Book Review

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The Principles of Life Tibor Ganti. (2003, Oxford University Press.) £70.00, $168.00, 220 pages.

To review this book is in some ways analogous to reviewing Gregor Mendel's *Experiments in Plant Hybridization (1865)* shortly after it had been rediscovered by Hugo de Vries in 1889. Both works contained dormant insights of fundamental importance.

In 1971 Tibor Ganti, a chemical engineer living in Communist Hungary, wrote a book called *Az elet principiuma* (The Principles of Life). It passed largely unnoticed in the West. Now in translation with essays from his other books, *The Principles of Life* is an original, logical, and parsimonious framework for thinking about life. Moreover, it has inspired a research program to synthesize minimal life from scratch.

His theories foreshadow and anticipate the cores of systems biology, evo-devo, and developmental systems theory by several decades. The book is the work of a genius, according to the late John Maynard Smith. As Ross Ashby applied cybernetics to the study of the brain, Ganti has applied cybernetic ideas with extreme clarity to the study of the fundamental organization of life.

The book is beautifully written for the layman. It is philosophically rigorous and introduces chemical models of minimal cells that are easily understood by non-chemists. The OUP edition is critically commentated by Eors Szathmary, a theoretical biologist who studied under Ganti, and James Greisemer, an eminent philosopher of biology. I present an outline of Ganti's theory below.

Ganti characterizes a unit of life as a unit that cannot be decomposed without losing any of the following properties: A unit of life performs metabolism, it is inherently stable, it contains an informational subsystem, and it is regulated and controlled. The simplest extant units of life are cells. Viruses are excluded because they have no metabolism. A biosphere of viruses lacking cells for their replication would face disaster. Neither are clouds or candle flames units of life, for they lack a subset of components that self-referentially constrain the properties of other parts of themselves, that is, an informational subsystem. Everyone would agree that a mule is alive; therefore, reproduction and hereditary are unnecessary features of units of life, but are clearly necessary for the continuing existence of a biosphere composed of units of life.

Units of life can be hierarchically organized. For example, a human is composed of cells that are themselves units of life. But the human itself is also an indivisible bounded unit of life, possessing a higher-order metabolic organization with specialized organs such as a gut and a brain that is a specialized informational control system. Nation states consisting of human units of life could also be considered to share the characteristics of life, since they arguably have a metabolism consisting of primary production, import and export, an informational control system consisting of government at its various levels, and a boundary that makes the country (to some extent) an indivisible unit. They are controlled and regulated dissipative structures.

Contrast this with John Maynard Smith's definition of units of evolution as units that multiply and have hereditary variation [8]. He goes on to define natural selection as an *algorithmic process* that occurs where there are units of evolution that have differential fitness.

One can immediately see that units of life and units of evolution are only partially overlapping sets. Not all units of evolution are alive; for example, entities in a genetic algorithm, viruses, and RNA molecules replicating using a Q-beta replicase are all units of evolution but not units of life. And not all units of life are units of evolution; for example, mules are not. All existing units of evolution depend on units of life for their maintenance. Now we have the conceptual machinery to ask ourselves whether this has always been the case. But let us continue with Ganti's argument for now.

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Ganti asked what the minimal unit of life could have been. The minimal unit of life is the unit of life that could exist without requiring another unit of life for its maintenance. He begins by reinterpreting Leibniz's notion that "living bodies are machines up to infinity" by asserting that the minimal unit of life would have been a fluid (chemical) automaton, in contrast to a mechanical automaton. This is because reproduction of properties in the fluid state is less subject to geometric constraints than in the solid state. For example, a chemical clock consisting of the oscillating Belousov-Zhabotinskii reaction in a test tube remains a clock when the contents of the tube are halved. The same is clearly not the case for the random halving of a wind-up mechanical clock, or for the random halving of the self-replicating machine of another great Hungarian, John von Neumann. Ganti's insight antedates the recent shift in interest in cellular automata and nanotechnology towards fluid self-reproduction [2, 15].

Ganti proposed in explicit chemical detail a design for a fluid automaton that satisfied the requirements for a minimal unit of life. This organization he called the chemoton. The chemoton is to a prokaryote what a glider is to a stealth fighter. Whereas a glider flies almost by itself, a stealth fighter depends on vast amounts of electronic control. Nevertheless, no amount of control would help a stealth fighter, unless it shared some fundamental properties with a glider, such as wings. Ganti hypothesizes that the chemoton could have existed before encoded catalysts, that is, before the capacity of nucleotide sequences to replicate and fold into shapes that catalyzed (i.e., channeled, regulated, and controlled) metabolic reactions, in a manner analogous to electronic control in the stealth fighter. He hypothesized a fundamental organization of living systems that underlies catalytic control and attempted thus to separate the regulated from the regulating system. We should view Ganti's work in relation to many of his contemporaries who were writing rather loosely about life as purely informational, often referring to sequences of DNA as alive, conflating units of evolution with units of life.

