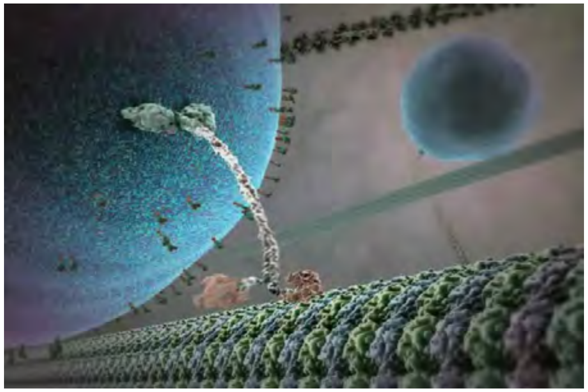
1. introduction to cell biology



the inner life of a cell, viel & lue, harvard [2006]

me239 statistics

some information about yourself

- 41.7% undergrad
- 58.3% grad student
- 58.3% ME
- average year: 3.7
- average year: 1.3
- 41.7% BME + 1 BioE

i am taking this class because

- I am interested in cells
- I am interested in mechanics
- I want to learn how to describe cells mechanically
- I want to learn how the mechanical environment influences the cell

cell mechanics is primarily part of my...

- 29.2% research
- 87.5% coursework

me239 statistics

background in cell biology and mechanics

- **cells** mostly undergrad coursework (75.0%), high school classes. some have taken graduate level classes (12.5%) and done research related to cell biology
- **mechanics** almost all have a solid mechanics background from either undergraduate degrees (75.0%) or graduate classes (25.0%).

three equations that you consider most important in mechanics

- hooks law / more generally constitutive equations
- newton's second law – more generally equilibrium equations
- stress equals force over area / laplace law

three things that you consider most exciting in cell biology

- cell migration, cell-cell communication
- mechanotransduction, interaction between cells and environment
- stem cells, stem cell therapy, cell differentiation

me239 statistics

what particular cells are you interested in and why...

- cardiomyocytes ... clinical implications, prevalence of cardiac disease
- stem cells ... potential benefit for patients suffering from numerous conditions
- read blood cells ... i think they are cool
- neural cells ... i love the brain
- skin cells, bone cells, cartilage cells

which scales are you most interested in?

- 12.5% cellular scale and smaller
- 45.8% cellular scale and larger
- 37.5% all scales

please describe why you are taking this class

- interaction between mechanics and organisms on cellular level
- because I like Ellen and my advisor told me to
- trying to figure out what to do with my life - i hope this class helps

me239 statistics

what kind of class materials would you prefer to use?

- 25.0% single textbook / focus on relatively basic knowledge
- 8.3% multiple textbooks / focus on relatively broad knowledge
- 20.8% recent manuscripts / focus on current state of the art knowledge
- 50.0% a combination of a textbook and some recent manuscripts

what kind of class format would you prefer?

- 4.2% blackboard only
- 41.7% slides and handouts
- 45.8% blackboard, slides, and handouts

which way would like to address the equations of cell mechanics?

- 45.8% theoretically on the blackboard / restricting ourselves to simple problems
- 4.2% computationally, e.g., with the help of matlab / more complex problems
- 58.3% combined theoretical and computational

me239 statistics

what kind of final project would you like?

- 20.8% single projects
- 58.3% projects in groups of two
- 50.0% research related projects with more freedom but less guidance
- 37.5% selected projects with less freedom but more guidance

additional comments

- would be nice if you could go easy on the undergrads
- maybe you could also cover lipid layer modeling

... thanks for your input, we'll try to address it as much as possible!

