I Introduction: Physics of Life

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1 Introduction

Life is described by biology, isn't it? All the various plants and animals, all the different organs and cell types, and all the myriads of proteins and signaling molecules and chemical reactions. What is "physics of life" supposed to be? There is probably no unique or generally accepted answer to this question. However, there are certainly several aspects of life and living organisms, where physics plays a crucial role.
What probably comes to mind first are physical techniques used to study and understand living systems. X-ray imaging and X-ray scattering, nuclear magnetic resonance (NMR) and magnetic resonance imaging, electron microscopy, and positron emission tomography (PET) are all methods developed in physics, and later applied to living systems. This is an important aspect of the interaction of physics with biology and medicine, but not the essence of "physics of life". Instead, we see the following key issues:

- **Materials and Material Properties**
  Organisms consist of macromolecules, like proteins and DNA, macromolecular aggregates, cells, tissues, organs, etc. These objects have material properties such as elasticity, deformability, surface and adhesive properties, as all other materials. For example, DNA has a bending and torsion modulus, and is electrically charged, properties which are important for understanding how very long DNA strands can be compacted into the tiny cell nucleus. Membranes surrounding cell organelles and cells have a bending rigidity and a shear modulus, but also a permeability for small molecules and water. The knowledge of material properties forms the basis for any quantitative understanding of living matter, in the same way as knowledge of the properties of various metals and plastics is required to construct a robot.

- **Macromolecules and their Interactions**
  The key players for the functioning of a cell are macromolecules. For a description of processes in the cell, not only the proteins involved have to be known by name. In addition, their structure, the charge distribution on their surfaces, the internal dynamics, and their interactions have to be characterized to allow for quantitative predictions based on statistical theories.

- **Rheology of Biofluids**
  Most organisms contain a large amount of fluids. These fluids are not static, but are moving and flowing. Examples are blood, the cerebrospinal fluid, and the cytoplasmic fluid. The behavior of these fluids is governed by the same hydrodynamic laws – the Navier-Stokes equation – as the flow of water in the oceans. Thus, the physics of fluids is crucial to understand the rheology of bioflows.

- **Non-Equilibrium Systems and Active Matter**
  Living systems are persistently out of equilibrium – an organism at equilibrium is dead. This persistent out-of-equilibrium state is maintained by continuous energy consumption. The physical understanding of out-of-equilibrium systems is much more difficult than well-established thermodynamics – and holds many surprising phenomena to be discovered. This will be among the most exiting areas in physics in the coming decades.

- **Structure versus Function**
  Condensed matter physics is mostly concerned with "structure" and "dynamics". What is

the structure of Ga interstitials in Si-matrices of semi-conductors? What is the structure of the fracture surface of a rod which breaks due to an overload? What is the conformation of a polymer in a compound material. In living systems, this is of course also important, but equally or even more important is "function". How does a signaling molecule cause a membrane channel to open, which then allows the influx of other molecules causing the cell to perform a task. For physicists, this requires a new way of thinking about dynamical systems, and opens the field to tackle completely new problems.

- **Complex Systems**
  Biological and living systems are typically very complex, with a large number of different components, highly dynamical conditions, spatially very inhomogeneous distributions, etc. This is a grand challenge for physics, because the main physics approach is to boil things down to the essential ingredients, and then to understand the underlying mechanisms in detail. It will certainly not be possible to understand all living matter in this way. However, it will be a very interesting journey to find the questions, problems and systems, where a clever reductionist approach can give fundamentally new insights into the processes of life.

- **Emergent Behavior**
  Ensembles of many interacting objects often show collective behavior, which does not depend on the detailed structural or dynamical properties of the individuals. An example is the formation of swirls in large schools of fish, which are seen for many different species. Another example is the turbulent behavior of many active bacteria on a substrate. These ensembles exhibit "emergent properties" that the smaller/simpler entities do not have.

  A good example for emergent behavior is the brain. The individual neurons are rather simple cells, similar to a transistor in electronics. But if 100 billion or so are coupled together in the human brain, they start to become self-conscious and think about stupid jokes. This emergent behavior is not a property of the neuron itself. An even better example is life itself. An organism consists mainly of hydrogen, carbon, and oxygen. Mix 100 kilograms of it together, shake well, so that everything falls in place, and it starts to run around and uses a cell phone.

- **Synthetic Biology**
  Richard Feynman (Nobel laureate in Physics 1965 for quantum electrodynamics) once said "what I cannot create, I do not understand". This statement can be interpreted in the context of biology and life sciences in such a way that we should aim at constructing artificial model systems, which recreate essential aspects of living systems. There is indeed a recent development in science, which is heading in this direction.

  Synthetic biology is nowadays defined as the artificial design and engineering of biological systems and living organisms for purposes of improving applications for industry or biological research. In general, its purpose can be described as the design and construction of novel artificial biological pathways, organisms or devices, or the redesign of existing natural biological systems.

- **Development and Tissue Growth**
  From the developing embryo to the caterpillar transforming into a butterfly, from an expanding bacterial colony to a growing tree, cells need to grow, divide, and rearrange to

build the final, fully developed state. Besides biochemical and other regulation mechanisms, mechanical forces and constraints are key players in morphogenesis and tissue patterning. Understanding these mechanical forces and their feedback to growth and patterning is thus mandatory for understanding development and growth. At the same time, these feedbacks and growth result in novel physical phenomena and unprecedented behavior.

- **Evolutionary Biology and Genomics**
  Chance and necessity in evolution is a fundamental theme of biology. How can this dynamics be understood, starting from its molecular basis, which lies in genes and their interactions? How do adaptation and functional innovation take place in the sea of stochastic changes of molecular evolution? How can genomic data and evolution experiments, for example in bacterial systems, be employed to develop and test statistical theories of evolution?

