1 Introduction to cell biology

1.1 Motivation

Why is the understanding of cell mechancis important? cells need to move and interact with their environment ◦ cells have components that are highly dependent on mechanics, e.g., structural proteins ◦ cells need to reproduce / divide ◦ to improve the control/function of cells ◦ to improve cell growth/cell production ◦ medical applications ◦ mechanical signals regulate cell metabolism ◦ treatment of certain diseases needs understanding of cell mechanics ◦ cells live in a mechanical environment ◦ it determines the mechanics of organisms that consist of cells ◦ directly applicable to single cell analysis research ◦ to understand how mechanical loading affects cells, e.g. stem cell differentation, cell morphology ◦ to understand how mechanically gated ion channels work ◦ an understanding of the loading in cells could aid in developing structures to grow cells or organization of cells more efficiently ◦ can help us to understand macrostructured behavior better ◦ can help us to build machines/sensors similar to cells ◦ can help us understand the biology of the cell ◦ cell growth is affected by stress and mechanical properties of the substrate the cells are in ◦ understanding mechanics is important for knowing how cells move and for figuring out how to change cell motion ◦ when building/engineering tissues, the tissue must have the necessary mechanical properties ◦ understand how cells is affected by and affects its environment ◦ understand how mechanical factors alter cell behavior (gene expression) ◦ how different cells interact with each other ◦ cell behavior may change under different conditions (stress) ◦ to be able to study the extend of role of different parts of a cell in its behavior ◦ to predict cell behavior or response in different conditions ◦ movement/motility of cell depends on mechanics ◦ load bearing, deformation of cells ◦ stability/integrity of cell is provided by cytoskeleton and influenced by its mechanical properties ◦ to understand cells better ◦ to manipulate cells as we want ◦ to generate something based on cell's characteristis ◦ under physiological change, how does cell mechanics change ◦ provide guidance for cell manipulation ◦ extract cell properties from experiment ◦ observe cell response

1.2 Introduction to the cell

Cells are the fundamental building blocks of life. They are the smallest units of an organism that can be characterized as living. Humans and many other organisms are **multicellular**, i.e., they consist of multiple cells. **Unicellular** microorganisms, i.e., organisms consisting of one single cell such as bacteria, algae, and fungi, were the first form of life on earth about 3-4 billion years ago. Robert Hooke was the first to use the word cell in 1665, however, in the context of non-living cork. Antonie van Leeuwenhoek was the first person to ever observe a cell under a microscope in 1674. The cell theory biologists use nowadays dates back to major contributions of Schwann and Schleiden in 1839, enhanced by contributios of Virchow in 1858.

The basic elements of the **classical cell theory** state that

- all living things are composed of cells,
- cells are the basic unit of structure and function in living things, and
- cells are produced from other cells.

We can distinguish between two types of cells, **prokaryotic cells**, i.e., cells without a nucleus such as bacteria, see figure 1.1, and **eukaryotic cells**, i.e., cells with a distinct nucleus which possess organized chromosomes that store genetic material, see figure 1.2. In humans alone, there are more than 200 different cell types of different form and function. Some characteristic numbers you might want to remember are the following:

- humans consists of approximately 100 trillion, i.e., 10^{14} cells,
- a typical cell size is 10μm
- smallest cells are less than 1μm in diameter while nerve cells can be up to a 1m long
- a typical cell mass is 1 nanogram.

It is characteristic for all biological cells to

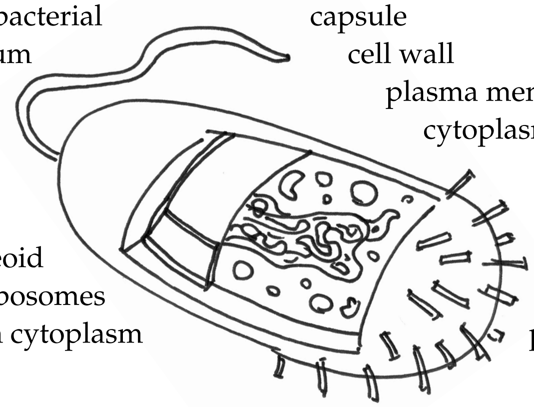

Figure 1.1: Prokaryotic cell. Cell without a nucleus such as bacteria.

- ◦ reproduce by cell division,
- ◦ metabolize raw materials into energy, and
- ◦ respond to external and internal stimuli.

Despite their functional variety, the basic structural elements of most cells are the same,

- ◦ networks of filaments maintain cell shape and organize its content and
- ◦ fluid sheets enclose the cells and its compartments.

