Cells are the fundamental building blocks of life. The understanding of their characteristic biological features, their motility, their biochemistry and their interaction with the environment is crucial when cells are to be applied, modified or engineered in health care and modern medical therapies. This class focuses on the mechanical aspects of the cell which can be two fold: On the one hand, cell biology and biochemistry influence the mechanical properties of the cell. On the other hand the mechanical environment, load, pressure, stress, or strain can influence the cell's shape and integrity, and eventually its biology and biochemistry. In the first part of this class, we will discuss how cell properties can be measured experimentally and how they can be characterized in the form of equations. Concepts of energy and entropy will be elaborated for different structural units of the cell: biopolymers, i.e., microtubules, actin, and intermediate filaments and biomembranes, i.e., the lipid bilayer that forms the cell membrane. Computational simulation tools will be introduced to explain and understand cell behavior in silico. In the second part, we address aspects of mechanotransduction which are part of active research in cell mechanics. We discuss different aspects of how cells sense loads and how signals are transmitted within the cell and through the extracellular matrix.

Can we make functional cardiomyocytes?

Isolated functional adult cardiomyocyte from inya-agha, klauke, davies, smith, cooper [2007]
fundamental building blocks - quantification

qPCR - up- & downregulation of specific markers

me239 mechanics of the cell - motivation

fundamental building blocks - structural arrangement

microarrays - up- & downregulation of specific markers

me239 mechanics of the cell - motivation

fundamental building blocks - assembly

and that’s why we need engineers!

imaging - identification of cellular microstructure

HESC-derived cardiomyocytes - courtesy of Jayakumar Rajadas

me239 mechanics of the cell - motivation
Fundamental building blocks - assembly

In vitro measurement vs in silico prediction

HESC-derived cardiomyocytes - courtesy of Jayakumar Rajadas

me239 mechanics of the cell - motivation

Functionality is controlled through the mechanome

1. Differentiation
   - from embryonic to functional adult

2. Heart failure
   - from healthy to eccentric hypertrophic

3. Wall thickening
   - from healthy to concentric hypertrophic

4. Dedifferentiation
   - from functional adult back to embryonic

And that’s why we need engineers!

Genome

Mechanome

Transcriptome

Proteome

Functionality is controlled through the mechanome

#4 Dedifferentiation - from functional adult to embryonic

In long term culture cells revert to embryonic phenotype

Bugalsky & Zak (1989)
Grading

Homework 30 %  three homework assignments, 10% each
Midterm 30 %  one single letter format page of notes allowed
Final Project 20 %  oral presentations graded by the class,
Final Project 20 %  written essay graded by myself ;-) 

Tue 05/18  Midterm
Thu 05/27  Final projects I
          Oral presentations evaluated by the class
Tue 06/01  Final projects II
          Oral presentations evaluated by the class
Tue 06/01  Final projects due
          Written essays due

me239 mechanics of the cell - grading
Mechanisms of Neuron Repair and Stem Cell Neural Differentiation:

Neural Stem Cell Growth and Differentiation in Spinal Cord Injury Research

Example: finite element simulation of pipette aspiration

Cell design contest

me239 mechanics of the cell - final project

me239 mechanics of the cell - homework
me239 mechanics of the cell - homework

Introduction I - Cell biology
Overview of the cell
Biochemistry
Biopolymers
Biomembranes

Introduction II - Cytoskeletal biology
Cytoskeletal composition and structure
Regulating cell structure and function
Stem cells

Introduction III - Structural mechanics
Equilibrium - stress
Kinematics - strain
Material behavior – stress strain relation
Energy and entropy

Biopolymers I – Energy
Structural mechanics of biopolymers
Tension, bending, and buckling

Biopolymers II – Entropy
Introduction to statistical mechanics
Freely jointed chain model
Worm like chain model

Biopolymers III – Polymerization
Polymerization kinetics
Actin, tubulin, and microtubules
Treadmilling
Amoeba

add’t information http://biomechanics.stanford.edu and coursework
Cytoskeletal mechanics I
Fiber bundle model
Filopodia

Cytoskeletal mechanics II
Chain network models
Red blood cells

Cytoskeletal mechanics III
Tensegrity models
Generic eukaryotic cells

example: amoeba

this single-celled amoeba crawls around by using actin polymerization to push out pseudopods, or false feet, to explore new territory. at the same time, organelles move in complex patterns within the cell.

alberts et al. [2008]

example: red blood cells

red blood cells must deform when they squeeze through small blood vessels. in this experiment, a red blood cell is pushed and deformed with laser tweezers. it quickly springs back to its original shape because it has an extremely tough cytoskeleton to which the plasma membrane is anchored. when the cell is placed in high salt solution, however, the shape changes dramatically, driven by the difference in ionic pressure; water rushes out of the cell causing spikelike protrusions to form as the cell collapses.

alberts et al. [2008]

example: white blood cells

neutrophils are white blood cells that hunt and kill bacteria. in this spread a neutrophil is seen in the midst of red blood cells. a staphylococcus aureus bacterium has been added. the bacterium releases a chemotaxant that is sensed by the neutrophil; the neutrophil becomes polarized, and starts chasing the bacterium which, powered by its flagella, swims in a random path, seemingly avoiding its predator. eventually, the neutrophil catches up with the bacterium and engulfs it by phagocytosis.

alberts et al. [2008]
Biomembranes I
Pipette aspiration
Laplace’s law
Liquid drop model
White blood cells and cartilage cells