- **Environment and Stimulation**
  Biological systems are not living in vacuum, but are constantly exposed to a large variety of external signals and stimuli. These include mechanical, optical, and electrical signals. Therefore, it is important to understand the response of living matter to such stimuli on all levels, from single molecules and cells to tissues. This has spawned the fields of biomechanics and bioelectronics. In the latter case, electronic devices are developed to stimulate nerve cells (neural prosthetics) or to detect reactions of cells to other environmental stimuli (biosensors). A particularly interesting recent development is optogenetics, where light signals are used to control genetically modified cells (typically neurons) in living tissues.

- **Multiscale Modeling**
  A detailed understanding of living systems requires a quantitative description. For complex systems in living matter, phenomena on very different length- and time-scales are often intimately linked together. As an example, the simulation of a cell in a microfluidic flow simultaneously requires the resolution of cell-wall interactions (nano-scale), cell deformation (micro-scale) and fluid flow (micro- or millimeter scale). From the theoretical side, this requires multiscale modeling approaches, which cover a wide range of scales. A high-fidelity modeling will need computing resources of the next generation of supercomputers.

Some general discussion on various aspects of "Physics of Life" can be found in Refs. [1–11].

2 Macromolecules and their Interactions

The chemistry and physics of synthetic macromolecules has been studied intensively in the last decades, starting essentially with work of H. Staudinger (Nobel Laureate in Chemistry 1953) and his colleagues in the 1920s. This has lead to a wealth of knowledge about the behavior of linear and branched macromolecules (= polymers) in dilute and concentrated solutions, culminating in the Nobel Prize in Physics for P.-G. de Gennes in 1991. In particular, it has been shown that many polymer properties depend not so much on the properties of a single monomer, but are dominated by the large number N of (nearly) identical units in such a chain molecule.

This implies that many properties are universal. For example, the end-to-end distance R_e of a polymer in good solvent scales as $R_e \sim N^\nu$, with $\nu = 0.58$ in three spatial dimensions.
Macromolecules are also the main building blocks of all biological cells. DNA is a linear polymer, which in its sequence of nucleic acids stores the genetic information. A complex machinery in the cell transforms this information into amino-acid sequences, which constitute functional units – the proteins. There is a large variety of proteins in the cell, each of which performs a specific task. Many proteins have globular shapes, but some proteins assemble into long filaments, like actin filaments and microtubules. Another type of self-assembly occurs for lipid molecules, which due to their amphiphilic character form bilayer membranes. These membranes form the outer envelope of the cell – the plasma membrane – and are present in the interior of the cell to form compartments. A special class of proteins is membrane proteins, which play an important role in the regulation of the transport of nutrients, signaling molecules, and waste products through the membrane.

2.1 DNA

The best-known polymer in living systems is probably the carrier of the genetic information, *deoxyribonucleic acid (DNA)*, see Fig. 1. It consists of a sequence of four monomers, the nucleotides adenine, thymine, guanine and cytosine, which in pairs form the famous double helix. Three subsequent bases encode for one amino acid. The genetic code specifies 20 standard amino acids.
In eukaryotic cells, DNA is tightly packed within the nucleus in the form of chromosomes [12, 13]. The (linear) contour length of DNA within a chromosome is typically of the order of centimeters, and is contained within the volume of the nucleus which has a diameter of a few microns. If this amount of DNA were simply compressed in such a small space, the resulting pressure would rip apart any conceivable cage. Such a tight packing is enabled through the interactions of DNA with so-called chromatin-proteins, which are cylindrical segments around which the DNA is wound. It is still a matter of debate how the mechanism of tight packing functions. It cannot be too tight, because the stored information must still be accessible for protein synthesis. In prokaryotic cells (bacteria), DNA is present as ring-like molecules, which are super-coiled through interactions with enzymes. These helical super-coiled DNAs float freely in the cell's plasma. It is thus clear that DNA only functions with the help of complex interactions with several types of proteins. This is the case for almost all processes in living matter: many different types of molecules work together to maintain life.

2.2 Proteins

Proteins are the machinery and the building blocks of life. Most of biological functions, from molecular motors to the cytoskeleton, from DNA replication to anti-virus protection, are performed – with a very few exceptions – by proteins. Proteins (also known as polypeptides) are linear chains of amino-acids, which fold into a globular or fibrous form. The amino acids are covalently connected by peptide bonds. Proteins are formed from a "library" of only 20 standard amino-acids. These amino-acids can be broadly differentiated into 8 hydrophobic amino-acids – normally buried inside the protein core –, 4 charged amino-acids – with their side chains often making salt bridges –, and 8 polar amino-acids – usually participating in hydrogen bonds as proton donors or acceptors.

