Biophysical Reviews and Letters, Vol. 1, No. 3 (2006) 223–230

World Scientific
www.worldscientific.com

THE PHYSICS OF BIO-SYSTEMS: FROM MOLECULES TO NETWORKS*

REINHARD LIPOWSKY

Max Planck Institute of Colloids and Interfaces
Science Park Golm, 14424 Potsdam, Germany†
lipowsky@mpikg.mpg.de

Chief Managing Editor, Biophysical Reviews and Letters

Received 9 January 2006

A Unifying Perspective on Biophysics

Biophysics is pursued by a complex scientific community. On the one hand, it is a highly interdisciplinary subject and involves many different disciplines: physics and biology as well as chemistry, materials science, bioengineering, pharmacology, physiology, and medicine. On the other hand, this large community is divided up into two subgroups, a large and a small one: Researchers in the large subcommunity apply physical methods in order to study *biological systems*, as created by the natural processes of life, whereas researchers in the other subcommunity look at *biomimetic systems*, as synthesized or constructed in the lab, in order to find new physical principles and mechanisms.

This division reflects both the complexity of the systems under consideration and the different traditions in the different disciplines. However, I don't think that it is particularly useful to emphasize these differences, e.g., by distinguishing between 'biological physics' and 'physical biology'. Instead, I would like to focus on the obvious fact that biological and biomimetic systems are intimately related. Indeed, the distinction between these two types of systems has already disappeared on the level of molecules, and I would like to advertise the view that this distinction will eventually disappear on higher levels as well. Thus, as indicated by the title of this editorial, my translation of 'biophysics' is the 'physics of bio-systems' where the term 'bio-systems' is an abbreviation for *both* biological systems *and* biomimetic ones.

*Editorial
†URL: http://www.mpikg.mpg.de/th

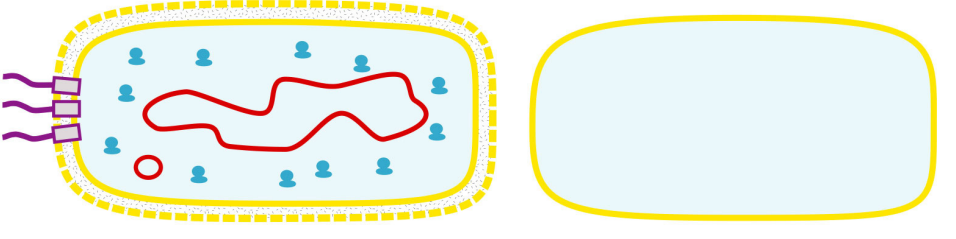
From Life to Matter and Vice Versa?

In order to illustrate this point of view, let us consider a bacterial cell as shown in Fig. 1(a). We all agree that such a cell is alive even though it represents a rather small bio-system. If we analysed its molecular composition, we would find proteins, nucleic acids, lipids and sugars, the four classes of biopolymers that are present in all living cells. In particular, an analysis of the inner membrane of E. coli would show that the core of this membrane consists of a lipid bilayer which is quite similar to those found in human cells.

Now, let us extract this inner membrane of E. coli and let us reconstitute this membrane in the form of a vesicle as shown in Fig. 1(b). Such a vesicle corresponds to a bacterium that has lost all of its interior structure and, thus, has lost most of its functions. However, we may imagine to recreate the original cell by adding more and more molecular components back to it. In this way, we would obtain a *continuum of bio-systems* that interpolates between a relatively simple biomimetic system, the vesicle, and a complex biological one, the bacterial cell.

Bio-Molecules, the Smallest Bio-Systems

At present, we cannot actually construct such a continuum of bio-systems at the level of bacterial cells. However, we are able to do such a construction for the smallest bio-systems which are provided by single bio-molecules. This is particularly obvious for proteins, which consist of linear sequences of amino acids and which can be produced using various methods of (cell-free) chemical synthesis or recombinant gene expression in different organisms. In this way, we can produce large amounts of natural proteins or create new, artificial ones which have new amino acid sequences or contain unnatural amino acids not found in biological cells.



