traced back to the classic work of Eigen, who framed it in terms of coupling between cycles by "parasitic" branches. It becomes especially critical when discussing networks of simple molecules in the prebiotic world. Organic chemistry is inherently non-orthogonal. For example, any thiol will react with most electrophiles and oxidizers in the mixture. Thus, primitive reaction networks will be highly interconnected, and the

formation of independent autocatalytic cores is unlikely. The high specificity of reactions comprising autocatalytic networks from nucleic acids and peptides was achieved by templating, but participating molecules are as complex as analogous self-replicators. The solution for problems of a reaction's orthogonality and molecular complexity might lie in the effects of compartmentalization and compositional information. Compartmentalization will reduce the effect of parasitic branching in the same way as compartmentalization of metabolic networks in biological cells prevents the spreading of benefits from advantageous mutation to surrounding cells. Composomes of micelles might be an interesting alternative to polymers as information carriers. Thus, more experimental work on systems that combine compartmentalization, autocatalysis, and some form of information storage is needed.

Joana Xavier
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The role of autocatalysis in exploring life's origins

Autocatalysis is a particularly remarkable concept in that it allows us to inspect the self-referential paradox in physical-chemical phenomena. Cellular life is the epitome of material self-reference. Several authors (including Kauffman, Dyson, Eigen, Schuster, Rosen, Ganti, Prigogine, Maturana, and Varela) posited some form of collective autocatalysis or chemical closure as central in the origins of life (OoL). The formalization of Kauffman's collective autocatalytic sets in RAF (reflexive autocatalytic food-generated networks) theory allowed us to show recently that collective autocatalysis is possible among universal biomolecules before the advent of genes and enzymes. This model of metabolic origins has been criticized on one interesting point: the networks identified are not catalytically closed, or circular; they are instead highly dependent on the environment not only for building blocks, but also for catalysts. This makes "traditional autocatalysis" (where *all* catalysts are produced by the system) not relevant to the origins of life. That should not surprise us. All life is today still highly dependent on universally essential external catalysts: metals. It is not new to say that metals are as inextricable from the OoL as they are from life. Recent experiments show that metals can catalyze multiple biochemical reactions alone. This is an interesting time for OoL research via autocatalysis, where a new balance between closure and catalytic dependence on the environment is uncovered. That complex environment, along with prokaryotes, makes a much more complex duo than hitherto considered. It remains to be seen if known "true" autocatalysts as ATP and NAD can be produced (1) in a potential ancestor that would then become partially (as it still depended on metals) autocatalytic or (2) independently (becoming then "activators" for the growing ancestor network). The future requires experiments, advanced computation, and a close look at physical-chemical boundaries in the establishment of primordial self-referential systems that preceded living cells.

DECLARATION OF INTERESTS

The authors declare no competing interests.