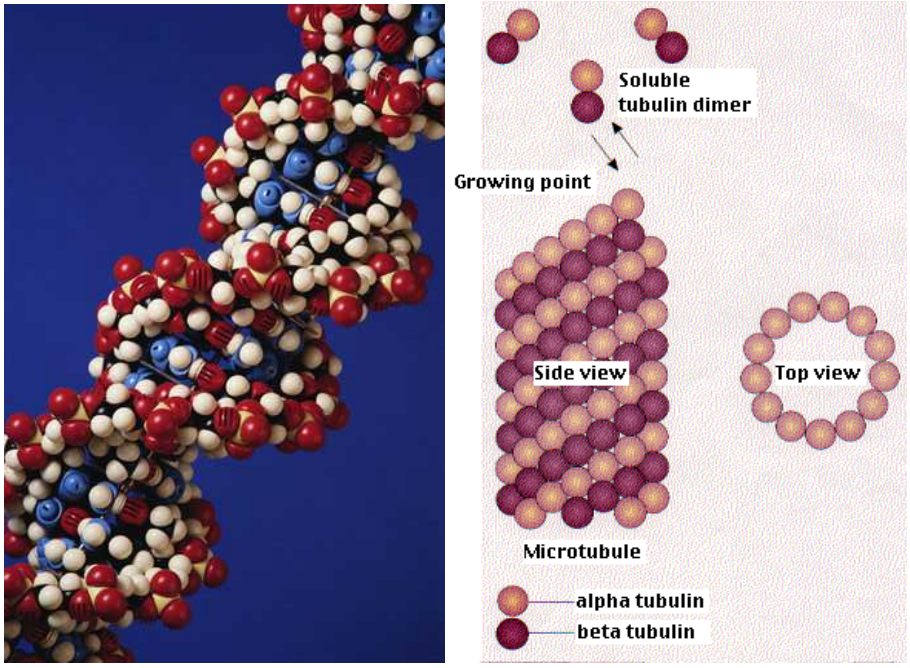

Fig. 1: *Structure of biopolymers. Left: DNA is a double-stranded helix. Right: Microtubules are assembled from dimers of* α *and* β *tubulin;* 13 *protofilaments from a hollow tube.*

Proteins were first described already in 1838 by the Dutch chemist Gerhardus Johannes Mulder and named by the Swedish chemist Jöns Jakob Berzelius.

The extraordinary versatility of proteins is achieved by folding the linear amino-acid chain into a three-dimensional structure. The particular sequential order of amino-acids defines the "primary structure" of a protein. One of the most distinguishing features of polypeptides is their ability to fold into a globular state. This folding occurs on two hierarchical levels. The "secondary structure" consists of α-helices, pieces of the chain which form tight staircase-like cylindrical units, and β-sheets, which form ribbon-like units. One of the important forces that stabilizes the secondary structure are hydrogen bonds between the amino-acids. These elements then order into a three-dimensional arrangement, which defines the "tertiary structure". The function of a protein strongly relies on the correct tertiary structure. An example of the protein aquaporin 1 with a high content of α-helices is shown in Fig. 2.

The extent to which proteins fold into a defined structure varies widely. Some proteins fold into a highly rigid structure with small fluctuations and are therefore considered to be single structure. Other proteins – called "intrinsically disordered proteins" – undergo large rearrangements from one conformation to another. Thus, not all proteins require a folding process in order to function.

While cells generate proteins with high fidelity, a consistent prediction of protein structure on the basis of their sequence alone has not been possible so far. Conversion of the DNA sequence into an amino-acid sequence is well understood, and a programmable synthesis is possible; however, the question "how does the three-dimensional structure emerge?" remains unanswered.

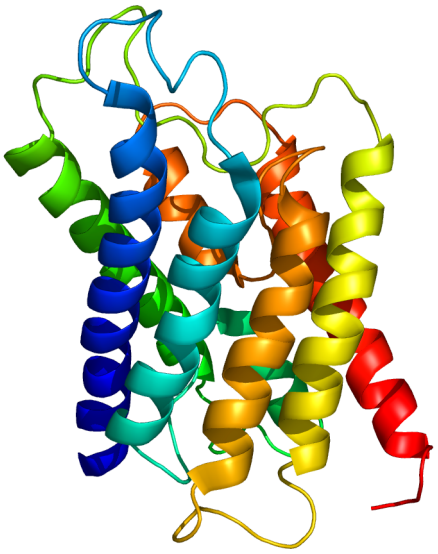

Fig. 2: *Aquaporin 1 is a member of the Aquaporin family. It was first discovered in red blood cells. In 2003, Peter Agre was awarded the Nobel prize for discovering this "water channel". This channel is used for rapid transportation of water across the cell membrane. It is very specific and only allows passage of water molecules, but is impermeable to hydrogen ions. Note the large content of α-helices. From Ref. [14].*

2.3 Biopolymer Filaments and Networks

An important biopolymer is *actin*, one of the three major components of the cytoskeleton. It participates in many important cellular functions, including muscle contraction, cell motility, cell division and cytokinesis, vesicle and organelle movement, cell signaling, and the establishment and maintenance of cell junctions and cell shape. Actin filaments (F-actin) consist of globular monomeric protein subunits (G-actin), which form a double-helical structure.
Another structural component of the cytoskeleton is *microtubules*. For instance, they contribute to a structural integrity of the cell, serve as the routes for vesicle transport, and facilitate the separation of chromosomes during mitosis. The structure of microtubules consists of a hollow tube of dimers of the protein subunits α and β tubulin, which are arranged in protofilaments, see Fig. 1.
An important aspect of biopolymers is their mechanical properties, which can be characterized by the persistence length, *i.e.* the length below which a polymer behaves essentially like a stiff rod, whereas it behaves like a random coil on much larger scales. The persistence lengths of DNA, actin and microtubules are $50\ nm$, $10-20\ \mu m$ and about $1\ mm$, respectively. These numbers can be connected to their functions and location in the cell. Very long DNA strands have to be curled up in the cell nucleus, which is only a few μm in diameter (the total length of a single DNA strand in the human genome is $1.8\ m$); DNA therefore has to very flexible. On the other hand, microtubules have to be very stiff, because they serve as the "highways" for vesicle transport; their persistence length therefore exceeds the cell diameter.
In contrast to synthetic polymers, biopolymers often do not have permanently polymerized and fixed structures. Instead, they are dynamic states of an active polymerization process, which proceeds with different rates at the two ends of the *polar* filaments. Actin belongs to this class

of "tread-milling" filaments. Microtubules have another type of active dynamics, which consists of periods (in time) of steady growth, which are interrupted by sudden depolymerization events ("catastrophes").

