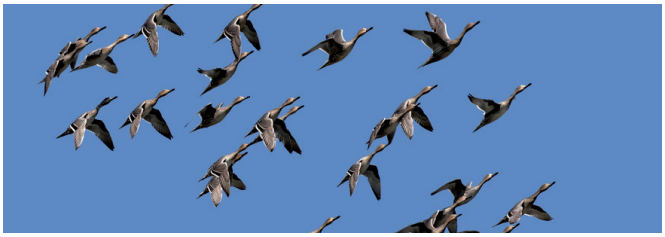
Biophysics

The parts and the whole

by Hubert Filser



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What properties differentiate living systems from non-living entities? LMU biophysicist Erwin Frey is at the forefront of attempts to develop a new understanding of the distinctive features of complex biological systems.

Conversations with Erwin Frey rapidly get down to fundamentals. For a slim volume, published over 70 years ago by the renowned Austrian physicist Erwin Schrödinger, has always fascinated Frey, and lies at the heart of his own research interests. Its title? – What is Life? "Back in the 1940s, Schrödinger asked how cellular processes could be understood in terms of the concepts and methods of physics," Frey explains. "For its time, the book was a daring step. But the question it asked can now be posed in a new context, for cells can now be investigated and measured in ways that were scarcely conceivable then."

Scientists are now in a position to tease out the basic physical principles that make life possible. Not surprisingly, they focus on the functions of the biological cell – the fundamental unit of all living systems. Cells are active, highly dynamic systems. "They possess far more complex attributes than any solid-state system, which exhibits mechanical, electrical or magnetic properties, such as a shear modulus or conductivity, but has no *function*", says Frey, who holds the Chair of Statistical and Biological Physics at LMU. "Biology is about dynamics, about collective phenomena."

Indeed, cells are now known to consist of networks of interactions based on nothing more than specific binding and dissociation events involving relatively simple molecular interfaces. These elemental processes give rise to complex and dynamic structures, and enable DNA to store the information necessary for cell replication and survival. "And everything is autonomously organized. That's what's really amazing! I want to understand the physics of living systems, in particular those basic properties and processes that are relevant to their self-organization as systems," says Frey. Following in the footsteps of the Munich biophysicist Erich Sackmann who pioneered the new field in the 1990s, and with whom he collaborated for many years, Frey and his colleagues seek to elucidate the processes that enable complex structures to be constructed on the basis of self-organization.

From genes as soloists to gene ensembles

This still young field, located at the interface between biology and physics, is developing at a furious pace. Its practitioners are no longer content to consider individual components of cells and their immediate physiological functions in isolation. They focus on the workings of whole systems, single cells, cell assemblies and whole organisms, viewing them as networks based on genetic information and its expression, metabolic pathways, regulatory circuits and patterns of interaction.

This perspective represents a break with the reductionist tradition in the biosciences. Classical molecular biology largely rested on attempts to link individual genes and their protein products and to particular functions. Molecular geneticists sought to identify the gene for a defined trait – red hair, colon cancer, grooming behavior or whatever. But it soon turned out that things weren't so simple. "We now know that every biological phenomenon is the result of orchestrated interactions between several or very many components," says Frey, "and this new paradigm requires a completely different approach."

So to comprehend cell functions not only requires knowledge of the individual components involved, but also dissecting the patterns of interaction in which these components are engaged. Often the parts can combine and interact in multifarious ways, and it is this very versatility that enables intricate structures with highly complex functions to form.

The tremendous growth in our understanding in recent years is largely attributable to the development of better

investigative techniques. Advances in experimental methods and imaging procedures now make it possible to follow the behavior of individual organelles and proteins in living cells – by labeling them specifically with fluorescent markers, for example. With the aid of so-called optical tweezers one can capture and manipulate single molecules. "We can now deploy eyes and hands at the molecular scale," as Erwin Frey puts it.