why cell mechanics is important

to understand interaction between cells and their environment • to improve the control/function of cells • to improve cell growth/cell production • to manipulate cells for medical applications • to treatment of certain diseases • to understand how mechanical loading affects cells, e.g. stem cell differentiation or cell morphology • to understand how mechanically gated ion channels work • to understand how the loading of cells could aid developing structures to grow cells or organize existing cells more efficiently • to understand macrostructural behavior • to build machines/sensors similar to cells • to understand how cell growth is affected by stress and mechanical properties of the substrate the cells are in • to understand how cells move and • to change cell motion • to build/engineer tissues with desired mechanical properties • to understand how cells are affected by their environment • to understand how mechanical factors alter cell behavior and gene expression • to understand how different cells interact with each other • to be able to study the impact of different parts of a cell on its overall behavior • to provide scientific guidance for targeted cell manipulation

the classical cell theory

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

hooke [1665] schwann & schleiden [1839], virchow [1858]

some facts and figures

- humans consists of ~100 trillion,i.e.,10^{14} cells
- humans consists of ~210 different cell types
- a typical cell size is 10 μm
- the 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

characteristics of cells

- cells **reproduce** by cell division
- cells **metabolize** raw materials into energy
- cells **respond** to external and internal stimuli

basic structural elements of most cell types

- **networks of filaments**
  to maintain cell shape and organize its content
- **fluid sheets**
  to enclose the cell and its compartments

why cell mechanics is important

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 to respond to them?

prokaryotic cells

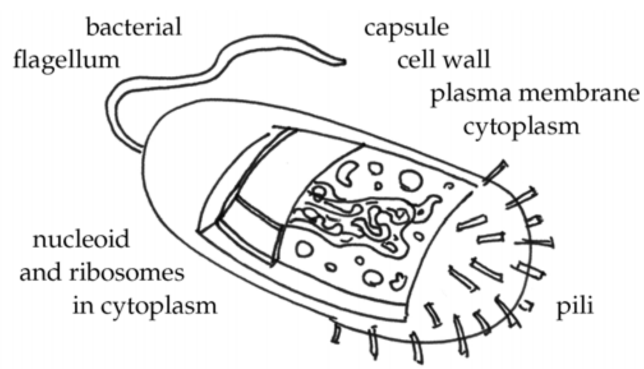


Figure 1.1 Prokaryotic cell. Cell without a nucleus.

example - mechanics of prokaryotic cells

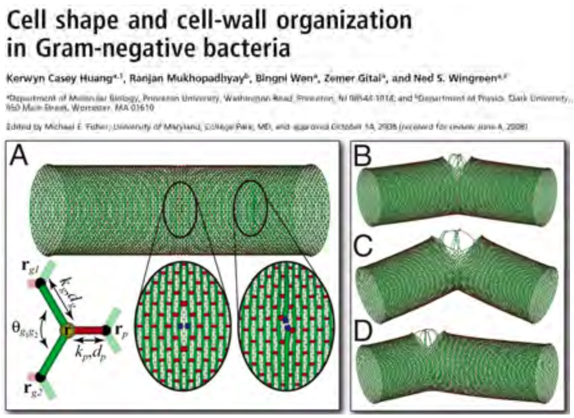


Figure 1.1.1 Elastic model of the peptidoglycan network predicts cracked cell shapes. Glycan strands shown in green are hoops that wrap around circumference of the cylinder, whereas peptide crosslinks shown in red are longitudinal. Both are in tension due to osmotic pressure.

eukaryotic cells

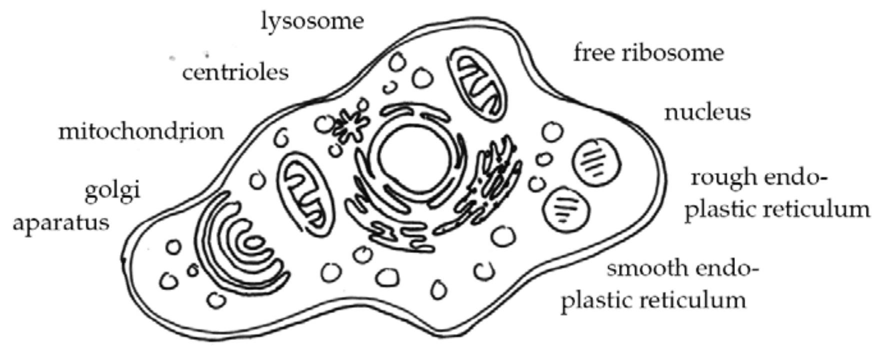


Figure 1.2 Eukaryotic cell. Cell without a distinct nucleus.