2.4 Membranes

The main component of a cell membrane is lipids, amphiphilic molecules with two hydrocarbon tails (see Fig. 3), which form bilayers in water. This was first shown experimentally by Gorter and Grendel (1925). They first extracted lipid molecules from the plasma membrane of red blood cells. By pouring the lipids onto a water surface, and comparing the area of the resulting patch with the surface area of the original cell surfaces, they concluded that the cell membrane consists of a lipid bilayer. Later, it turned out that their arguments contained several errors, they had for example underestimated the size of the original cell surface. However, these errors canceled out each other to a large extent, so that their conclusion was nevertheless correct. Nowadays, it is well established that the major component of the cell membrane is a lipid bilayer. Within cell membranes, there are usually a variety of other molecules embedded (an artistic impression is given in Fig. 4). The macromolecules and macromolecular complexes, that are embedded in the membrane, regulate exchange of matter with its surroundings. For example, ion channels are complexes which regulate exchange of specific ions.

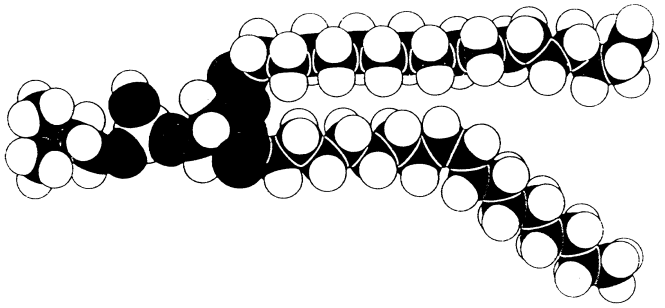

Fig. 3: *Phosphatidyl-choline (PC) is a typical example of a membrane lipid. The polar head (left) is connected to two hydrocarbon tails (right).*

Membranes consisting of lipids and (bio-)polymers are quite easily deformable. A typical example of such a biological membrane is the "skin" of a red blood cell (see Sec. 4 below), the size of which is in the few micrometer range. Due to the flexibility of the membrane, a red blood cell can pass through micro-vessels with a diameter four times smaller than its own size. In addition, they are easily deformed by solvent flow, which is important for blood flow in the microvasculature.

Biological membranes have a very complex structure, as they are composed of many different types of lipids, cholesterol, and proteins, which can assemble into rafts or other supramolecular structures. Thus, fundamental insights on membrane properties are often obtained through the study of more basic "physical" membranes, which have a much simpler composition in comparison to biological membranes.

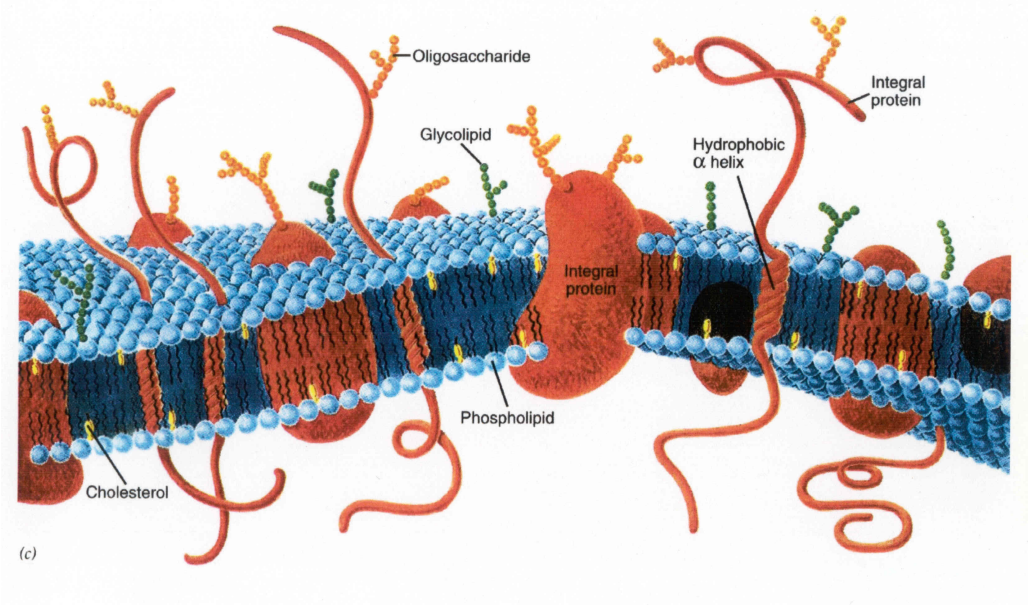

Fig. 4: *Artistic impression of a cell membrane in which many macromolecules and macromolecular complexes are embedded. From Ref. [15].*

3 Biological Materials and their Properties

Biological materials are extremely complex composites, characterized by intricate structural and mechanical properties [16–18]. The main building blocks are macromolecules (e.g., DNA, proteins, lipids – see Sec. 2), which then are assembled into a fascinating variety of macromolecular aggregates and structures (e.g., filaments, membranes, cells). In turn, macromolecules and cells continue to organize into further complex assemblies, yielding biological tissues, organs, and finally complete organisms. Therefore, from the structural point of view, a number of hierarchical classes of composite biological materials (i.e., macromolecules, cells, tissues, etc.) are generally defined and investigated.

