THIRTY YEARS OF RESEARCH ON THE ORIGIN OF LIFE

BY HAROLD MOROWITZ
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Right: Harold Morowitz. **Above:** Gathered around SFI's first workstations during the 1987 "Matrix of Biological Knowledge" workshop in Santa Fe are (clockwise from back left) Jotun Hein, Chris Overton, Kimberle Koile, and an unknown participant.

Biogenesis – the generation of a life form from nonliving material – was among the first topics of interest at SFI. Manfred Eigen and Peter Schuster were early consultants. Their 1978 paper on "The Emergence of Hypercycles," which postulated the self-reinforcing linkage of reaction cycles as an explanation for the self-organization of prebiotic systems, was the kind of big-question research envisioned for Santa Fe, and the paper was widely acclaimed for its potential to advance the study of life's origin.

Over SFI's 30-year history, these two leading scientists have served on the Institute's Science Board, as journal editors, and as external faculty and visitors, and they continue to serve today.

By 1987, the explosion of computer studies in biology led to the call for a summer workshop on what we called the "Matrix of Biological Knowledge." Having obtained modest support from the National Institutes of Health (NIH), the Department of Energy (DOE), and the Sloan Foundation, the workshop's organizing committee – made up of representatives chosen by the funding organizations – was looking for an institution that could supply housing and flexible work space, and that would not eat up our limited funds in overhead.

George Bell of Los Alamos National Lab (LANL), who was a consultant to the group, told the planning committee about the newly born Santa Fe Institute, the Institute's cooperative arrangement for meeting space with St. John's College, and his perception of a willingness on SFI's part to negotiate overhead with programs that fit their vision.

A few weeks later, George Cowan and I were in the Mother Superior's office in the newly rented Cristo Rey Convent, the Institute's then-headquarters. We negotiated with remarkable speed. After all, we needed each other, and Cowan introduced Ginger Richardson, who was to handle our arrangements with St. John's.

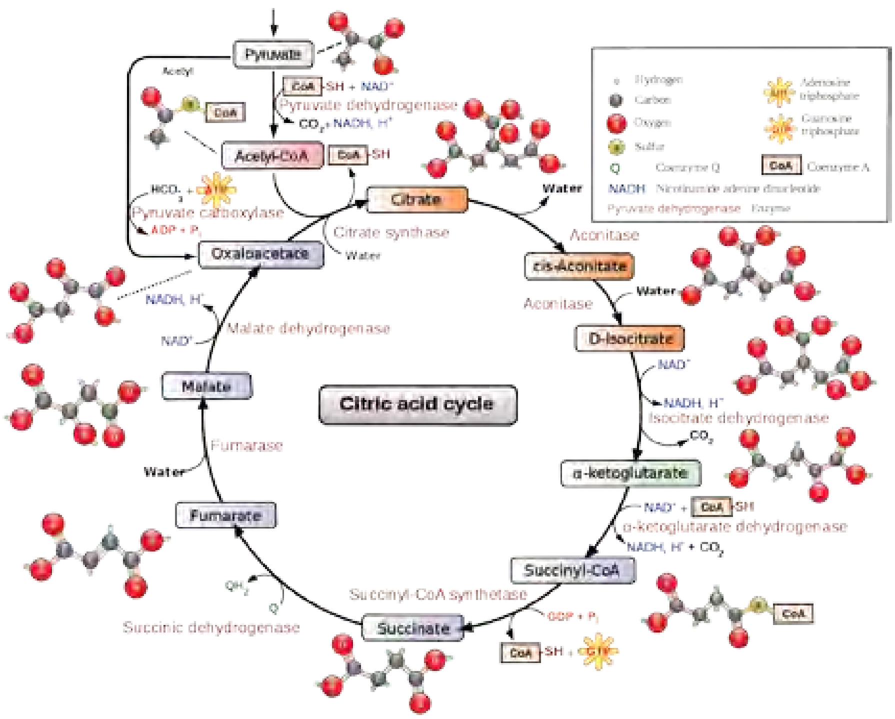
The summer program was to be run by biophysicist Temple Smith, then of Harvard; James Willett, then of NIH; and myself, then of Yale. We recruited a faculty to be in attendance from one day to one month. Advertisements in the journals *Nature* and *Science* brought us 29 participants, largely graduate students, postdocs, junior faculty members, and industrial representatives.