organelles

organelles are **specialized subunits** within a cell that are enclosed by their own **lipid membrane**. the name organelle indicates that these subunits have a similar function to the cell as have organs to the human body. larger organelles such as the nucleus are easily visible with a light microscope. different types of organelles may be found in a cell depending on the cell's function.

typical organelles and their characteristic functions

- nucleus - maintenance of DNA and transcription of RNA
- endoplastic reticulum - translation and folding of new proteins
- golgi apparatus - storage and sorting of proteins
- mitochondrion - energy production / conversion of glucose to ATP

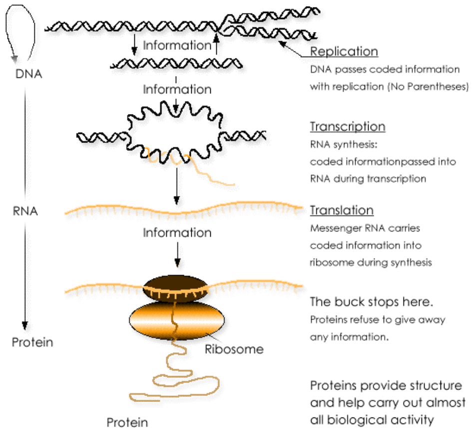
cytoplasm

all material within a cell, with the exclusion of the nucleus, is defined as **cytoplasm**. the cytoplasm contains **organelles**, all other **substructures** within the cell, and the largely aqueous **cytosol**. substructures that perform particular specialized functions but do not possess a distinct membrane are typically not considered organelles.

substructures without a membrane and their functions

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

the central dogma



http://www.ict-science-to-society.org/pathogenomics

nucleus

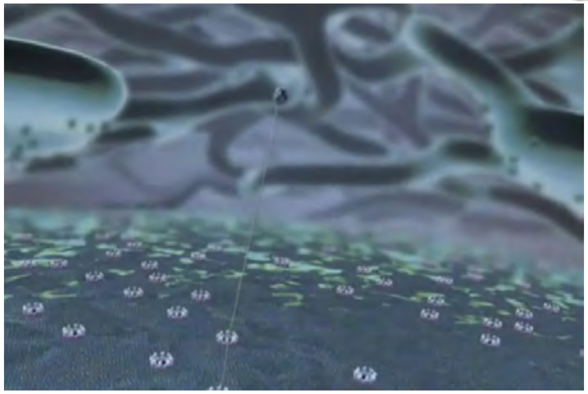


Figure 1.2.1 The nucleus is a membrane-enclosed organelle found in eukaryotic cells. Its function is to maintain the integrity of genes and control the activities of the cell by regulating gene expression. Because the nuclear membrane is impermeable, nuclear pores are required to allow movement of molecules across the envelope. These pores allow the import of particles containing mRNA and proteins into the cytosol.

the inner life of a cell, viel & lue, harvard [2006]

free ribosomes

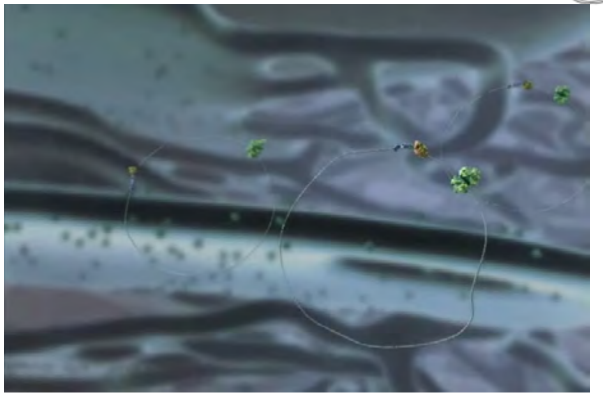


Figure 1.2.2 Free ribosomes translate the mRNA molecules into proteins. Some of these proteins will reside in the cytosol. Others will associate with specialized cytosolic proteins and be imported into mitochondria or other organelles. The synthesis of cell secreted and integral membrane proteins is initiated by free ribosomes which then dock to protein translocators at the surface of the endoplasmic reticulum.