The elucidation of structural and mechanical properties of biological materials is a significant scientific endeavor. A starting point here is the knowledge of involved components, such as the constituent macromolecules, molecular components for supramolecular assemblies and so on. However, even a complete knowledge about involved constituents does not generally permit direct predictions of their hierarchical organization. One of the prominent examples of supramolecular structures is cell membrane [19], which is schematically shown in Fig. 4. Biomembranes are typically composed of many different lipids and proteins, which self-organize through a number of physical interactions, including hydrophilic/hydrophobic and ionic interactions, Van der Waals and electrostatic forces. Understanding of these interactions is essential for the prediction of structural characteristics of various supramolecular assemblies.

Clearly, structural properties of biological materials are associated with their mechanical properties and function [16–18]. For instance, a lipid bilayer assembly of a cell membrane results in a bending elasticity of the overall membrane, while a non-uniform distribution of intra-membrane components may lead to the presence of spontaneous curvature (i.e., a preference to curve to the inside or the outside of the cell, as the two leaflets are usually not identical). This gives a cell the means to control membrane properties by adjusting the membrane composition. In

addition, trans-membrane proteins within a biological membrane allow the control of its permeability characteristics for the exchange of water, ions, and small molecules between the cell plasma and the extracellular space.

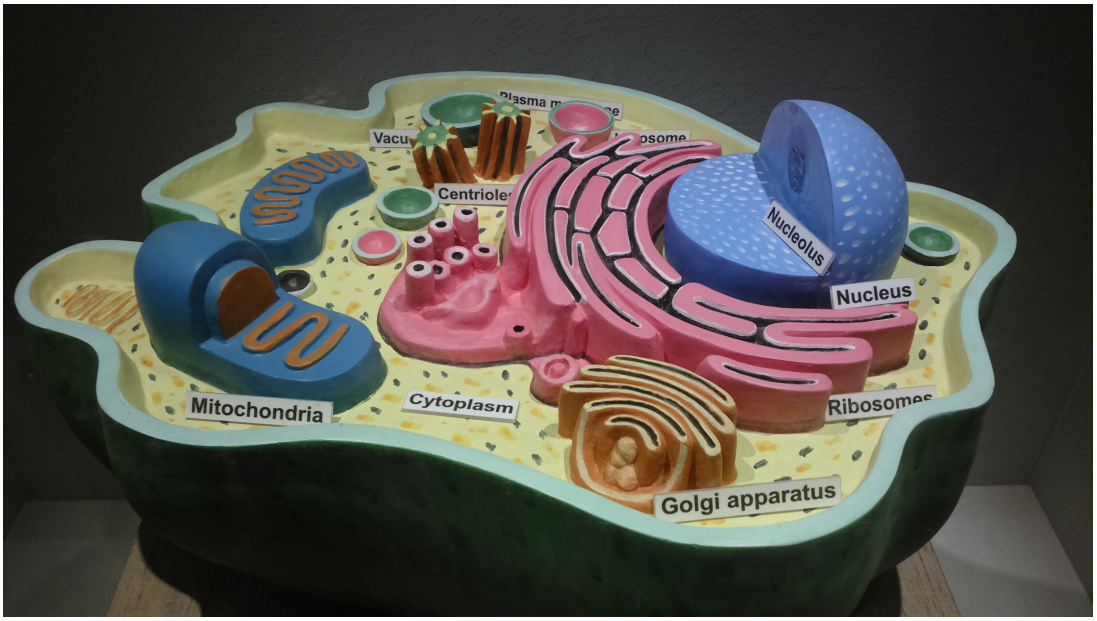

Fig. 5: *Illustration of the major structures inside an eukaryotic (animal) cell. From the Indian Museum, Kolkata, India.*

Cell mechanics is a large sub-field of biophysics, which concerns the material properties and behavior of living cells [20,21]. Here, the main aim is to understand and predict cell's mechanical properties and behavior starting from cellular structures (see Fig. 5), and relate them to cellular functions. Mechanical properties, such as elasticity, adhesiveness, and viscosity, can be probed by a number of experimental techniques, including micropipette aspiration [22], optical tweezers [23], flow cytometry [24], etc. It is important to keep in mind that these overall mechanical properties arise from a number of contributions from different cellular components, including cell's membrane, cortex, bulk cytoskeleton, organelles, etc. In addition, biological cells are generally able to adapt or respond to various mechanical deformations, making their properties dependent on applied stress, strain, and strain rate. Such mechano-sensitive adaptations proceed through cytoskeletal re-organization and force generation, and therefore biological cells are often referred to as active materials. Furthermore, biological cells might be motile, can initiate cell division or programmed cell death called apoptosis.

Many biological materials have mechanical properties that are far superior to those in existing synthetic materials [18]. For example, spider silk has impressive mechanical properties, because its strength is comparable to steel, while its density is lower than that of cotton. This motivates large scientific efforts for the development of bioinspired (or biomimetic) materials in order to take advantage of the versatile properties of biological materials. Another major goal here is to establish synthetic "biocompatible" materials which can be introduced into the human body, leading eventually to the substitution of tissues and organs.