(a) (b)

Fig. 1. (a) Schematic view of E. coli, the most abundant bacterium in our guts: Its cell has a roughly cylindrical shape with a length between 2 and 4 μm and contains many biomolecules and supramolecular assemblies such as circular DNA strands and about 20000 ribosomes (small particles). The cell is enclosed by two membranes which are separated by a crosslinked protein layer. The inner membrane consists primarily of phospholipids; the outer membrane contains many glycolipids. Three rotary motors are shown on the left, which move the bacterium's flagella and which are anchored in this compound membrane (only the initial segment of the flagellae is shown); (b) A vesicle enclosed by a single lipid/protein membrane that has the same composition as the inner membrane of E. coli.

In recent years, a variety of biophysical detection and manipulation methods has been developed which enable us to study the behavior of single, individual molecules. These methods include fluorescence probes, scanning probes, force spectroscopy, and optical tweezers. Using these experimental tools, we can study the molecular conformations and the changes in these conformations as we vary the basic architecture of the molecule. As a result, we find that the behavior of these molecules varies in a systematic manner as we introduce small changes in their architecture. Therefore, at this single molecule level, there is no longer any sharp distinction between 'biological' and 'biomimetic'.

Molecular Assemblies and Superassemblies

Likewise, on the next level of complexity corresponding to molecular assemblies, we can construct artificial membranes, filaments or even ribosomes which are indistinguishable from their natural counterparts in the living cell. Membranes typically contain a large number of lipid and protein components as well as sugar groups attached to both types of macromolecules. Filaments are usually built up from a single protein component such as actin or tubulin. Ribosomes consist of about 50 proteins and RNA. In addition to these polymer assemblies, biological systems can also contain small crystallites and minerals that are formed by the growth of ion clusters.

We can go on and create 'assemblies of assemblies' or superassemblies by crosslinking different types of assemblies. A simple example is provided by a molecuar motor that acts as a crosslinker between a vesicle and a filament, see Fig. 2.

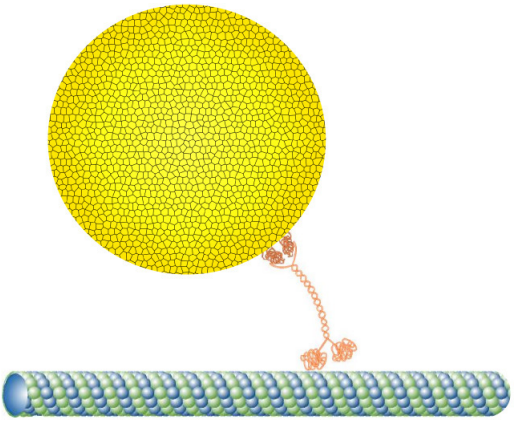


Fig. 2. Bio-system composed of a kinesin motor (middle) and two different molecular assemblies, a microtubule (bottom) and a lipid vesicle (top). The motor acts as a crosslinker between the filament and the vesicle. The filament thickness is about 25 nm, the stalk of the motor about 80 nm. The vesicle membrane has a thickness of 4 nm. Addition of ATP molecules, that are too small to be visible on the scale of this cartoon, leads to directed movement of motor plus vesicle towards one end of the polar filament.

If we added ATP molecules to this bio-system, the motor protein would start to move along the filament in a directed fashion.

The Living Cell as a Complex Assembly

The bio-system shown in Fig. 2 contains several different assemblies of molecules but is still rather simple compared to the superassemblies that provide the architecture of the living cell. The bacterial cell in Fig. 1(a), for instance, may be viewed as a superassembly of biomolecules, ribosomes, and membranes. It is believed that the first organisms, which appeared on earth, resembled such bacterial or procaryotic cells and that the next more complex organisms, the eucaryotic cells (with a nucleus), arose from a combination of several such procaryotic ones.

If we were able to look into a living cell with nanometer resolution, we would see an image as in Fig. 3. In this figure, one sees many different molecules and molecular assemblies which form a rather crowded solution even though about 70 volume percent of the cell consist of water. Furthermore, Fig. 3 shows a snapshot of a rather dynamic situation which is characterized by many nanoscale processes and chemical reactions, which I will address further below.