the inner life of a cell, viel & lue, harvard [2006]

endoplasmic reticulum

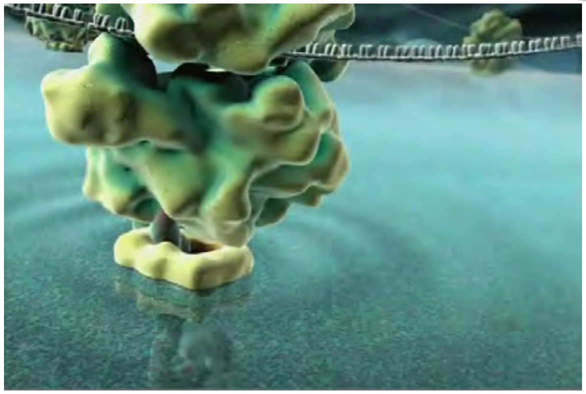


Figure 1.2.3 The endoplasmic reticulum forms an interconnected network of tubules, vesicles, and cisternae within cells. Rough endoplasmic reticulums synthesize proteins, while smooth endoplasmic reticulums synthesize lipids and steroids.Cell secreted proteins accumulate in the lumen of the endoplasmic reticulum, while integral membrane proteins become embedded in the endoplasmic reticulum membrane.

the inner life of a cell, viel & lue, harvard [2006]

golgi apparatus

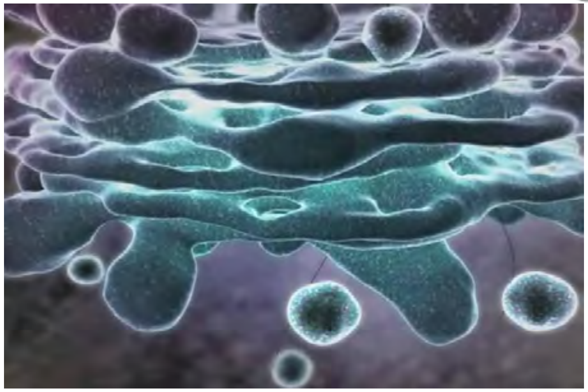


Figure 1.2.4 Proteins are transported from the endoplasmic reticulum to the Golgi apparatus by vesicles traveling along the microtubules. Protein glycosylation initiated in the endoplasmic reticulum is completed inside the lumen of the Golgi apparatus. Fully glycoslated proteins are transported from the Golgi apparatus to the plasma membrane.

the inner life of a cell, viel & lue, harvard [2006]

mitochondria

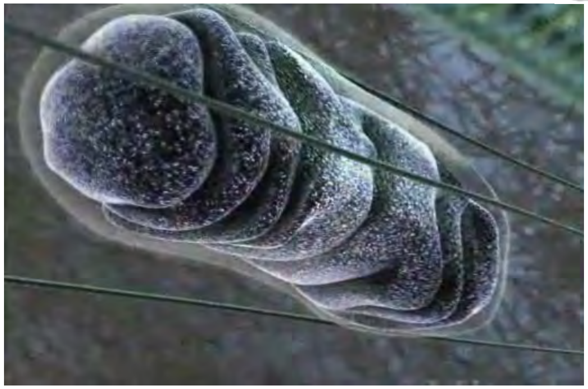


Figure 1.2.5 Membrane bound organelles like mitochondria are loosely trapped by the cytoskeleton. Mitochondria change shape continuously and their orientation is partly dictated by their interaction with microtubules. Mitochondria supply the cell with energy and are often referred to as the power house of the cell.