In conclusion, most biological materials possess outstanding and adaptive mechanical properties. These properties emerge from the complex hierarchical structures and are tightly coupled to biological functions of such materials. Elucidation of the material properties of biological systems requires understanding of structural organization and mechanical characteristics at

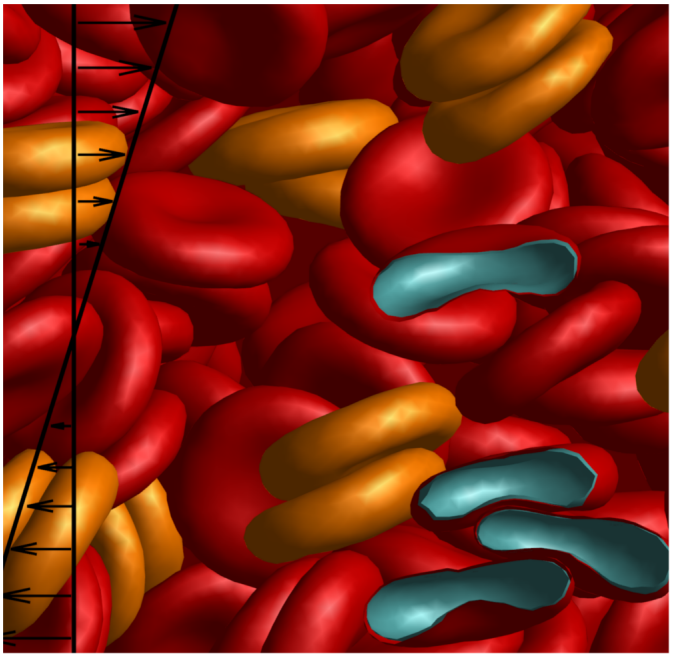

Fig. 6: *Simulation snapshot of blood in shear flow. RBCs are shown in red and in orange, where orange color depicts the rouleaux structures formed due to aggregation interactions between RBCs. The image also displays several cut RBCs with the inside drawn in cyan to illustrate RBC shape and deformability. Reused with permission from Ref. [25].*

multiple length scales starting from macromolecules, to supramolecular assemblies, cells, and finally organs, and whole organisms. Here, physics provides its indispensable contribution by the application of a variety of physical methods and the establishment of physical models and mechanisms in order to understand living systems.

4 Rheology of Biofluids

Fluids constitute a major part of all living organisms. Examples are blood, lymphatic liquid, cytoplasmic and cerebrospinal fluids. Biofluids are generally not simple viscous fluids like water, but are suspensions of cells and macromolecules, and are therefore often called "complex fluids". Complex fluids [26] may exhibit an intricate mechanical response to applied stresses or strains, such as viscoelasticity, shear-thinning or shear-thickening viscosity, yield stress, etc. Rheology concerns the flow of matter (primarily liquids) and aims to characterize the response of complex fluids to applied stresses. A particularly interesting question in rheology is how to connect macroscopic properties of complex fluids (e.g., shear-thinning) with the behavior and interactions of suspended particles or molecules in flow.

Rheology of blood has been subject to extensive investigations [27,28], since the flow properties of blood are clearly very important for organism functioning. Blood transports oxygen and nutrients to cells of the body, removes waste products, and circulates many important molecules and cells. Furthermore, changes in its flow properties are often correlated with various blood disorders and diseases, such as anemia, hypertension, malaria, etc. Blood is a suspension of blood cells, various proteins, and dissolved ions. The major cellular component (about 45% by volume as illustrated in Fig. 6) corresponds to red blood cells (RBCs), and therefore mechanical

and flow properties of RBCs determine rheological characteristics of blood.
RBCs in whole blood form aggregates called "rouleaux", which resemble stacks of coins (see Fig. 6) [27, 29]. The RBC aggregation is facilitated by the plasma proteins and results in a significant increase of blood viscosity at low shear stresses [27, 29]. Moreover, whole blood exhibits a yield stress (a threshold stress for flow to begin) due to the RBC aggregation [27]. This means that under very low stresses blood behaves similar to a solid. Overall rheological properties of blood are characterized by strong shear-thinning and weak elasticity. The shear-thinning characteristics of blood arise from the RBC ability to aggregate, deformability, and dynamics in flow [25, 30].
Understanding of fundamental rheological properties of biofluids is important for the prediction of their flow characteristics within an organism. This knowledge is also crucial for many biomedical and bioengineering applications, such as the development of blood substitutes, clinical tests, and drug delivery carriers.

5 Out-of-Equilibrium Physics and Living Matter

Classical non-equilibrium systems are driven out of equilibrium by external forces. Water is pumped through a pipe, heat flows from hot to cold, and currents follow a potential difference. The defining property of living matter is that the force driving it out-of-equilibrium originates from the microscopic constituents themselves. Bacteria swim in a fluid, motor proteins move the filaments in the actin cytoskeleton, and cells grow and divide. It is always that some microscopic components (e.g., motor proteins, flagella) are responsible for the activity. Typically, living matter is divided in two distinct classes. The first class is *microswimmers* or *active matter*, whose constituents generate forces or stresses, leading to active contributions in the force balance. The second class is called *growing matter* or *growing tissues*, and can be characterized by mass-balance violated through an active source or sink.
Examples range across all length scales: from swimming *Escherichia coli* that rotate helical flagella to swim [31], over active polymers in the cell that constantly polymerize and depolymerize and are connected by molecular motors to create stresses [32], to large schools of fish or groups of sperm that move collectively [33], as well as growing and developing biological tissues [34].

5.1 Active Matter, Self Propulsion, and Microswimmers

Motion, in one way or another, is a hallmark of life. Within the cell, motor proteins generate forces that move filaments and vesicles around. The whole cytoskeletal network is very dynamic and active. On a larger scale, cells move through soil, fluid, or tissues.
Motion is generated by motor proteins. Examples are myosin in the actin cytoskeleton that lets cells crawl, axonemal dyneins that allow the flagellum of sperm cells to beat, or myosin in sarcomeres to contract our muscles. The basis of activity and motion is always molecular motors converting chemical energy into forces. Thus, the system is driven out of equilibrium by locally generated forces. Sometimes, the activity can be described by an elevated effective temperature [35], which captures the increased kinetic energy of the particles due to their continuous propulsion. However, often this description is inappropriate, and the activity manifests itself in phenomena not considered by equilibrium physics. Nevertheless, equilibrium concepts and analogies can sometimes be useful to depict what is going on. For example, collections of self-

