How nonequilibrium thermodynamics speaks to the mystery of life

Stephen Ornes, *Science Writer*

In his 1944 book *What is Life?*, Austrian physicist Erwin Schrödinger argued that organisms stay alive precisely by staving off equilibrium. "How does the living organism avoid decay?" he asks. "The obvious answer is: By eating, drinking, breathing and (in the case of plants) assimilating. The technical term is metabolism" (1).

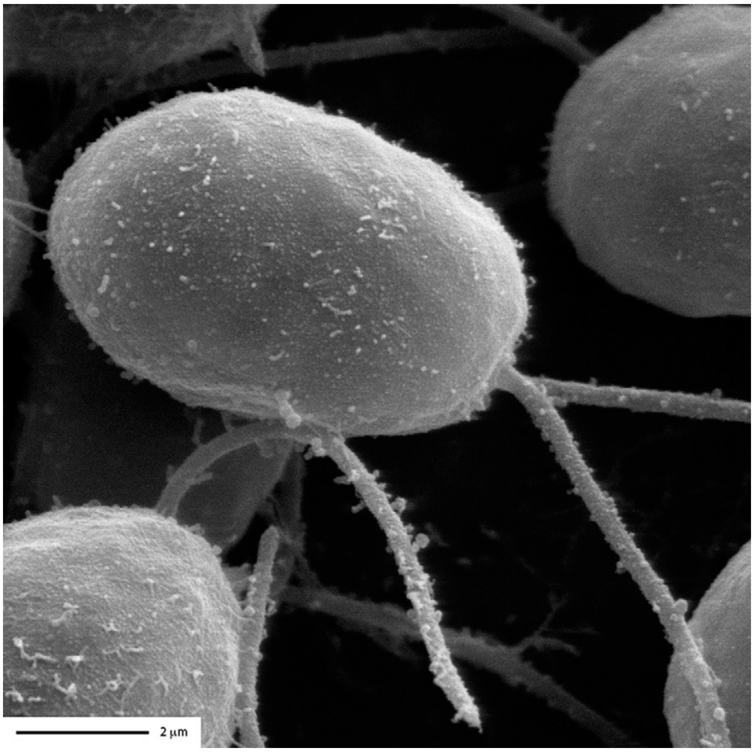
However, the second law of thermodynamics, and the tendency for an isolated system to increase in entropy, or disorder, comes into play. Schrödinger wrote that the very act of living is the perpetual effort to stave off disorder for as long as we can manage; his examples show how living things do that at the macroscopic level by taking in free energy from the environment. For example, people release heat into their surroundings but avoid running out of energy by consuming food. The ultimate source of "negative entropy" on Earth, wrote Schrödinger, is the Sun.

Recent studies suggest something similar is happening at the microscopic level as well, as many cellular processes—ranging from gene transcription to intracellular transport—have underlying nonequilibrium drivers (2, 3).

Indeed, physicists have found that nonequilibrium systems surround us. "Most of the world around us is in this situation," says theoretical physicist Michael Cross at the California Institute of Technology, in Pasadena. Cross is among many theorists who spent decades chasing a general theory of nonequilibrium systems, and he says interesting things happen when systems remain out of equilibrium. "One of the biggest surprises is that driving a system far from equilibrium doesn't just lead to turbulence. It leads to structure, and the most fascinating one is life."

Far from Balanced

Starting about 25 years ago, physicists began to predict that microscopic systems far from equilibrium could, in theory, undergo some decrease in entropy. In 1994, mathematician Denis Evans and chemist Debra Searles mathematically proved the "Fluctuation Theorem," which says that it's possible to observe violations of the second law in large systems, although decreasing exponentially in likelihood over time (4). Since then, physicists have derived several similarly surprising theoretical predictions about negative entropy, which are often grouped together as fluctuation theorems (5). Such predictions don't break the second law of thermodynamics as much as bend or extend it. They show that the second law, originally formulated to describe macroscopic systems like engines, actually describes average behavior.



Attributes of living organisms, such as the flapping hair-like flagella of these single-celled green algae known as *Chlamydomonas*, are providing insights into the thermodynamics of nonequilibrium systems. Image courtesy of Dartmouth Electron Microscope Facility.