the inner life of a cell, viel & lue, harvard [2006]

biopolymers

unlike 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 stretched or 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**.

the four types of biopolymers

- carbohydrates
- lipids
- proteins
- nucleic acids

biopolymers

biopolymers are made up 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

- genes: RNA and DNA
- gene products: peptides and proteins
- biopolymers not coded by genes: lipids, polysaccharides, and carbohydrates

biopolymers are **extremely 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**.

biopolymers

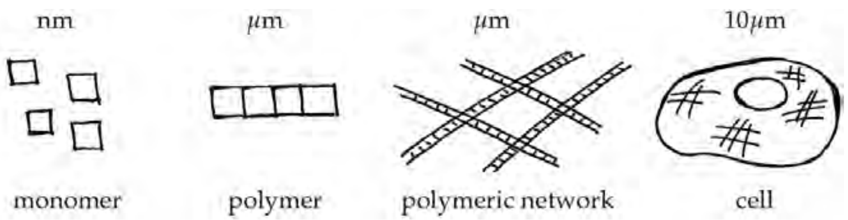


Figure 3.1. Biopolymers. Characteristic length scales on the cellular and sucellular level..

the cytoskeleton

the **structural integrity** of the cell is maintained by a complex network of **tensile** and **compressive** one-dimensional **elements** called the cytoskeleton.

function of the cytoskeleton

- to maintain cell shape
- to protect the cell
- to help to generate cellular motion
- to enable intercellular transport
- to assemble and disassemble dynamically

the cytoskeleton

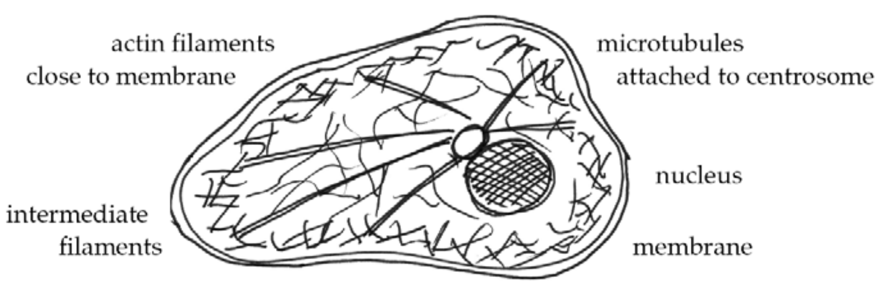


Figure 1.3. Eukaryotic cytoskeleton. The cytoskeleton provides structural stability and is responsible for force transmission during cell locomotion. Microtubules are thick hollow cylinders reaching out from the nucleus to the membrane, intermediate filaments can be found anywhere in the cytosol, and actin filaments are usually concentrated close to the cell membrane.

the cytoskeleton

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 α and β 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.

actin filaments

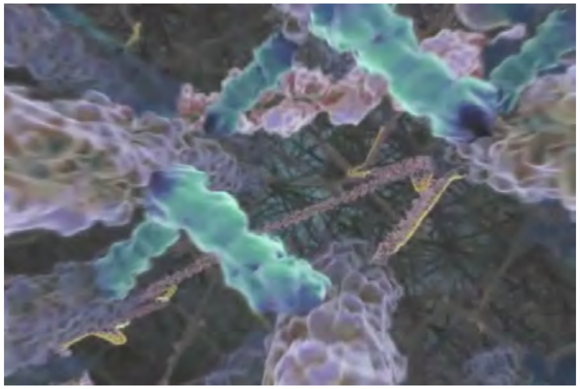


Figure 1.4.1 Actin filaments form tight parallel bundles which are stabilized by cross-linking proteins. Deeper in the cystol the actin network adopts a gel-like structure, stabilized by a variety of actin binding proteins.