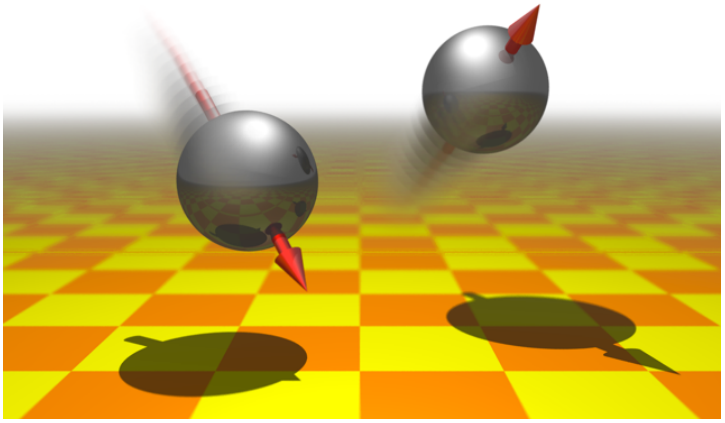

Fig. 7: *Schematic of active Brownian spheres moving near a surface. From Ref. [42].*

propelled disks with repulsive interactions spontaneously "phase separate" [36], motile tissues undergo "glass-like arrest" as density or adhesion increases [34, 37], or non-equilibrium surface accumulation occurs. The physics of active matter and microswimmers has gained increasing attention in recent years; comprehensive reviews can be found in Refs. [33, 38–41].

A particular illustrative example microswimmers in confinement is a sperm swimming between two planar surfaces. For many different cells and microorganisms, microswimmers are found to accumulate at surfaces. From a physics perspective, the simplest form of a microswimmer – the proverbial "spherical cow" – is a simple self-propelled Brownian sphere. It has a preferred direction of motion in the body-centered reference frame, along which it moves with a nearly constant velocity. However, this preferred direction performs rotational Brownian motion, like a passive particle. Passive Brownian particles would have a uniform distribution between the walls; however, if they run around in a bounded space, they are bound to hit a wall sooner or later (see Fig. 7).

The decoupling of the rotational degrees of freedom from translational motion allows for a theoretical treatment via a Fokker-Planck equation. The solution of this equation quantifies the following physical mechanism of wall accumulation. Particles are driven to one of the chamber walls depending on their initial orientation. Less particles remain in the center. Particles at the walls get stuck as long as their direction of motion still points toward the wall. Only when this direction has changed enough – a slow process driven by rotational diffusion – they are able to move again away from the wall.

This effect – that moving particles are bound to hit and accumulate at confining surfaces – is very generic [43], ranging from self-propelled rods and spheres to idealized run-and-tumble particles, and from swimming sperm cells and bacteria (like *E. coli*) to micro-algae (like Chlamydomonas) [44]. Thus, the minimalistic approach of physics provides a useful basis for many biological systems.

5.2 Tissue Growth

"The ability of cells and tissues to respond to mechanical force is central to many aspects of biology" [46]. The prime example of growing matter is biological tissue. Cells grow and divide, they die and disappear. Other forms of growing materials are bacterial colonies or possibly polymers during polymerization. Biological tissues form functional parts of organisms, com-

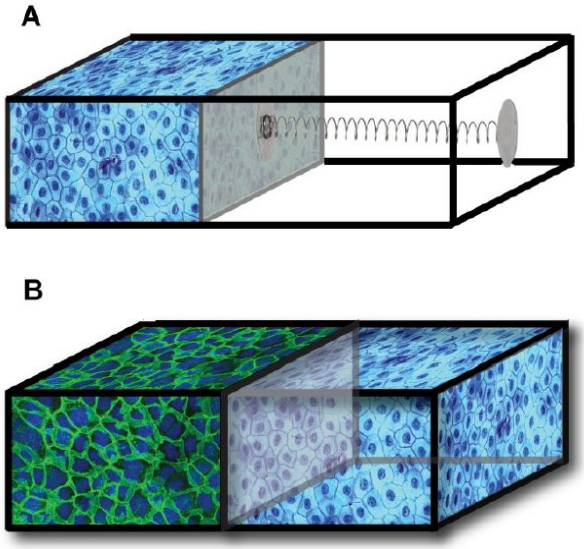

Fig. 8: *Illustration of homeostatic pressure.* ***A*** *The homeostatic pressure is the steady state pressure (cell growth and division balanced by cell death) of a tissue.* ***B*** *Two tissues can compete purely by mechanical forces if separated by a movable wall. From Ref. [45].*

posed of cells. They develop during embryogenesis, and most are under constant renewal over the course of their lifetime. In the past decades, it has become increasingly clear that physics, and especially mechanics, play an important role in cellular and tissue growth. Nowadays, it is well accepted that "mechanical feedback regulates proliferation" [47]. With the development of new experimental techniques and *in vitro* models, a deeper understanding of how cell growth couples to forces emerges.

A simple, heuristic argument for the physics of growth is a thermodynamic analogy: Growth is a change of volume. In terms of thermodynamics, pressure is the conjugated variable to volume. Therefore, it seems natural to assume a feedback between pressure and cellular growth.

Mechanical feedback on growth has been implemented in many different ways [48, 49]. One intuitive approach is to expand the growth rate in powers of the pressure around the zero growth-rate pressure – the *homeostatic pressure* [45], illustrated by a simple *gedankenexperiment* (see Fig. 8). A tissue is grown in a finite compartment, bound in one direction by a movable piston connected to a spring. As the tissue grows, it compresses the spring. Eventually, the growth forces of the tissue are not strong enough to further compress the spring. This force (divided by the area of the piston) is the homeostatic pressure. This is an intrinsic "material" property of the tissue type. In the second gedankenexperiment, the spring is replaced by a second tissue with a higher homeostatic pressure. Now the pressure equilibrates to an intermediate pressure between the two homeostatic pressures. At this pressure, the first tissue shrinks, while the second one grows. Thus, the first tissue steadily shrinks, until it finally vanishes, due to the higher pressure exerted by the second tissue.