A few computers on loan from IBM put us in business. Within a week of starting, the

RIGHT: NERISSA ESCANLAR; ABOVE: SFI ARCHIVE

Reading **George Cowan's memoir** 20 years later I saw his hidden hand at work. He wrote: "I felt that the Morowitz/Kauffman interests represented the potentially most important theme at SFI and gave them my full support." **I suspect Kauffman and I still have a bit of arguing to do.** — Harold Morowitz biologists and chemists were at the keyboards and the computer scientists were poring over Lehninger or Stryer, leading scholars whose textbooks shed light on our emerging understanding of bioenergetics and metabolic chemistry. (For those interested, a 200-page report of the summer's activity is still available.)

Under Cowan's unseen hand, we were visited by Garrey Carruthers, then-Governor of New Mexico; Charles DeLisi of DOE; and Pete Domenici, then-U.S. Senator from New Mexico. Thus, the broader world was informed of what we were up to. My invitations brought William Gay of NIH, James Rodman of the National Science Foundation (NSF), and Harold Schoolman of the National Library of Medicine, who helped introduce us to the scientific community. The list of faculty and attendees of this workshop are now among the leaders in biological computer informatics and large-scale databases, names like Bruce Schatz, Peter Karp, Jotun Hein, Anthony



The citric acid cycle is a series of chemical reactions used by aerobic living organisms to generate energy. The cycle provides precursors for the biosynthesis of compounds.

Nicholis, and Chris Beecher.

Thoughts about life's origin were among the many perspectives being discussed at St. John's that summer. Around that time, MacArthur Fellow Stuart Kauffman was putting his thoughts to biogenesis at the SFI convent, and Chris Langton at LANL was developing the construct of Artificial Life (A-life). Langton's vision led to major conferences and publications that established the field and its relation to life's origin. He joined the institute in 1991. Kauffman was establishing a viewpoint that autocatalytic loops could self-select from very complex chemical arrays and lead to highly ordered biochemistry. New disciplines were being established.

When I got involved with SFI after the 1987 workshop, the discovery of reductive autotrophs – bacteria growing in the absence of oxygen and synthesizing all organics from one-carbon compounds (i.e., carbon dioxide, carbon monoxide, methane, methanol) – was leading me to the notion of biochemical complexity emerging from the simplicity of the periodic table of elements. Reading George Cowan's memoir 20 years later I saw his hidden hand at work. He wrote: "I felt that the Morowitz/Kauffman interests represented the potentially most important theme at SFI and gave them my full support." I suspect Kauffman and I still have a bit of arguing to do on these approaches.

Walter Fontana arrived at SFI in 1991, beginning a very different and more mathematically formal approach to life's origin. He began a collaboration with Leo Buss of Yale that has been well described by science author and journalist George Johnson in his book *Fire in the Mind*: "In the early 1990s Fontana, the Santa Fe Institute chemist, and his colleague, the Yale biologist Leo Buss, began collaborating on a theory of how life arose and then arrayed itself in a grand architecture of tiers piled on tiers." They were among the original developers of algorithmic chemistry, an important theoretical approach. With his SFI association continuing in one capacity or another, Fontana has developed sophisticated formal approaches to chemistry and how chemical complexity emerges.

Andreas Wagner attended the 1993 SFI summer school and thus began another long-term association as a scientist interested in fundamental questions relating to originating and maintaining planetary life. He was one of the first to stress the importance of metabolism and the metabolic chart. This interest in metabolism is reflected in the work of other SFI researchers since.