"Physicists first take the system apart"

These technological advances in turn form the basis for the next step – the quantitative analysis of processes within the cell itself. "Life is astonishingly complex," Frey remarks, "but its crucial functional units may perhaps be amenable to understanding." He therefore seeks to identify and characterize such basic and – hopefully – simple modules. "The first thing a physicist does is to take the system apart, in order to understand its basic components," he notes, and this is how he approaches living systems. The strategy is based on the premise that Nature can be understood, obeys universal laws and is not the product of an arbitrary system of forces. That does not imply that we seek a complete understanding of life or evolution. But perhaps we can understand what makes cellular processes special."

By studying the building blocks Frey hopes to gain insight into the complexity of the whole. As a biophysicist he views living systems in terms of three basic physical concepts. He analyzes the role of forces, seeks to understand how geometry and spatial organization affect biological pattern formation, and how cells collectively measure distances in space and intervals in time.

The answers to these questions provide the input for a model that captures in basic physical terms the behavior of a generic cell – and ultimately of the whole organism. By probing the behavior of its parts Frey hopes to obtain a comprehensive picture of the whole. It is an arduous but clearly defined undertaking – provided one is willing to follow where it leads and keeps one's eye on the big picture.

When biophysicists think of forces, they automatically think of polymers. So Frey and his colleagues set out to characterize the mechanical properties of the biopolymers that confer upon cells their ability to exert force and/or resist deformation – during cell division, for instance. Evolution has invented two different types of polymers made up of repeating protein subunits that serve these functions: Filaments made up of actin subunits, and microtubules, hollow tubes made of two different forms of tubulin. Together, these polymers provide the basis for the cytoskeleton, and they interact with dedicated molecular motors that convert chemical into mechanical energy. These are the sorts of functional machines that give physicists something to work on.

Resilient and flexible polymer networks

"In the cytoskeleton actin filaments are arranged higgledy-piggledy, like a pile of jackstraws," says Frey. Here, evolution has come up with a way to build a network that is found nowhere else in nature. These amazing protein assemblies are at once resilient and flexible, and can both withstand large loads and exert strong forces. In combination with their myosin motor proteins, actin filaments enable cells to change their form and actively migrate, as they must do when recruited from the circulation to the site of a wound.

The theoretical concepts which the LMU researchers use to understand biophysical phenomena are often drawn from unexpected sources. Thus, some years ago, Frey made a special study of the distribution of flux lines in high-temperature superconductors, because motile actin filaments in cells form very similar patterns. "In both cases, we are dealing with the physics of lines of force," says Frey.

As well as incorporating insights from diverse areas of physics, Frey's theoretical models of cells take the basic mechanical properties of the materials involved into account. Most cells undergo continuous shape change, sending out thin projections on one side, detaching from the substrate on the other. For the actin fibers that form the cytoskeleton (like the microtubules) are polarized, losing subunits from one end, and adding new ones at the other, and this constant reorganization exerts mechanical force. "This is actually how cells move," says Frey, "by means of a very sophisticated recycling system. The same types of building blocks are repeatedly subjected to cycles of assembly and disassembly, and this ongoing modulation of binding forces constitutes the basis for many of the most striking phenomena seen in cells.

Every new insight adds a fragment to the biophysical mosaic, helping to build up a picture of the phenomena that specifically characterize living systems. Beginning from subcellular assemblies, Frey and his team apply these insights to whole cells, and systems comprising many cells. Many cell types form sheets that are held together by protein complexes that act like zippers. When cells migrate, these links must be broken in a controlled manner. To do so, cells must "know" which parts of the assembly are

exerting the most tension, and in what direction. In eukaryotic cells, this information is relayed to the genes that regulate junction detachments by fibers that anchor the nucleus to the cell membrane. "Mechanics and information processing are tightly coupled processes," says Frey.

A centrally localized protein ring

One of Frey's current projects relates to this problem of how cells "read" space, and asks how dividing cells localize the plane of cleavage? In the rod-shaped cell of the bacterium *E. coli*, this plane is marked by a ring of FtsZ protein, which forms in mid-cell and progressively constricts the cell.