Now, let us consider the overall architecture of an eucaryotic cell which has a typical size of tens of micrometer. The spatial organization of such a cell is primarily determined by its membranes which form a maze of nested spatial compartments as shown in Fig. 4. Indeed, in addition to the outer cell membrane,

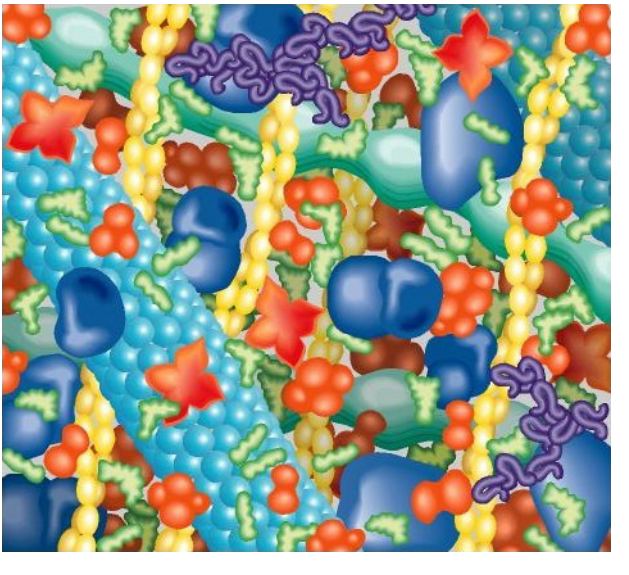


Fig. 3. View into a living cell with nanoscale resolution which reveals many different molecules and molecular assemblies. These structures form a rather crowded solution even though 70 volume percent of the cell consist of water. The width of this image corresponds to 125 nm.

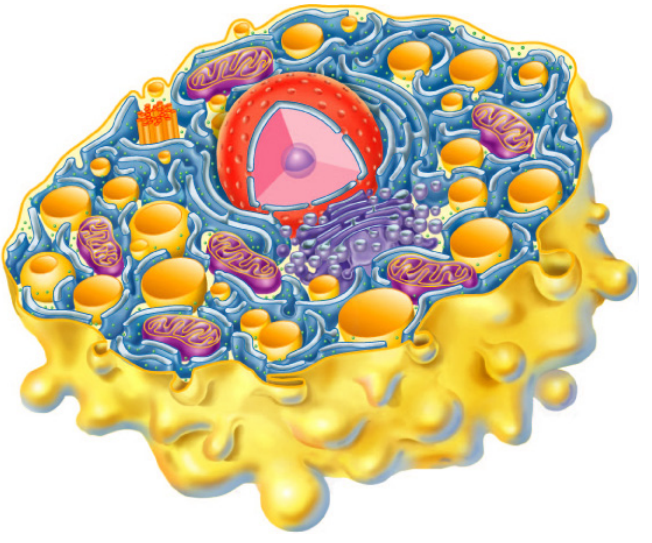


Fig. 4. Eucaryotic cell viewed as a superassembly of different membranes. The cell is bounded by its outer cell membrane and, in addition, contains a large number of interior membranes, whch enclose various organelles such as the cell nucleus (large organelle in the middle), the endoplasmic reticulum (lamellae between the nucleus and the plasma membrane), Golgi apparatus (separate stack of lamellae in front of the nucleus), a large number of mitochondria etc. These membranes form a large number of highly nested spatial compartments. Note that these membranes consist of lipid bilayers with a thickness of about 4 nm whereas the overall size of the eucaryotic cell is tens of micrometers.

one finds many additional membranes which enclose various organelles such as the cell nucleus, the endoplasmic reticulum, the Golgi apparatus, a large number of mitochondria etc.[a]

It is again important to note that the membrane architecture in Fig. 4 is not static but highly dynamic. Indeed, if we monitored the time evolution of this architecture, we would discover a lot of membrane movements. First, small vesicles bud off from the plasma membrane and from various membrane-bounded organelles. These vesicles are then transported to other locations within the cell, typically using a transport system which is similar to the one displayed in Fig. 2. Finally, the vesicles bind to their target organelles and merge with them by membrane fusion. The physical mechanisms underlying these different processes have been recently studied in much detail and are governed by a variety of molecular machines.