the inner life of a cell, viel & lue, harvard [2006]

actin filaments

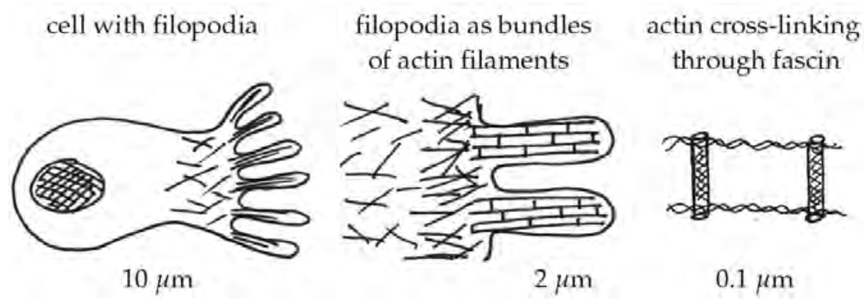


Figure 4.3. Bundles of actin filaments tightly crosslinked through fascin are known as filopodia. The mechanical properties of filopodia play an essential role in various different physiological processes including hearing, cell migration, and growth.

actin - polymerization

Figure 1.4.2 The actin network is a very dynamic structure with a continuous directional polymerization and disassembly. Filaments, capped at their minus ends by a protein complex, grow away from the plasma membrane by the addition of actin monomers to their plus end.

the inner life of a cell, viel & lue, harvard [2006]

microtubules

Figure 1.4.3 The cytoskeleton includes a network of microtubules created by the lateral association of protofilaments formed by the polymerization of tubulin dimers.

the inner life of a cell, viel & lue, harvard [2006]

microtubules - polymerization

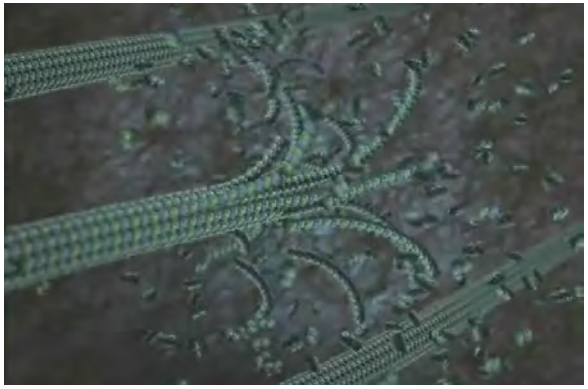


Figure 1.4.4 While the plus ends of some microtubules extend toward the plasma membrane, proteins stabilize the curved conformation of protofilaments from other microtubules, causing their rapid plus end depolymerization.

the inner life of a cell, viel & lue, harvard [2006]

microtubules - motor proteins

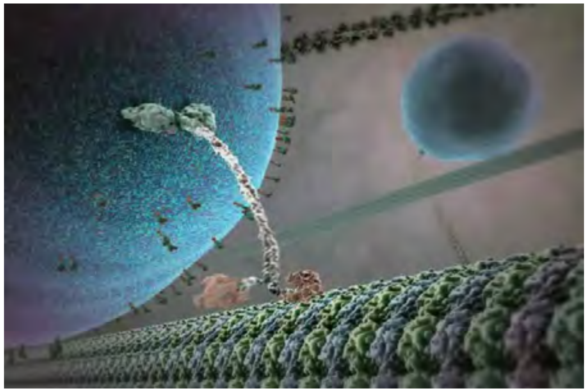


Figure 1.4.5 Microtubules provide tracks along which membrane bound vesicles travel to and from the plasma membrane. Kinesins are motor proteins that travel along microtubules carrying important cargo. In this case, the kinesin is carrying a vesicle, which is essentially a bubble full of proteins and other important molecules that are needed at other parts of the cell.