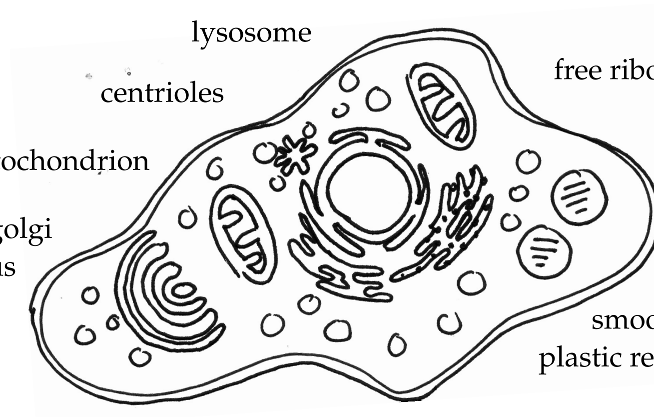

Figure 1.2: Eukaryotic animal cell. Cell with a distinct nucleus.

From a mechanical point of view, all cells have a remarkably similar layout; they are even made up of similar subunits. For example, the protein actin, one of the cell's principal filaments, can be found in almost all cells ranging from yeast cells to human cells. By studying the remarkable similarity of the cell's biochemistry and biomechanics, we aim at finding systematics and **basic paradigms that help to explain cellular form and function**. By characterizing biological cells with the help of the fundamental laws of physics, we hope to answer the following questions:

How do cells maintain their shape?
What are the mechanical properties of the individual components that give the cell it's strength and elasticity? What are their stability limits?

How do cells move?
What are the structural components that support cellular motion? How is motion generated according to Newton's laws which teaches us that cells need to adhere to push themselves forward?

How do cells transport material?
What are the mechanisms by which proteins are transported from their production site to their working site?

How do cells interact with their environment?
What are the cell's mechanisms to sense environmental changes and respond to them?

1.3 Introduction to biopolymers

A typical finding is that other than most engineering materials like steel or concrete, cells are extremely **soft**, almost liquid like. Their mechanical behavior and their microstructure resemble those of rubber. Rubber consists of a network of polymeric chains that become more resistant to deformation when heated. This is somewhat counterintuitive since most engineering materials you might know behave the other way around. Polymeric materials are characterized by **entropy** rather than **energy** and we will see in the next section what that actually means. The first investigations in the context of entropy of natural rubber are attributed to Gough 1805. We can distinguish four main biopolymers

- carbohydrates
- lipids
- proteins, and
- nucleic acids.

They are made of **monomers** and **polymers**. Monomers are smaller micromolecules such as nucleic acids, amino acids, fatty acid, and sugar. Assembled together as repeating subunits, monomers form long macromolecules which are referred to as polymers. Typical examples of biopolymers are

- genes: RNA, DNA
- gene products: peptide, protein, and
- biopolymers not coded by genes: lipid, polysaccharide, and carbonhydrate.

Think of one-dimensional engineering structures such as steel rods. Engineering rods are usually straight, they don't really change their shape in response to thermal fluctuations in their energy. In contrast, biopolymers are very flexible. Upon thermal fluctuations, they may bend from side to side and jiggle around. This is the nature of soft matter related to the notion of entropy.

1.4 Introduction to the cytoskeleton

The structural integrity of the cell is maintained by a complex network of tensile and compressive one-dimensional elements, the cytoskeleton. The cytoskeleton is the cellular scaffold which

- maintains cell shape
- protects the cell
- helps to generate cellular motion, and
- assembles and disassembles dynamically
- enables intercellular transport.

The eukaryotic cytoskeleton consists of three main kinds of cytoskeletal filaments

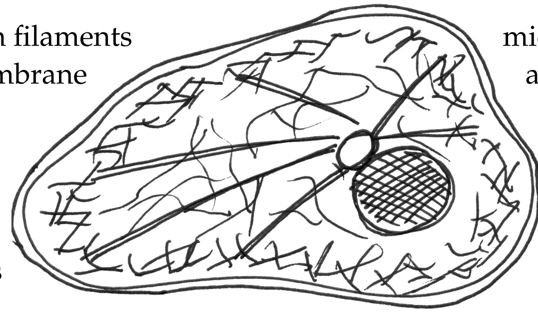

Figure 1.3: Eukaryotic cytoskeleton, consisting of thin actin filaments and intermediate filaments which act as tensile ropes and thick hollow microtubules which act as compressive trusses

- actin filaments or microfilaments,
- intermediate filaments, 8-12nm in diameter, and
- microtubules, hollow cylinders, 25nm in diameter with a 15nm lumen.

Actin filaments are 7nm in diameter and consist of two intertwined actin chains. They are tension bearing members of the cell. Being located close to the cell membrane, they are responsible for inter- and intracellular transduction. Together with myosin, they from the contraction apparatus to generate muscular contraction of skeletal and cardiac muscle.

Intermediate filaments are 8-12nm in diameter and thus more stable than actin filaments. They are also tension bearing within a cell. Anchoring at organelles, they organize and maintain the three dimensional structure of the cell.

Microtubules are hollow cylinders, 25nm in diameter with a 15nm lumen. They are comprised of 13 protofilaments consisting of $\alpha-$ and $\beta-$tubulin. Microtubules are organized by the centrosome, but reassemble dynamically. Unlike actin and intermediate filaments, microtubules can also bear compression. In addition, they form a highway for intracellular transport.