Multiscale Motility and Force Generation

Two types of molecular machines have been recently studied in great detail: growing filaments and stepping motors molecules, compare Fig. 2 and Fig. 5. These two

[a]Mitochondria are bounded by two membranes and are believed to have a common ancestor with gram-negative bacteria such as E. coli.

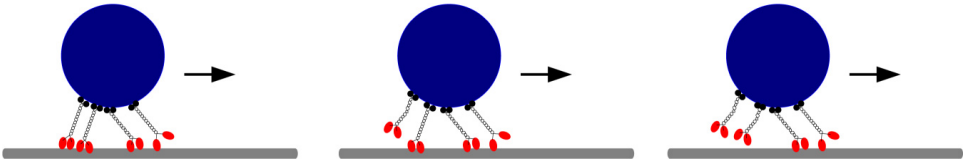


Fig. 5. Cargo transport by several molecular motors which move along an immobilized filament. Each motor can unbind from and rebind to the filament, which implies that the number of motors that actually pull the cargo varies with time.

types of molecular machines are primarily responsible for the ability of living cells to undergo dramatic morphological transformations. Indeed, these cells squeeze themselves through very narrow pores, they can extend long 'feet' in order to crawl along surfaces, and they can divide themselves up into two daughter cells.

Both filaments and motor molecules are built up from proteins but use distinct mechanisms for force generation. Filaments are rod-like structures with a thickness of about 10 nanometers but a length of many micrometers. One end of the filament grows by the addition of nanometer-sized building blocks and, in this way, generates a pushing force. Stepping motors are proteins with two identical 'legs', which are about 10 nanometers in size, compare Fig. 2. When in contact with a filament, the motor undergoes a certain conformational transformation, a so-called power stroke, and generates a pulling force.

Because of its small size, a single nanomachine generates a rather small force which is of the order of a few picoNewtons (10^{-12} Newtons). In addition, a single nanomachine is rather sensitive to its environment and is easily perturbed by thermal collisions with the surrounding molecules. It is quite remarkable, however, that all forces generated by living cells and organisms arise from the combined action of groups of such nanomachines. A simple example is provided by the cooperative transport of cargo particles such as vesicles by several molecular motors, see Fig. 5.

In this way, single cells can exert forces in the nanonewton range, and animals can generate forces of hundreds of newtons. Thus, biological systems are able to cover a very wide range of forces between a few picoNewtons (10^{-12} Newtons) and several 100 Newtons. In order to mimic this amazing ability, one must integrate bundles of filaments and groups of motors into larger and more complex systems. This provides a fundamental challenge for the bio-nanosciences.

The Living Cell as a Complex Network

When we considered the cell's architecture and viewed it as a complex assembly, see Fig. 3 and Fig. 4, we focused on the physical interactions between the different molecules and nanostructures. If we want to understand the cell's versatility and motility, we have to take into account that all of these molecules participate in

