

An oil painting of Hungarian biologist Tibor Gánti.
PAINTING BY LÁSZLÓ GULYÁS

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He may have found the key to the origins of life. So why have so few heard of him?

Hungarian biologist Tibor Gánti is an obscure figure. Now, more than a decade after his death, his ideas about how life began are finally coming to fruition.

BY MICHAEL MARSHALL

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PUBLISHED DECEMBER 14, 2020 • 13 MIN READ

When biologist Tibor Gánti died on April 15, 2009, at the age of 75, he was far from a household name. Much of his career had been spent behind the Iron Curtain that divided Europe for decades, hindering an exchange of ideas.

But if Gánti's theories had been more widely known during the communist era, he might now be acclaimed as one of the most innovative biologists of the 20th century. That's because he devised a model of the simplest possible living organism, which he called the chemoton, that points to an exciting explanation for how life on Earth began.

The origin of life is one of science's most perplexing mysteries, partly because it is several mysteries in one. What was Earth like when it formed? What gases made up the air? Of the thousands of chemicals that living cells now use, which ones are essential—and when did those must-have substances arise?

Perhaps the hardest question is the simplest: What was the first organism?

For scientists attempting to re-create the spark of life, the chemoton offers an attractive target for experiments. If non-living chemicals can be made to self-assemble into a chemoton, that reveals a pathway by which life could have formed from scratch. Even now, some research groups are edging startlingly close to this model.

And for astrobiologists interested in life beyond our planet, the chemoton offers a universal definition of life, one not tied to specific chemicals like DNA, but instead to an overall organizational model.

"I think Gánti has thought deeper about the fundamentals of life than anybody else I know," says biologist Eörs Szathmáry of the Centre for Ecological Research in Tihany, Hungary.

Life's beginning

There is no agreed scientific definition of life, though not for want of trying: A 2012 paper identified 123 published definitions. It's challenging to write one that encompasses all life but that excludes everything non-living with life-like attributes, such as fire and cars. Many definitions say

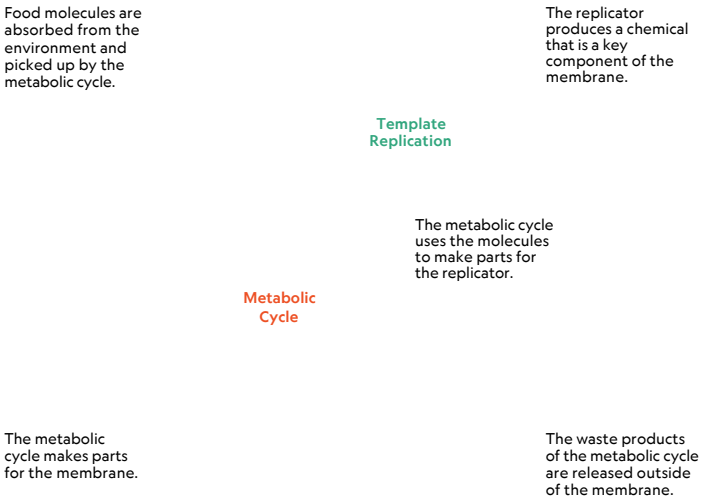
that living things can reproduce. But a rabbit, or a human, or a whale on its own cannot reproduce.

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In 1994 a NASA committee described life as "a self-sustaining chemical system capable of Darwinian evolution." The word "system" can mean an individual organism, a population, or an ecosystem. That gets around the reeproduction problem, but at a cost: vagueness.

How a chemoton works

A theoretical model for the simplest form of life requires three interlocking mechanisms: a **metabolic cycle**, for turning food into energy; **template replication**, for reproduction; and a **membrane**, to delineate the organism.



CHRISTOPHER TURNER
SOURCE: LEONARDO BICH AND SARA GREEN, *SYNTHESE*, APRIL 2017

What few people knew at the time was that Gánti had offered another way two decades earlier.

Tibor Gánti was born in 1933 in the small town of Vác, in central Hungary. His early life was colored by conflict. Hungary allied itself with Nazi Germany in World War II, but in 1945 its army was defeated by the Soviet Union. The totalitarian regime would dominate eastern Eurasia for decades, with Hungary becoming a satellite state, like most other eastern European countries.

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Fascinated by the nature of living things, Gánti studied chemical engineering before becoming an industrial biochemist. In 1966 he published a book on molecular biology called *Forradalom az Élet Kutatásában,* or *Revolution in Life Research*, a dominant university textbook for years—partly because few others were available. The book asked whether science understood how life was organized, and concluded that it did not.