Biomembranes II
Lipid bilayers
Soap bubbles
Cell membranes

Biomembranes III
Mechanics of biomembranes
Tension, shear, and bending

example: neuronal cells

to demonstrate the fluidity of the lipid bilayer, a piece of the plasma membrane of this neuronal cell is pulled out with laser tweezers. remarkably, moving this membrane tubule rapidly back and forth does not rupture the plasma membrane, which flows quickly to adapt to the mechanical distortion.

me239 mechanics of the cell - biomembranes

Mechanotransduction I
Intercellular and intracellular signaling
Ion channels
Bone cells

Mechanotransduction II
Electrical signaling and electrophysiology
Huxley-Hodgkin model
Nerve cells

Mechanotransduction III
Electromechanical signaling and excitation contraction
FitzHugh-Nagumo model
Skeletal muscle cells and heart cells

example: hair cells

the stereocilia that project from hair cells vibrate in response to sound waves. here the bundle of stereocilia projecting from a single hair cell is pushed with laser tweezers to simulate this movement. movement opens stress-activated ion channels in the plasma membrane, leading to membrane depolarization. this is translated into the perception of sound. moving an individual stereocilium demonstrates the flexible attachment of these structures to the cell body.

me239 mechanics of the cell - signaling
example: epithelial cells

These epithelial cells express green fluorescent cadherin. They are grown at low density, so that isolated cells can be observed. Initially, labeled cadherin is diffusely distributed over the whole cell surface. As cells crawl around and touch each other, cadherin becomes concentrated as it forms the adhesion junctions that link adjacent cells. Eventually, as the cell density increases further, the cells become completely surrounded by neighbors and form a tightly packed sheet of epithelial cells. Alberts et al. [2008]

example: fibroblasts

Fibroblasts grown in vitro in a culture dish form a confluent monolayer of cells. Cells in a monolayer are relatively static; contacting each other inhibits their migration. Such cell layers can be wounded experimentally by scratching them with a needle. In such an experiment, we can observe that the fibroblasts at the edge of the wound become migratory and quickly move to repair the gap. Such cell migration is important for wound repair in an intact organism. Alberts et al. [2008]

example: glial cells

In this experiment, glial cells from the rat brain are grown in cell culture. Calcium concentrations are visualized with a fluorescent dye that becomes brighter when calcium ions are present. In the presence of small amounts of a neurotransmitter, individual cells light up randomly as ion channels open up and allow calcium ions to enter the cell. Occasionally, calcium waves are transmitted to adjacent cells through gap junctions at regions where the cells contact each other. Alberts et al. [2008]

example: heart cells

Single heart muscle cells spontaneously contract when grown in cell culture. This cell is grown on a flexible rubber substratum. Each time the cell contracts, it pulls on the substratum which becomes wrinkled. Although individual heart cells can beat with their own rhythms, they are coordinated in an intact heart so that all cells beat synchronously. Alberts et al. [2008]
... the 42 things to remember ...

01 Even simple mechanics can give a lot of insight...
02 ... but different cell types can have totally different mechanical characteristics!
03 Most cells consist of a cytoskeleton and organelles embedded in a membrane.
04 And as always, energy minimization rules!
05 But the free energy can consist of an energetic and an entropic contribution!
06 For jiggly filaments, the entropic term dominates the energetic term.
07 Biofilament entropy can be modeled by the statistics of long chain molecules.
08 Based on the chain shape uncorrelated or correlated chain models can be used.
09 Correlated chains can be characterized through the persistence length.
10 Polymerization governs the dynamic assembly and disassembly of filaments.
11 Cell movement is driven by filament assembly at the leading edge.
12 Treading is the simultaneous growth and shrinkage at opposite filament ends.
13 Filament growth is limited by buckling when pushing against the outer envelope.
14 The Euler buckling modes explain filopodia buckling and filament crosslinking.
15 The interaction with the environment lowers the critical buckling length.
16 Homogenization can relate subcellular and cellular mechanical properties.
17 The flexible membrane of red blood cells can be modeled as a spring network.
18 Six fold networks explain the rigidity of red blood cells, four fold networks don’t.
19 The cytoskeleton is made of microtubules, intermediate filaments and actin.
20 Tensegrity models view the cell as trusses tied together by pre-stressed ropes.

... the 42 things to remember ...

22 Lightweight engineering structures use tensegrity concepts similar to some cells.
23 Membrane phospholipids consist of hydrophilic heads and hydrophobic tails.
24 The lipid bilayer is the energetically favorable configuration of phospholipids.
25 The Law of Laplace can describe both soap bubbles and cell membranes.
26 Surface tension is important in thin membranes and in micropipette aspiration.
27 Depending on their stiffness, cells can act as elastic solid or liquid drop.
28 Structural elements display in plane tension and shear and out-of-plane bending.
29 The tension and shear equation is of 2nd order, the bending equation of 4th order.
30 Mechanotransduction is the conversion of forces into biochemical signals.
31 Its complex cascades of biochemical events are illustrated in funny figures.
32 To improve understanding, it is usually probed in tension, compression, or shear.
33 The cell membrane is selectively permeable.
34 Membrane transport is passive along and active against concentration gradients.
35 Cells consist mainly of water with charged sodium, potassium, and chloride ions.
36 At the resting state, cells are negatively charged.
37 At rest, concentration gradient and membrane potential are balanced.
38 Action potentials are responsible for an all-or-none response of excitable cells.
39 Pacemaker cells continuously re-excite themselves, muscle cells usually don’t.
40 Stem cells differentiate according to their mechanical environment.
41 Cell mechanics uses weird super large and super small units.
42 Cell mechanics still faces lots of exciting open problems that will be fun to solve!