The chemical detail in which Ganti specified the chemoton allowed people to write computer simulations as early as 1975 [1, 3]. Recently there has been an explosion of models of the chemoton and its variants [4, 9, 11]. This is in stark contrast to Maturana and Varela's autopoiesis theory, contemporary with Ganti's theory, which also attempted to define the organization of living systems. Models of autopoiesis are typically conceptual and not grounded in real chemistry [10]. These models give little insight into how to instantiate a physical autopoietic system. *The Tree of Knowledge* is to *The Principles of Life* what a Zen koan is to Euclid's *Elements*.

What is the chemoton? A chemoton is a design for a protocell that consists of three coupled autocatalytic subsystems. An autocatalytic system is one described by the following general chemical equation: $X + A \rightarrow 2A$. At least one A is required for the production of more A, using X as food. The first subsystem of the chemoton is a boundary consisting of a phospholipid membrane. Such a membrane grows by spontaneous incorporation of membrane molecules. A major research effort is currently underway to construct self-replicating protocells and micelles [13]. The membrane encloses the second subsystem: a formose cycle metabolism that eats formaldehyde, a food molecule that forms spontaneously, on the early Earth and in Stanley Miller's famous primordial soup physical simulator, to produce a vast array of sugars such as ribose (the backbone of RNA) and glycerol (a constituent of membranes). The third subsystem is the informational subsystem, which consists of non-enzymatic self-replicating RNA templates. One crucial insight is that the system is stoichiometrically coupled. This means that equal quantities of each subsystem are always produced, giving the system considerable robustness to variations in the actual rates of each reaction. Enclosed metabolism and stoichiometric coupling has been absent in recent attempts to synthesize protocells [7, 12], for it is not trivial to obtain.

Whether a chemoton is possible depends on a host of empirical questions. The importance of chemoton theory is that it has allowed these questions to be framed explicitly.

The first question is: How plausible is the formose cycle metabolism as a basis for the minimal unit of life? Chemists have managed to make a formose cycle metabolism in a flow reactor, and have shown that its constituents grow autocatalytically, but the problem is that it has a notorious capacity to engage in side reactions that deplete its constituents faster than they can be produced. The chemical generative capacity of the formose cycle is what makes it attractive, but it is also its downfall. However, there is growing support for metabolic evolution. Recent computer models have shown that natural selection acting between protocells containing a formose cycle metabolism could select for beneficial satellite autocatalytic cycles that act as non-encoded catalysts of the core autocatalytic cycle, even in the absence of templates [5]. Recent bioinformatics studies show that all living systems contain an autocatalytic core based on a small set of non-encoded catalysts; for example, at least one molecule of ATP is required to make more molecules of ATP (Eors Szathmary, personal communication). Chemical experiments are planned that will enclose formose cycle metabolisms within lipid compartments, with artificial selection being used to select non-encoded catalysts that maximize the yield of one of the many side-reaction sugars.

The second question is: How plausible is non-enzymatic template replication? No one has managed to make a sequence any longer than six nucleotides in length that is capable of self-replication in the absence of already evolved replicase enzymes [14]. Recent computer simulations and experiments have shown that the central problem is uncontrolled elongation of nucleotide strands that sequester motifs that could potentially self-replicate [15]. One proposed solution is that the earliest sequences capable of replicating themselves may have had the capacity to cut themselves out of elongating strands.

Finally, let us return to the question that Ganti has allowed us to ask: Could units of evolution exist before units of life? Leaving aside the clay replicators of Cairns-Smith for now, what is becoming clear from recent work on protocell synthesis is that considerable self-organization or natural selection would have been required for a chemoton to form. In what order metabolism, boundary, and template replication system became assembled is not known. However, since nucleotides require a complex ordered metabolism for their synthesis, it is likely that metabolic organization must have preceded template replication. Computer models show that a metabolism enclosed in a compartment capable of multiplication (by phase separation and external agitation) is a unit of evolution with limited heredity [6]. Such an intermediate stage may have been necessary for the discovery by natural selection of increasingly complex forms of self-reference made possible by nucleotide-based template replication.

In summary, *The Principles of Life* is essential reading for anyone interested in the fundamental organization of living units and their origin. It is especially suited to researchers in artificial life because it contains the seeds of countless models of chemical self-replicating systems. Such systems are so complex that chemists will need novel simulation methods to understand them. Furthermore, it may well be that to produce open-ended evolution, the evolutionary algorithm must be physically situated and embodied. Ganti's chemoton is central to this endeavor and is at the heart of many real discoveries.

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