A second illustrative example relates to the material properties of a growing or self renewing tissue. As cells in a tissue divide and die, each such event locally relaxes some stress. For polymer melts or other complex fluids, stress relaxation leads to viscous behavior on long time scales. Consequentially, tissues should be regarded as fluids on time scales much longer than their self-renewal time [50].

6 Grand Challenges, and Major Goals

The importance of "Physics of Life" has been recognized by the *Federation of American Scientists* already in 2003, when the goals of "Understanding of Complex Systems" and "Applying Physics to Biology and Medicine" were identified as two out of seven Grand Challenges in Physics for the 21st century [51]. A similar conclusion was reached by a committee of the *National Research Council (USA)* in a 2007 study: "What are the prospects for Condensed-Matter and Materials Physics in the early part of the 21st century?", where "What is the physics of life?" and "What happens far from equilibrium and why?" were identified as two out of six Grand Challenges [52].
These grand challenges are challenges for the fields of biology and physics alike. Physics has thrived on a reductionist approach: from universality of critical phenomena in statistical physics, to entropy and free-energy minimization in thermodynamics. Unraveling the underlying concepts that describe a multitude of phenomena has been key to progress in the physical sciences. On the other hand, in biological systems details often matter, and even though life follows the same physical laws, the complexity often renders answers from basic principles alone unfeasible. Thus, new principles for complex systems – "thermodynamics of live matter" – are needed to truly understand physics of life.
In the pursuit of a full understanding "Physics of Life", many major goals and objectives are on the way, or close-by. This concerns, in particular:

- A cell is already a very complex system. This renders it difficult to understand its essential mechanisms and processes. A possible approach to resolve this problem is the construction of a "Minimal Cell", both from the experimental and theoretical sides. This can be done in a step-by-step process: start with a closed fluid membrane, integrate a passive actin network, add motor proteins to make the cytoskeleton active, integrate membrane channels and pumps for material exchange, add metabolic processes for lipid synthesis, etc. Alternatively, an existing, functioning cell can be simplified by successively removing more and more of its components. Both approaches are very interesting to pursue.

- Information processing is an essential aspect of biological function on the cellular, tissue, and organismal levels. How are different signaling events segregated spatially in a cell without any membranous separation? The cytosol is an amazingly crowded space with many trafficking pathways which are independently regulated. How is this possible? For example, in neurons many independent synaptic inputs converge together to generate a post-synaptic response. The relative importance of these signals and their collaboration – or lack thereof – and the role of spatial organization, remains to be elucidated [11].

- Biological structures operate at multiple levels, from nano-scale molecules to meter-scale systems. Understanding the individual scales is a requisite for deeper insights into the whole system. Most importantly, these insights have to be combined and integrated into a multi-scale framework.

- Network dynamics are omnipresent in biological systems. This ranges from complex metabolic networks, signaling cascades and gene regulatory networks on the microscale to food chains and complex environmental networks on the macro-scale. Can these networks be characterized to an extent that quantitative predictions or optimizations are possible? Is spatial organization of metabolism relevant or essential? How does the network respond to external signals or perturbations?

- Activity is a hallmark of life. Unraveling the "thermodynamics of active matter" is clearly a challenge for the physical sciences. There has been significant progress recently to generalize thermodynamic concepts to non-equilibrium systems in the theoretical framework of "stochastic thermodynamics" and "fluctuation theorems", and their applications to molecular machines [53]. Can these concepts be generalized for other kinds of non-equilibrium systems?

- The continuity equation (mass conservation) has been at the basis of many physical descriptions of matter. How do we deal with changing numbers as cells grow, divide, and die, as proteins are synthesized, and filaments are polymerized dynamically? Are fundamentally new theories with additional growth terms required, as suggested by the description of tissue growth? Is it alternatively better to handle these systems as multi-component systems, where one component is converted into another?

- Biological systems are not always in a "healthy" state, but are often hampered by diseases. Diseases have two aspects in research: on the one hand, it is important to understand their origins and contribute to the design of new treatment options; on the other hand, they offer new avenues to better understand the mechanisms and processes of the organism itself. In many cases, diseases have important physical aspects; e.g., a blood clot physically blocks the flow of blood in a blood vessel, a growing tumor presses mechanically on neighboring organs. The "Physics of Disease" deals with many important diseases, such as cardiovascular diseases, cancer, neurodegenerative diseases, bacterial and viral infections, etc.

- Nature has generated all kinds of micro-machines. Can similar or novel approaches be used to construct artificial microrobots, which autonomously fulfill some tasks in medicine or environment? Can many of such microrobots work together in swarms to perform even more complex tasks?

- The coupling of the nervous system to electronics opens up the possibility of neuroprosthetics, i.e. prosthetic devices which can be directly controlled, or whose input can directly interact with the brain ("artificial eye that can see").

- Neuromorphic engineering, also known as neuromorphic computing, is the idea to employ very-large-scale integration (VLSI) systems containing electronic analog circuits to mimic neuro-biological architectures present in the nervous system [54,55]. Such designs may help to reduce the large energy consumption of present-day chip designs, and furthermore may lead to unprecedented algorithmic options and performance. Can the new insights into brain organization and function contribute to the design of new neuromorphic computer chips?

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