the inner life of a cell, viel & lue, harvard [2006]

microtubules - centrosome

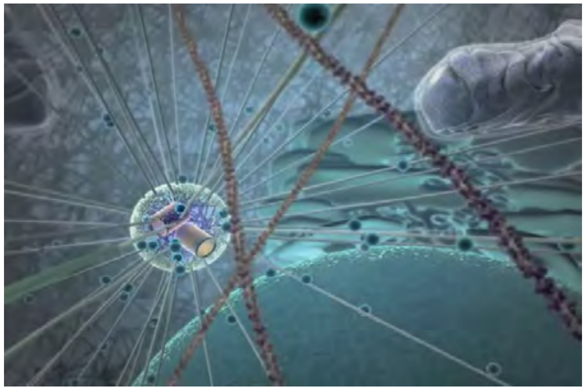


Figure 1.4.6 All the microtubules originate from the centrosome, a discrete fibrous structure containing two orthogonal centrioles and located near the cell nucleus.

the inner life of a cell, viel & lue, harvard [2006]

networks of filaments

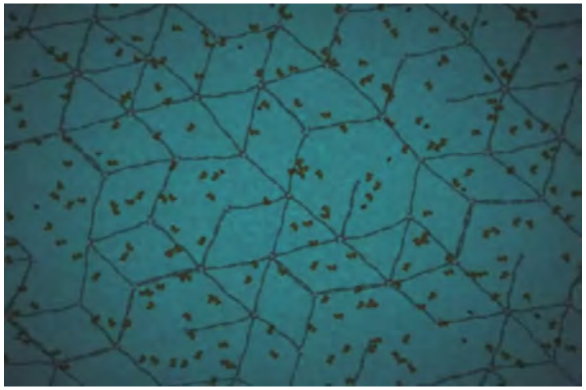


Figure 1.4.7. Beneath the lipid bilayer, spectrin tetramers arranged into a hexagonal network are anchored by membrane proteins. This network forms the membrane skeleton that contributes to membrane stability and membrane protein distribution.

the inner life of a cell, viel & lue, harvard [2006]

the cell membrane

all cellular components are contained within a cell membrane which is **extremely thin**, approximately 4-5nm, and **very flexible**. inside the cell membrane, most cells behave like a liquid as they consist of more than 50% of water. the cell membrane is **semi-permeable** allowing for a controlled exchange between intracellular and extracellular components and information.

mechanisms of transport through the membrane

- passive transport driven by gradients in concentration
- active transport that does require extra energy; it is regulated by ion channels, pumps, transporters, exchangers and receptors

the cell membrane

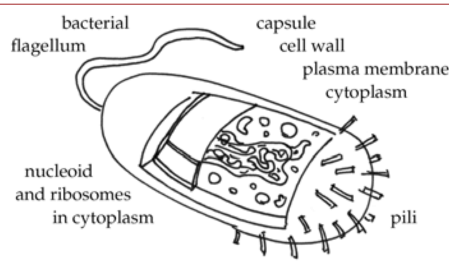
the barrier between the inner and outer cell is the cell membrane, a **bilayer** consisting of **phospholipids** of a characteristic structural arrangement. in aqueous solutions, these phospholipids essentially display two kinds of non-covalent interactions.

non-covalent interactions of phospholipids

- 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 tend to be oriented towards the water phase while the hydrophobic tails are oriented towards the oil phase.

the cell wall



in most cells, the **internal pressure** is much higher than the surrounding pressure. 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.

the cell membrane

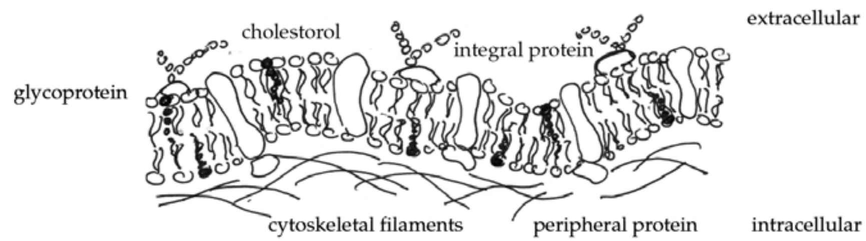


Figure 1.3. Cell membrane. Phospholipic bilayer with hydrophobic water-avoiding tails and hydrophilic water-loving heads.