Frey's group successfully simulated the process of ring localization, based on a novel mechanism. This involves the three proteins MinC, D and E, which shuttle between the ends of the cell. The shuttling movement is driven by interactions between MinD and MinE, which form a complex that transiently and repeatedly binds to the cell membrane, and is released after some delay upon completion of a biochemical reaction. This cycling behavior gives rise to a bipolar distribution, with both proteins concentrated at the cell poles. MinDE also inhibits polymerization of FtsZ, so the ring forms where the MinDE level is lowest – in mid-cell. The geometry of the cell plays a crucial role in the process, and in spherical *E. coli* mutants the bipolar distribution fails to form.

Again making use of simulations and mathematical modeling, the LMU team also asked how the polymer ring might form on the inner surface of the cell membrane. The results indicated that, above a certain threshold concentration, curved protein polymers can self-organize into rotating rings. The group then went on to show that the driving force behind this instance of pattern formation in E. coli is indeed the concentration of FtsZ subunits available. These two studies underline the importance of the second fundamental principle addressed by Frey's work: pattern formation. "The ability to generate robust patterns in time and space," says Frey, "was decisive for the evolution of cellular organization, and was the key step in the development of multicellular organisms." Pattern formation is thus another cornerstone of life.

From minimal modules to synthetic cells

It can take years to find the right solutions to some questions. How cells and cell assemblies measure distances and times is one such problem. Here Frey cites his studies of how the molecular motor kinesin 8 enables cells to measure the lengths of microtubules. This mechanism is now well understood. Kinesin molecules "walk" along the microtubules, with and without attached freight and always in the same direction. Their unidirectional motion is based on a ratchet mechanism. After the fashion of a cogwheel railway, bulges on the surface of the motor protein fit neatly into the grooves between the subunits of the microtubules. Sometimes a motor protein runs into an obstacle and a traffic jam develops. Crowding phenomena are typical for dynamic systems, and Frey's group analyzes them using computer models and simulations, and compare the results with experimental data.

What properties differentiate living systems from non-living entities? LMU biophysicist Erwin Frey is at the forefront of attempts to develop a new understanding of the distinctive features of complex biological systems. Source: charlathan/fotolia.com

Here lies one of the strengths of the new field: Theoretical and experimental work go hand in hand, and so complement each other. "As theoreticians, we benefit enormously from the work of experimenters," Frey says. "If we ever succeed in reconstructing such systems, it should be possible to combine different minimal modules and, step by step, try to recapitulate important cellular functions. – In the long term, this could contribute to the development of an artificial cell, which would help us toward a better understanding of biological processes."

We now come to the last of the issues

that Frey's work focuses on: the collective movement of cell sheets. Living systems display many surprising kinds of self-organized behavior, including coordinated movements of large numbers of units. Well known examples include the formation of flocks and swarms by birds and fishes. But similar phenomena can be observed at the cellular level. And there are certain basic patterns which, under certain conditions, appear on all of these scales. Understanding why that is so might provide further insights into the general principles that distinguish living from non-living systems.

Bosons on their best behavior

Here too, Frey is willing to strike out in unexpected directions. This perhaps reflects the fact that he has worked in the field of quantum phase transitions, and has an eye for stimulating analogies with phenomena in apparently unrelated areas of physics. "Not so long ago, and just for fun, we had a look at the behavior of a particular class of quantum particles, so-called bosons," he says. Bosons prefer the company of their own kind. If bosons are initially distributed uniformly among all available quantum states, they will congregate over time in states of lower energy, and in the end only a few states will be populated. "The dynamics can be described in the same way as a game in which different strategies compete until only the successful ones are left."

Frey's demonstration that game theory is applicable not only to the analysis of the role of group dynamics in decision-making, but also to systems at the quantum level is a particularly striking example of the power of abstract modelling. The behavior of bacteria faced with the choice of an optimal survival strategy can be analyzed in a similar framework. There thus appears to be an overarching physical principle, which holds equally for us humans, for microbes and for the submicroscopic world of quantum particles. And perhaps this principle is the real goal of Frey long quest. And indeed, this may be the only way one could possibly answer the question: What is Life? "The key to the whole," as Frey asserts, "lies in its parts."

Translation: Paul Hardy

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