The quest to unravel the mysteries surrounding life’s origin continues to captivate scientists. In fact, the central question revolves around how an abiotically formed mixture of non-living chemicals (no-life) gave rise to the early self-reproducing and evolving living cells, called protocells (life). In simpler terms, the question is: what bridged no-life to life? Alexander Oparin’s book, The Origin of Life, pioneered a scientific approach to these questions; yet, 100 years later, scientists are still grappling with the profound question of how life, with its remarkable ability to replicate and evolve, emerged from the chaotic mix of chemical compounds on our early planet.

**THE ABIGENESIS CONUNDRUM**

The central debate in this field of abiogenesis is the study of how life could have arisen spontaneously and naturally from non-living substances. The popular answer revolves around two major complementary lines of study: one focuses on the prebiotic synthesis of life-like small molecules, and the other centres on the prebiotic synthesis of RNA, a complex molecule believed to have the capacity for self-replication. However, there is currently an unbridged chasm between a mixture of numerous scattered organic compounds, large and small, and the formation of the first reproducing protocells.

To resolve this problem, we need spontaneously formed containers. It is widely accepted that key molecules capable of forming such containers are lipid molecules. Such amphiphilic assemblies can gather specific molecules from the complex mix of chemicals around them. But there is another challenging aspect to this: figuring out how these early assemblies could make copies of themselves, in the case of vesicles, including both the outer lipid shell and the chemical content inside. Two decades ago, Professor Doron Lancet from the Weizmann Institute of Science, Israel, and colleagues began the unravelling of this enigma.

**THE LIPID SALVATION**

In living cells today, there are four main classes of small organic molecules: amino acids (building blocks of proteins), nucleobases (building blocks of DNA and RNA), sugars, and lipids. It is only lipids that can readily form labile (easily breakable) multi-molecular ensembles, such as the membranes surrounding cells and protocells as well as the much smaller micelle particles, which are known to be simple efficacious chemical factories, competing with present-life complex proteins. Primordial lipid ensembles thus provide both compartmentalisation and chemical specificity that might lead to self-reproduction capacities. The reason lipids can perform such marvels is their amphiphilic nature; they consist of two parts: water attracting heads and water repelling tails. This laid the foundation for Lancet’s ‘lipid first’ alternative for the famous ‘RNA first’ argument.

**THE ROLE OF LIPID MICELLES**

A novel perspective in the research on the origin of life has thus ushered in a paradigm shift. Rather than exclusively focusing on the study of how certain molecules might have formed before life existed, scientists are now exploring how simple lipid molecules, copiously present in ancient oceans, could have
One of the most important findings of the research is that the catalytic networks within lipid micelles (a team of molecules working together, where certain molecules speed up the entry of some others) might have enabled self-reproduction, meaning micelles could reproduce themselves by a mechanism analogous to metabolism in living cells (Figure 2) (Lancet, D, Zidovetzki, R, Markovitch, O, 2018).

**THE GRADED AUTOCATALYSIS REPLICATION DOMAIN (GARD) MODEL**

Over the span of 20 years, Lancet and his team developed the Graded Autocatalysis Replication Domain (GARD) model – a computational chemistry approach that simulates the chemical reactions and processes that could have occurred in the prebiotic era. The GARD model builds upon the earlier foundations of the Collectively Autocatalytic Set (CAS) model (Kauffman, SA, 1986), which predicts that catalytic networks may give rise to self-reproduction. GARD adds

autonomously come together. In a recent paper (Kahana, A, Lancet, D, 2021), the researchers point out that it is the modest nanoscopic micelles that had numerous advantages as early protocells, despite the fact that they did not have an inner water volume (Figure 1). Within these tiny protocellular structures, networks of molecules can collaboratively function, akin to a team, because all molecules are crowded in a miniscule volume, initiating a critical step towards the emergence of life.

**Figure 1:** Nanoscopic micelles: Seeking early protocellular simplicity and efficacy (Kahana, A, Lancet, D, 2021).

Scientists are now exploring how simple lipid molecules, copiously present in ancient oceans, could have autonomously come together.

Importantly, these lipid micelles are far from random assemblies; they possess an innate capacity for self-organisation. However, this organisation is not in terms of spatial position or order of amino acids as in a protein. Instead, the organisation is expressed in terms of composition. In a simplified example, imagine an environment in which all types of lipids have the same concentration. Upon micelle growth driven by molecule accretion, the network dynamics are capable of biasing the inner composition, with some being in high amounts and others being small or rejected entirely. This behaviour is analogous to highly specific membrane transport mechanisms controlling the content of present-day cells.

The truly surprising aspect is that not only do lipid micelles have capacity to self-organise, but they can also maintain a constant composition upon growth. This means that these micelles have a built-in system to ensure that their lipid composition would remain stable as they get bigger. This is called ‘homeostatic growth’, another capability of reproducing living cells. When these entities split into two, the offspring are very similar to each other, just like when living cells reproduce.

**Figure 2:** Micellar self-reproduction driven by homeostatic compositional preservation happens rarely in privileged micelle configurations, called composomes (Lancet, D, Zidovetzki, R, Markovitch, O, 2018).
prospects for the gradual development of bacterium-like Last Universal Common Ancestors (LUCA), passing through a myriad of protocellular quasi-species over hundreds of millions of years. In this evolutionary vein, the team’s research not only delves into the early stages of how life began, but also suggests the potential for a shift from simple micellar protocells to more complex vesicular counterparts. They point out that it is possible to envisage the chemical steps that would lead to new functionalities, including metabolism-like synthesis of new metabolites, vesicular membrane transporters, as well as RNA and its translation device (Kahana, A, Lancet, D, 2021).