the lipid bilayer

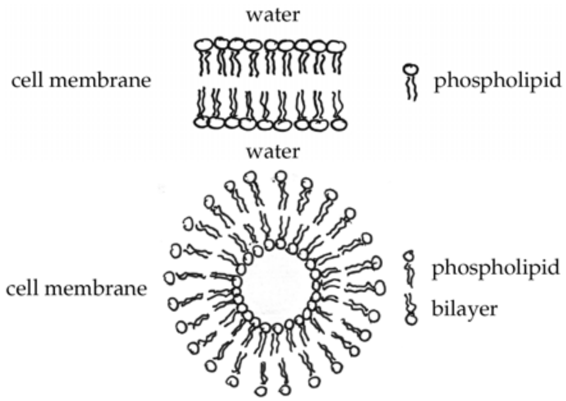


Figure 5.16. Lipid bilayer of the cell membrane. Characteristic arrangement of phospholipid molecules with hydrophilic polar head group being oriented towards the aqueous phase while the hydrophilic tails are oriented towards the non-polar inside.

the lipid bilayer

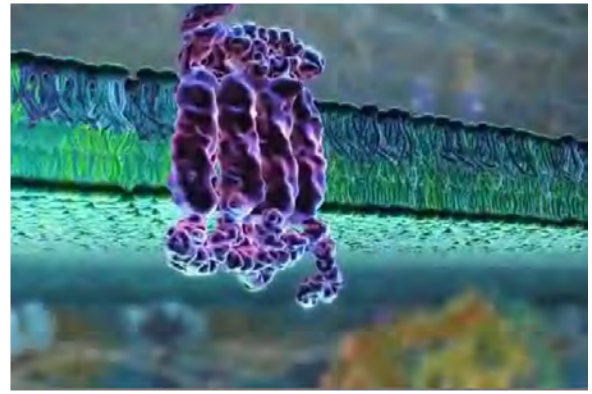


Figure 1.5.1. Lipid bilayer of the cell membrane. Characteristic arrangement of phospholipid molecules with hydrophilic polar head group being oriented towards the aqueous phase while the hydrophilic tails are oriented towards the non-polar inside.

the inner life of a cell, viel & lue, harvard [2006]

the lipid bilayer - lipid rafts

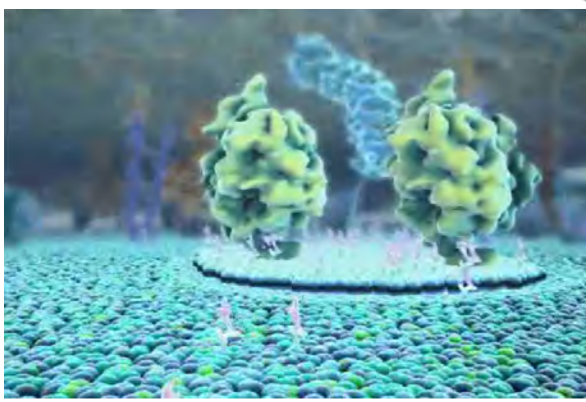


Figure 1.5.2. The lipid bilayer of the cell membrane is by no means static and homogeneous. Lipids are a class of molecules stacking together to form the membrane which can be understood as a sea on which things are floating. The rafts floating on this sea are called lipid rafts.

the inner life of a cell, viel & lue, harvard [2006]

the inner life of a cell

- short 3D computer graphics animation demonstrating various biological mechanisms that occur within a white blood cell in the human body
- many of the animated processes are inherent to other eukaryotic cells
- animation created for harvard's department of molecular and cellular biology
- animated processes are result of alain viel's phd work
- creators at XVIVO who made the movie: david bolinsky, former lead medical illustrator at yale, lead animator john liebler, and mike astrachan
- 14 months of creation for 8.5 minutes of animation, launched 2006

http://multimedia.mcb.harvard.edu/anim_innerlife.html