In 1971 Gánti tackled the problem head-on in a new book, *Az Élet Princípiuma,* or *The Principles of Life.* Published only in Hungarian, this book contained the first version of his chemoton model, which described what he saw as the fundamental unit of life. However, this early model of the organism was incomplete, and it would take him another three years to publish what is now regarded as the definitive version—again only in Hungarian, in a paper that is not available online.

Miracle year

Globally, 1971 was something of a banner year for research into the origin of life. In addition to Gánti's underdog work, science put forward two other important theoretical models.

The first came from American theoretical biologist Stuart Kauffman, who argued that living organisms must be able to copy themselves. In speculating about how this might have worked before cells formed, he focused on mixtures of chemicals.

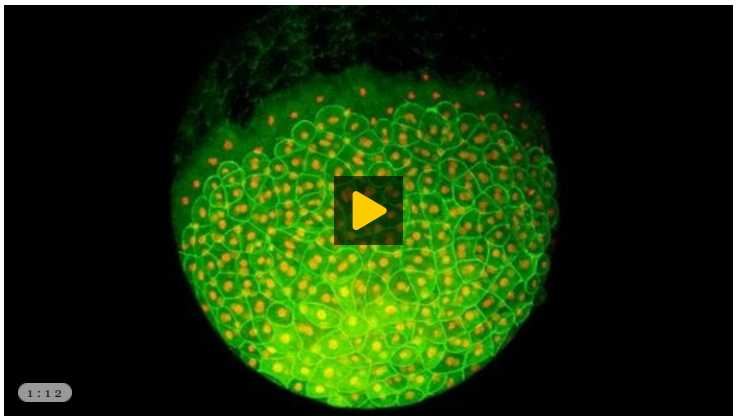
Suppose, he argued, that chemical A drives the formation of chemical B, which then drives the formation of chemical C, and so on, until something in the chain makes a fresh version of chemical A. After one cycle, two copies of each set of chemicals will exist. Given sufficient raw materials, another cycle will yield four copies, and continue exponentially.

Kauffman called such a group an "autocatalytic set," and he argued that such groups of chemicals could have been the foundation for the first life, with the sets becoming more intricate until they produced and used a range of complex molecules, such as DNA.

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In the second idea, German chemist Manfred Eigen described what he called a "hypercycle," in which several autocatalytic sets combine to form a single larger one. Eigen's variant introduces a crucial distinction: In a hypercycle, some of the chemicals are genes and are therefore made of DNA or some other nucleic acid, while others are proteins that are made-to-order based on the information in the genes. This system could evolve based on changes—mutations—in the genes, a function that Kauffman's model lacked.

Gánti had independently arrived at a similar notion, but he pushed it even further. He argued that two key processes must take place in every living organism. First, it has to build and maintain its body; that is, it needs a metabolism. Second, it has to have some sort of information storage system, such as a gene or genes, that could be copied and passed on to offspring.



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Gánti's first version of this model was essentially two autocatalytic sets with distinct functions that combined to form a larger autocatalytic set—not so different from Eigen's hypercycle. However, the following year Gánti was questioned by a journalist who pointed out a key flaw. Gánti

assumed the two systems were based on chemicals floating in water. But left to themselves, they would drift apart, and the chemoton would "die."

The only solution was to add a third system: an outer barrier to contain them. In living cells, this barrier is a membrane made of fat-like chemicals called lipids. The chemoton had to have such a barrier to hold itself together, and Gánti concluded that it also had to be autocatalytic so that it could maintain itself and grow.

Here at last was the full chemoton, Gánti's concept of the simplest possible living organism: genes, metabolism, and membrane, all linked. The metabolism produces building blocks for the genes and membrane, and the genes exert an influence over the membrane. Together they form a self-replicating unit: a cell so simple it could not only arise with relative ease on Earth, it could even account for alternate biochemistries on alien worlds.

Forgotten model

"Gánti captured life really well," says synthetic biologist Nediljko Budisa of the University of Manitoba in Winnipeg, Canada. "It was a revelation to read." However, Budisa discovered Gánti's work only around 2005. Outside of Eastern Europe, it remained obscure for decades, with only a few English translations on the market.

The chemoton appeared in English in 1987, in a paperback with a rather rough translation, says James Griesemer of the University of California, Davis. Few noticed. Szathmáry later gave the chemoton pride of place in his 1995 book *The Major Transitions in Evolution*, co-written with John Maynard Smith. This led to a new English translation of Gánti's 1971 book, with additional material, released in 2003. But still the chemoton remained niche, and six years later Gánti was dead.