1.5 Introduction to biomembranes

All cellular components are contained within a cell membrane the mechanical properties of which we will explore throughout this class. The cell membrane is extremely thin, approximately 4-5nm, and flexible, which allows the cell to easily adjust its shape in response to environmental changes. Just think of red blood cells which have to be squeezed through extremely tiny vessels much smaller than the size of the cells themselves. Inside the cell membrane, the cell almost behaves like a liquid. Cells consist to more than 50% of water which actually has a composition similar to sea water. The cell membrane is semi-permeable; it allows for a controlled exchange between intracellular and extracellular components and information. We can distinguish between

◦ passive transport through the membrane driven by gradients in concentration and
◦ active transport through the membrane that would require extra energy.

Active transport is regulated by ion channels, pumps, transporters, exchangers, and receptors. The extracellular fluid around the cells consists of

◦ charged ions, e.g., calcium, potassium, and sodium
◦ nutrients, e.g., glucose, oxygen, amino acids, and vitamins, and
◦ regulatory chemicals, e.g., steroids and hormones.

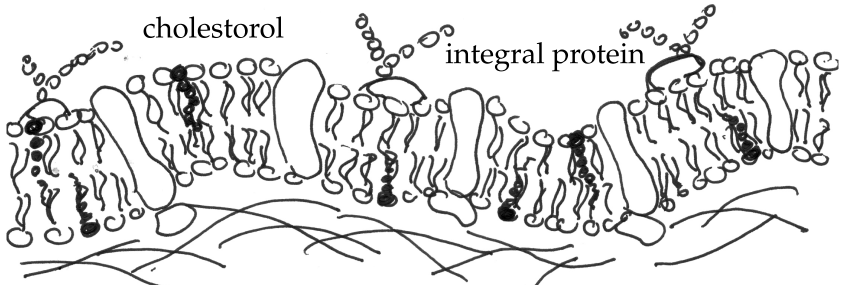

Figure 1.4: Cell membrane. Phospholipid bilayer with hydrophobic water avoiding tails and hydrophilic water loving heads.

The barrier between the inner and outer cell is the cell membrane, a bilayer consisting of phospholipids of a characteristic structural arrangement, see figure 1.4. In aqueous solutions, these phospholipids essentially display two kinds of non-covalent interactions which are referred to as

◦ hydrophobic, water avoiding non-polar residues
◦ hydrophilic, water loving polar head groups

This behavior is similar to fatty acids or oil in water, where the hydrophilic polar heads would typcially be oriented towards the water phase while the hydrophobic tails would be oriented towards the oil phase.

In most cells, the internal pressure is much higher than the surrounding pressure, somewhat like in a balloon. The cell membrane thus has to be strong enough to prevent the explosion of the cell. Plant cells and most bacteria have found an efficient solution to withstand the internal pressure, their cells have an external wall to reinforce their cell membrane and balance the pressure difference across it.

Organelles are specialized subunits within a cell that are usually enclosed by their own lipid membrane. The name organelle illustrates that these subunits have a similar function to the cell as have organs to the human body. Larger organelles such as the cell nucleus are easily visible with a light microscope. Many different types of organelles may be found in a cell depending on the cell's function. Typical examples of organelles in eukaryotic cells and their characteristic functions are

- nucleus: maintenance of DNA and transcription of RNA
- endoplasmic reticulum: tranlation and folding of new proteins
- Golgi apparatus: storage and sorting of proteins
- mitochondrion: energy production through conversion of glucose to ATP
- vacuole: storage and homeostasis
- chloroplasts: photosynthesis in plant cells

Substructures that perform particular specialized functions but do not possess a distinct membrane are typically not considered as organelles. Typical examples of such structures without membranes are

- ribosome: complexes of RNA that express genetic code from nucleic acid into protein
- flagellum: tail-like structures that enable locomotion
- cytoskeleton: polymeric network to maintain cell shape

All the material within a cell, with the exclusion of the nucleus, is defined as cytoplasm. The cytoplasm contains organelles as well as the largely aqueous cytosol.

What are the three things you hope to learn in this class? **biology** overview of cellular biology become more comfortable with cell biology what is a cell / how is it build more details on microtubules structure which kind of models are there to describe a cell **mechanics** overview of mechanics cell modeling and simulation viscoelastic modeling of tissue behavior why different tissues have such different mechanical properties how cells influence matrix mechanics mechanical properties of microtubules **biomechanics** be more able to fuse engineering and cell biology basic mechanics applied to biology how mechanical environment relates to structure and how structure relates to optimized function mechanics of cell movement / cell motility how cells respond to stress / deformation how mechanics can be utilized to analyze biological structures how cells move and adhere cell deformation under force mechanical behavior of cells cell mechanical property change under different environment how to drive mechanical properties of a protein / molecule by performing MD or similar simulations