CHARTING NEW HORIZONS

The GARD model, as described by Lancet, provides the dynamic journey from simple lipid micelles to complex protocells, offering new insights into how life may have originated and evolved on Earth. It highlights the significance of locally available compounds coming together to form complex, life-like entities. Lancet and his team not only provide a novel understanding but also open up new avenues for research in the domain.

The GARD model, supported by computational simulations and experimental evidence, suggests that growing and splitting lipid assemblies can reach a dynamic state where their chemical composition is self-reproduced.

systems, all having catalysis as their foundation, eventually leading to what we recognise as living organisms.

The GARD model represents a crucial advancement in the study of life’s origin. Its simulations predict the dynamic behaviour as described above, which leads to a reproduction point, termed ‘composome’ (Figure 2). GARD demonstrates the feasibility of self-replication much before the advent of utterly complex molecules such as DNA and RNA, as well as catalysis ahead of complex proteins. This opens new avenues for exploring the emergence of life-like behaviour at very early stages.

The team highlights that the transition from non-life to life involved chemical entities that possessed catalytic properties, which can lead to self-reproduction. These capabilities are considered crucial steps in the emergence of life because they set the stage for the development of more complex, organised, and self-sustaining systems, all having catalysis as their foundation, eventually leading to what we recognise as living organisms.

Experimental findings published over the last few years, as summarised (Kahana, A, Lancet, D, 2021), strengthen the foundation of the GARD model and emphasise the plausibility of early emergence of life-like networks. They bridge the gap between primordial soup and early protocells as described in empirical observations, bringing us closer to understanding the origins of life on Earth. Significantly, GARD simulations also predict that the reproducing point would be reached much more readily than expected, because that point is a dynamic attractor, a state toward which a network tends to progress (Kahana, A, Segev, L, Lancet, D, 2023). The plausibility of reproducing micelles is enhanced by the fact that the oceans of planet Earth can harbour $10^{33}$ micelles (Figure 3) (Lancet, D, Zidovetzki, R, Markovitch, O, 2018).

FROM MICELLES TO COMPLEX PROTOCELLS

Once self-reproduction begins, mutations and natural selection emerge as a possibility. The most important implication of this transition is thus the likelihood of early Darwinian evolution (Segré, D, Lancet, D, 2000). This evolutionary potential opens up new metabolites, vesicular membrane transporters, as well as RNA and its translation device (Kahana, A, Lancet, D, 2021).

CHARTING NEW HORIZONS

The GARD model, as described by Lancet, provides the dynamic journey from simple lipid micelles to complex protocells, offering new insights into how life may have originated and evolved on Earth. It highlights the significance of locally available compounds coming together to form complex, life-like entities. Lancet and his team not only provide a novel understanding but also open up new avenues for research in the domain.
Behind the Research

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Research Objectives

The team developed a model for reproduction at life’s origin via spontaneous selective clustering of small lipid molecules in the primordial environments.

Detail

Bio
Professor Doron Lancet completed his BSc degree in chemistry, PhD in immunology, and postdoctoral training at Harvard and Yale. As a professor at the Weizmann Institute of Science, Israel, Lancet pioneered molecular studies of olfaction and human genomics, and then developed a chemo-computational model, experimentally supported, showing how lipid assemblies can reproduce chemical information. This provides a pre-RNA path for life’s origin under prebiotic conditions.

Amit Kahana received his BSc in biology from Ben-Gurion University, and his MSc on the GARD origin of life model with Professor Doron Lancet at the Weizmann Institute of Science, both in Israel. He is now studying for his PhD in chemistry at the University of Glasgow, UK in the laboratory of Professor Lee Cronin. The main focus of his current research is the origin of life and assembly theory for mapping chemical complexity space.

Roy Yaniv received his BSc in biology and MSc in cell biology and immunology from Tel-Aviv University, Israel. He is a scientific editor and writer in the field of the origin of life in Lancet’s laboratory, at the Weizmann Institute of Science, Israel. He is also a scientific editor at the Davidson Institute of Science Education in Israel, a non-profit organisation aimed at promoting and nurturing scientific education. In parallel, he heads the post-production editing department at Henry Stewart Talks (HSTalks), a British company that provides audio-visual presentations in the fields of biomedicine and life sciences for institutions worldwide.

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References


Personal Response

What do you believe are the most promising implications of your research on the origins of life for our understanding of life’s emergence on Earth and potentially, elsewhere in the Universe?

Our research provides a rigorous chemical framework that constitutes a complete path from simple chemistry to bacterial complexity. We demonstrated that spontaneously formed amphiphile assemblies, initially nanoscopic micelles, will naturally undergo chemical catalytic modifications, leading to self-reproduction. This generates a population with some mutations (quasi-species) that can undergo natural selection and therefore, portray early Darwinian evolution. Along this path, micelles can evolve into more elaborate vesicular protocells that can endogenously synthesise new and larger molecules, leading to increasing protocellular complexity. Given half a billion years of evolution, it is not unlikely that a bacterium-like Last Universal Common Ancestor (LUCA) will emerge. As catalytic reproducers appear highly prevalent on an entire planet, and a network reproduction state is a dynamic attractor, the likelihood of extraterrestrial life seems much higher than anticipated.