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To some extent, Gánti did not help his model find favor: he was known to be a difficult colleague. Szathmáry says Gánti was stubbornly wedded to his model, and paranoid to boot, making him "impossible to work with."

But perhaps the biggest problem for the chemoton model was that in the last decades of the 20th century, the trend in research was to strip away the complexity of life in favor of ever more minimalist approaches.

For example, one of the most prominent hypotheses still in vogue today is that life began solely with RNA, a close cousin of DNA.

Like its more famous molecular relative, RNA can carry genes. But crucially, RNA can also act as an enzyme and accelerate chemical reactions, leading many experts to argue that the first life needed nothing but RNA to get started. However, this RNA World hypothesis has gotten pushback, particularly because science hasn't found a type of RNA that can copy itself unaided—think of RNA-powered viruses like the coronavirus that need human cells to reproduce.

Other researchers have argued that life began with proteins and nothing else, or lipids and nothing else. Such ideas are a long way from Gánti's integrated approach.

A real chemoton?

However, scientists in this century have turned the tide. Researchers now tend to emphasise the ways the chemicals of life work together, and how these cooperative networks might have emerged.

Since 2003, Jack Szostak of Harvard Medical School and his colleagues

have built increasingly lifelike protocells: simple versions of cells containing a range of chemicals. These protocells can grow and divide, meaning they can self-replicate.

In 2013, Szostak and his then-student Kate Adamala persuaded RNA to copy itself within a protocell. What's more, the genes and membrane can be coupled: as RNA builds up inside, it exerts pressure on the outer membrane, encouraging the protocell to grow larger.

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Szostak's research "is very Gánti-like," says synthetic biologist Petra Schwille of the Max Planck Institute for Biochemistry in Martinsried, Germany. She also highlights the work of Taro Toyota at the University of Tokyo in Japan, who has made lipids inside a protocell, so that the protocell can grow its own membrane.

One argument against the idea of a chemoton as first life has been that it requires so many chemical components, including nucleic acids, proteins, and lipids. Many experts found it unlikely that these chemicals would all arise from the same starting materials in the same place, hence the appeal of stripped-back ideas like the RNA World.

But biochemists have recently found evidence that all the key chemicals of life can form from the same simple starting materials. In a study published in September, researchers led by Sara Szymkuć, then at the Polish Academy of Sciences in Warsaw, compiled a database using decades of experiments that sought to make life's chemical building blocks. Starting with just six simple chemicals, like water and methane, Szymkuć found it was possible to make tens of thousands of key ingredients, including the basic components of proteins and RNA.

None of these experiments has yet built a working chemoton. That may simply be because it's tricky, or it may be that Gánti's exact formulation is not quite how the first life worked. Still, what the chemoton gives us is a way to think about how life's components work together, which increasingly drives today's approaches to understanding how life got started.

It is telling, adds Szathmáry, that citations of Gánti's work are now accumulating rapidly. Even if the exact details differ, the current approaches to the origin of life are much closer to what he had in mind—an integrated approach that is not focused on just one of life's key systems.

"Life is not proteins, life is not RNA, life is not lipid bilayers," Griesemer says. "What is it? It's all those things hooked together in the right organization."

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Michael Marshall is a science writer based in Devon, U.K. His book *The Genesis Quest* is about the origin of life on Earth and is out now. Follow Michael on Twitter.

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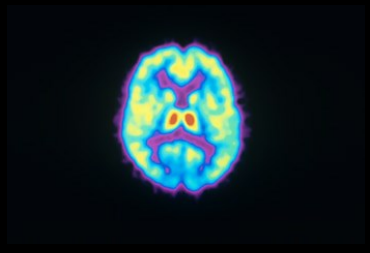
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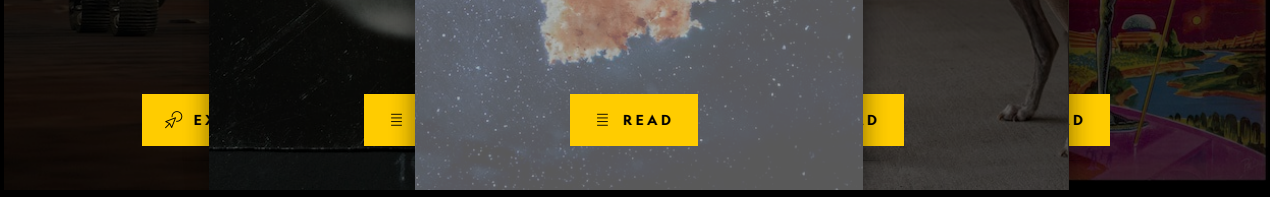


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