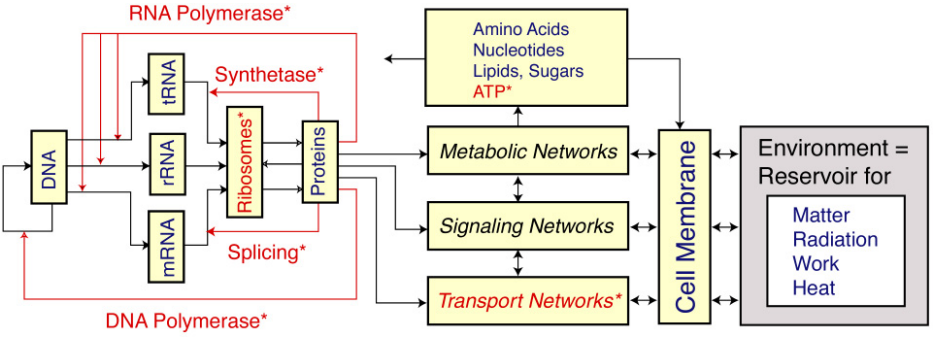


Fig. 6. Schematic representation of the biomolecular networks that are present in the living cell. The network on the left is responsible for the assembly of DNA, RNA, and proteins starting from nucleotides, amino acids, and molecular assemblers that consume ATP. Both the precursor molecules and the 'fuel molecule' ATP are produced by metabolic networks. The transport networks lead to force generation via cytoskeletal elements and to ion transport via membrane pumps. The signaling networks are able to recognize and discriminate different patterns in the environment of the cell. All of these networks are interconnected and form a large and rather entangled supernetwork. All interactions with the environment are mediated through the outer cell membrane.

chemical reactions. In fact, there is a large number of different reactions and processes which form a complex network as shown in Fig. 6.

As indicated in this figure, the cell produces many of its main building blocks by its metabolism. The corresponding chemical reactions are catalyzed by proteins, which act as enzymes. As a result of this metabolic networks, one obtains amino acids, nucleotides, lipids, sugars as well as as ATP molecules. The latter molecules drive the molecular machines which assemble DNA, RNA, and protein molecules, see the corresponding network on the left of Fig. 6. Likewise, these ATP molecules also provide the 'fuel' for membrane pumps and cytoskeletal machines which are included in the transport networks of Fig. 6.

For metabolic networks, graph theory has been used for a long time. During the last couple of years, network representations have also been developed for the physical interactions of proteins and for the regulation of gene activity. In fact, the concept of networks and activity patterns is rather general and can be applied to many different bio-systems such as tissues, i.e., large assemblies of cells, or societies, i.e., large populations of organisms.

Recent studies of network models as applied to various bio-systems have elucidated two complementary aspects. On the one hand, the local properties of these networks have been characterized in terms of recurrent motives and modules. On the other hand, these networks have also been classified in terms of their global properties such as their degree distribution. The latter distribution determines the probability $P(k)$ that a randomly selected node has k connections attached to it, see Fig. 7. Metabolic networks, for example, seem to have a scale-free degree distribution that is characterized by power laws.

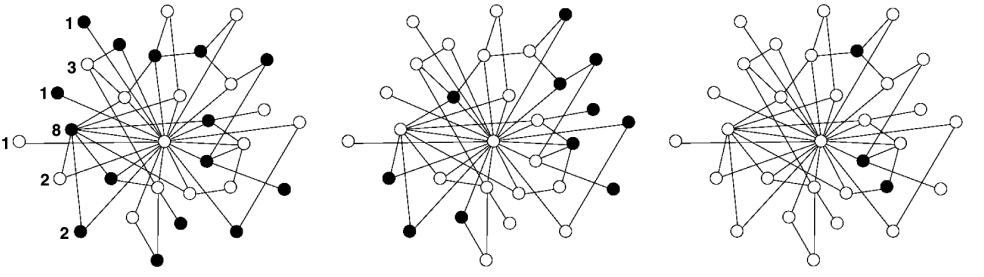


Fig. 7. Three subsequent snapshots of the activity pattern on a rather small scale-free network with 31 nodes and 50 connections. The active and inactive nodes are white and black, respectively. For the initial pattern on the left, about half of the nodes are inactive (black); for the final pattern on the right, almost all nodes are active (white). Each node of the network has a certain degree which is equal to the number of connections attached to it; this number is explicitly given for some nodes on the left. The node with the largest degree is located in the middle of the network and has 21 connections.

Summary and Outlook

In summary, the physics of bio-systems is a rather lively research field with many challenges both for experimentalists and for theorists. Even if one focuses on the nanoregime, this research field covers a whole hierarchy of systems: single molecules such as proteins and nucleic acids; molecular assemblies such as membranes and filaments; 'assemblies of assemblies' or superassemblies such as the transport systems based on molecular motors, filaments, and membranes. It addresses the physical and chemical interactions in these systems which lead to multiscale motility and force generation. It also represents a very promising field for the fruitful application of network models.

I hope that the new journal 'Biophysical Reviews and Letters' will attract many good submissions about these different topics in the near future.