Steen Rasmussen was at LANL (beginning in 1988), and he has maintained a constant interaction with scientists at SFI with shared interests in A-life, the origin of life, and synthetic biology. Many of the fundamental studies he has contributed to have been of interest to the origin of life community. He has focused on the physics of complexity and the difference between living and nonliving materials.

In 2000 Eric Smith joined SFI, first as a postdoc, then as faculty, and in 2011 as external faculty. Since the origin of life has been one of his central areas of scholarly research, his work has provided a nucleus for Shelley Copley (University of Colorado), Rogier Braakman, and myself to maintain an ongoing research collaboration on biogenesis during these years.


NOAA

Researchers searching for the origin of life have discovered some of the deepest-branching organisms on the tree of life in extreme environments found near hydrothermal vents and chimneys on the ocean floor.

Discussing our work with the late Carl Woese of the University of Illinois in the early 2000s led to a key moment in origin of life research at SFI when we sought and were awarded a major multi-institution NSF grant titled "From Geochemistry to the Genetic Code." The five-year grant (2005–2010), which was stretched to eight, was centered at the Institute. The principle investigators were Eric Smith (SFI), myself (SFI and George Mason University), Shelley Copley, Nigel Goldenfeld and Carl Woese (University of Illinois), and George Cody (Carnegie Institute of Washington's Geophysics Laboratory). One of the ongoing activities was a one-week conference each summer that provided an opportunity for researchers from diverse disciplines to discuss interdisciplinary problems. The breadth of interest at SFI provided a milieu for this approach.

From 2011 to 2013 while he was at SFI, Rogier Braakman worked on intermediary metabolism, carbon incorporation, and phylogeny. This continued the studies of the NSF program at SFI. He made outstanding progress in the emergence and early evolution of biological carbon fixation.

The NSF grant called for two important outreach activities: a summer school for high school science teachers on the origin of life, one in Santa Fe and another in Fairfax, Virginia; and establishment of a cooperative project with the office of the Secretary of Cultural Affairs of the State of New Mexico (represented by Mimi Roberts) and New Mexico Highlands University to develop a museum

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Stromatolites, pillars formed by the sedimentary deposit of microorganisms, are evidence of the first single-celled microbial life thought to have arisen some 3.5 billion years ago. Here, modern stromatolites in Shark Bay, Australia.

presentation on the origin of life. That exhibit, completed in 2012, is now on permanent display at the Museum of Natural History in Albuquerque and offers an accessible summary of the current understanding of the chemical origin of life.

Where are we today? The thrust of the SFI approach has brought us to the point where we understand that life is a planetary phenomenon, and we comfortably accept life as the fourth geosphere along with the lithosphere, the atmosphere, and the hydrosphere. We are comfortable about minerals evolving along with the biota. Core metabolism is on the order of 3.8 billion years old and intermediary metabolism has been relatively unchanged over that period. Life's emergence consists of layers separated by phase changes (floors and ceilings), leading to separable entities and eventually to individuality, making Darwinian evolution possible.

We have an impressive and growing understanding of the chemistry and geochemistry that take us from the periodic table of the elements to the monomer level. Polymers present a level of complexity with a far greater range of chemical sophistication. An active site may be influenced by four or five side chains, allowing a combinatoric explosion of possibilities tamed by the underlying small-molecule ecological constraints.

This is an aspect of the emergence of cells and the protein nucleic acid coding for which we still lack a satisfactory theoretical approach. There are three higher forms of organization: the emergence of ribosomal translation of peptides and with it a genetic code, the integration of redox and phosphate energy systems, and the compartmentalization observed in cells.

In other words, we are able to describe levels of complexity known to exist in present-day organisms, but we lack a satisfactory understanding of how they became that way. This constitutes a challenge to today's scientists interested in the origin and complexity of life.

The answers to these still-big questions loom over the Sangre de Cristo Mountains and in the minds of the scientists here and around the world. Extracting them should provide the Institute and other scientists plenty to do in this area for the next 30 years. ◀

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