The kinds of structures that arise far from equilibrium are well documented and poorly understood. Convection is a good example: if the bottom of a cup of water is heated, then physics equations explain how that heat dissipates through the liquid in stripe-like shapes. But if the heat source remains in contact with the cup, so the bottom is perpetually warmed, then the heat dispersion forms intricate patterns that aren't easy to predict or understand with physics. These baffling structures appear not just in fluid convection but at many scales.

Gas giant planets in the outer solar system display characteristic striped patterns in their atmospheres, driven by nonequilibrium conditions. Snowflakes have sixfold symmetry, reflecting the crystal structure of water molecules, but the intricate patterns on their branches

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are a nonequilibrium phenomenon. Those patterns change over time as the snowflake falls and grows.

"Patterns in nonequilibrium systems tend to be time-dependent and irregular," says Henry Greenside, a theoretical physicist at Duke University in Raleigh, North Carolina. "They endlessly change from one structure to another, in a rather unpredictable way."

Physicists have been observing nonequilibrium processes—those driven by outside forces—since the 19th century. The Navier–Stokes equations, which describe how fluids move, can describe what happens far from equilibrium. But describing what happens isn't the same as explaining when or why it occurs; scientists still don't understand the underlying mechanics that drive pattern formation. More recently, in the mid-to-late 20th century, researchers used high-precision, detailed experiments to try to establish a unifying theory of nonequilibrium thermodynamics that would bring formalism to the field: something like the case of statistical mechanics, which provides a molecular explanation for equilibrium behavior.

Although that line of research did yield insights into some systems—those that weren't too far from equilibrium—physicists' efforts largely stalled, says Greenside. He notes that theorists ran into an intellectual wall, unable to explain the diversity of patterns or when they occur. "With the turbulence of stars, for example, it's hard to do systemic experiments. And you can't recreate the Earth's atmosphere in any simple way," says Greenside. "Most of the patterns we still don't understand. We don't know how one pattern switches to another."

Into the Cell

More recently, physicists searching for universal principles have been "dwarfed," Greenside says, by researchers pursuing nonequilibrium phenomena in other fields, including fluid dynamics, plasma physics, meteorology, astrophysics, and biology. The cell in particular has attracted a lot of attention because it's a hotbed of nonequilibrium activity. Recent studies have demonstrated how nonequilibrium systems play a role in gene transcription (2), diffusion in the cytoplasm (6), transporting material between cells with molecular motors (7), cell signaling (8), and other processes.

"In living systems, recently, there have been some genuine advances in understanding universal ways in which they are out of equilibrium," says theoretical physicist Fred MacKintosh at Rice University in Houston, Texas. MacKintosh studies molecular nonequilibrium behaviors to better understand movements within cells. In previous work, he and his collaborators tracked such processes by attaching single-walled carbon nanotubes to transport proteins within a cell (9). The nanotubes glow in the near-infrared part of the spectrum, giving away the movements of the proteins.

Earlier this year, MacKintosh's team published a new method that identifies nonequilibrium processes at the cellular level (10). Their strategy, inspired by the well-known nonequilibrium behavior of a microorganism flapping hair-like flagella, involves studying the "detailed balance" within a system: that is, the total of all transitions undergone by the system. Equilibrium requires that all transitions be balanced so the net change is zero; in nonequilibrium systems, this balance is broken. A system out of equilibrium will exhibit a fluid motion that looks like a current of some kind.

Ultimately, this method of studying nonequilibrium could even have medical applications. Metabolism, which was mentioned by Schrödinger as an example of nonequilibrium at work, can be seen as a probe for growth of cancerous cells, because they grow out of control compared with healthy cells.

A PET (positron emission tomography) scan exploits this property when imaging cancer: it detects growths by looking for cells with high metabolic activity. MacKintosh says one of his "pipe dreams" is that his method might be scaled up to the tissue-level, where it might be used as a noninvasive probe for cancer.

A useful diagnostic is a long way from the heady underpinnings of the idea. MacKintosh says that although he's still a theorist, and works with other theorists who want to develop a formal theory of nonequilibrium systems, he counts himself among the physicists now more concerned with understanding real cases in the natural world. Nonequilibrium thermodynamics may have roots in theoretical physics, but after more than a century of gestation, the idea is gaining followers among scientists chasing the secrets of life.

"Clearly, living systems have to be out of equilibrium," says MacKintosh. "What is maybe more surprising is when you find out that there's a common way in which this out-of-equilibrium appears."

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