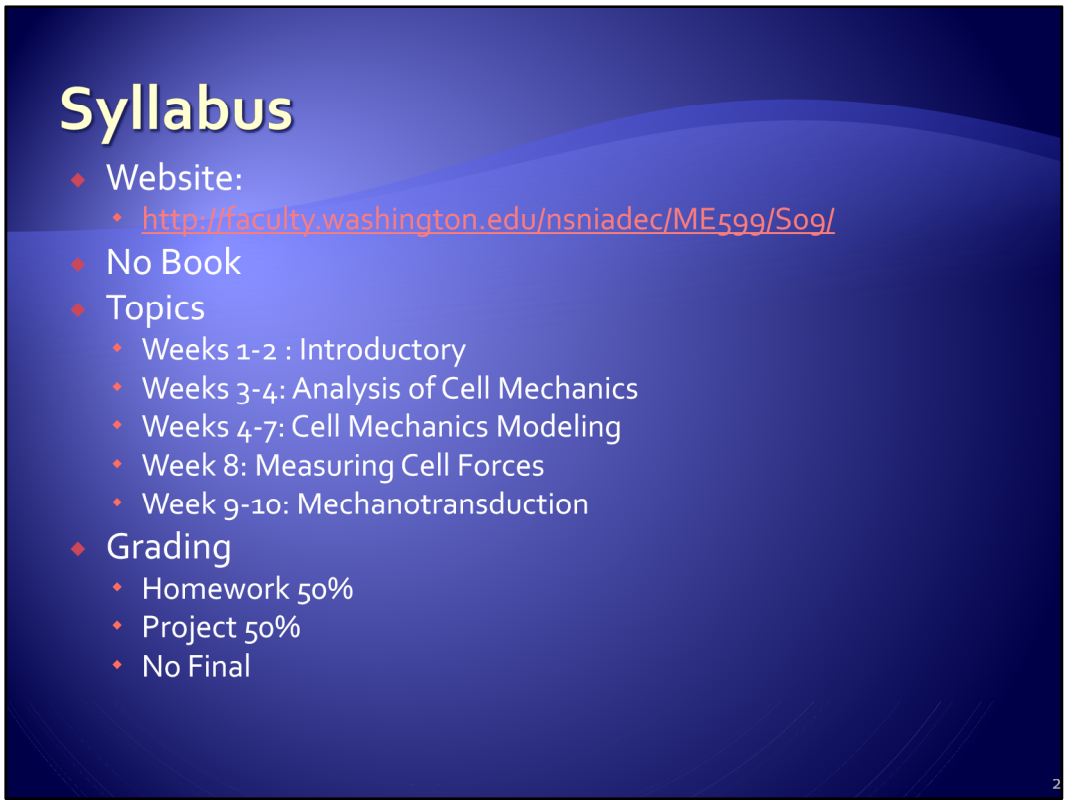
Session 1

ANALYSIS AND MODELING OF CELL MECHANICS



All course material will posted on the website.

Some material is UW NetID secured: Slides from lectures, PDFs of papers or book chapters. Please let me know if you cannot access the files.

Homework will be about once a week for a total of 8.

Project will be to build your own cell mechanics model from one of the topics covered in class (weeks 4-7). You will use this mathematical framework to try to simulate the data from an experimental analysis paper (weeks 3-4). At least, you will try to match the model the the experimental data in one figure. I will give more details on what I want for the project in a few weeks.

Introductions

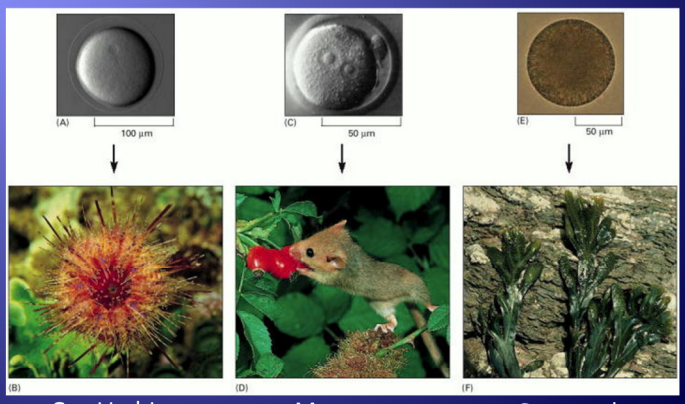
In 1665, Robert Hooke wrote *Micrographia* at the age of 28. This was the 2nd publication of the Royal Society (later known as the Royal Society of London), for whom Hooke first served as Curator of Experiments and later as a full member. In *Micrographia*, Hooke wrote about his observations of the "physical description of minute bodies, made by a magnifying glass with observations and inquiries thereupon.. In particular he described what he saw when he looked at a slice of cork through a microscope lens and noticed some "pores" or "cells" in it that remined him of the cells of an abbey. Hooke believed the cells had served as containers for the "noble juices" or "fibrous threads" of the once-living cork tree. He thought these cells existed only in plants, since he and his scientific contemporaries had observed the structures only in plant material.

This book was widely read and launched an interest in microscopy studies and microscope manufacturing. Anton van Leeuwenhoek, a Dutch dry-goods dealer, read Hooke's book and it inspired him to study the microscopic world. He is credited with inventing a glass process technique of pulled glass wire that were reheated to make glass spheres at the end which he then ground down into microscopic lenses. He wrote to the Royal Society about his discovery of "animalcules" – bacteria in saliva and protozoa in pond water. These observations of single cell living organisms were met with skepticism by the Royal Society so Hooke was asked by the Society to confirm Leeuwenhoek's findings.

The drawing to the top right was created by Hooke. Hooke was the first person to use the word "cell". Hooke also wrote Hooke's Law -- a law of elasticity for solid bodies. Not bad for a great forefather in the field of Mechanics.

What are cells?

- The basic functional units of life (composed of numerous components with distinct mechanical characteristics)
- Origins:



Sea Urchin Mouse Seaweed

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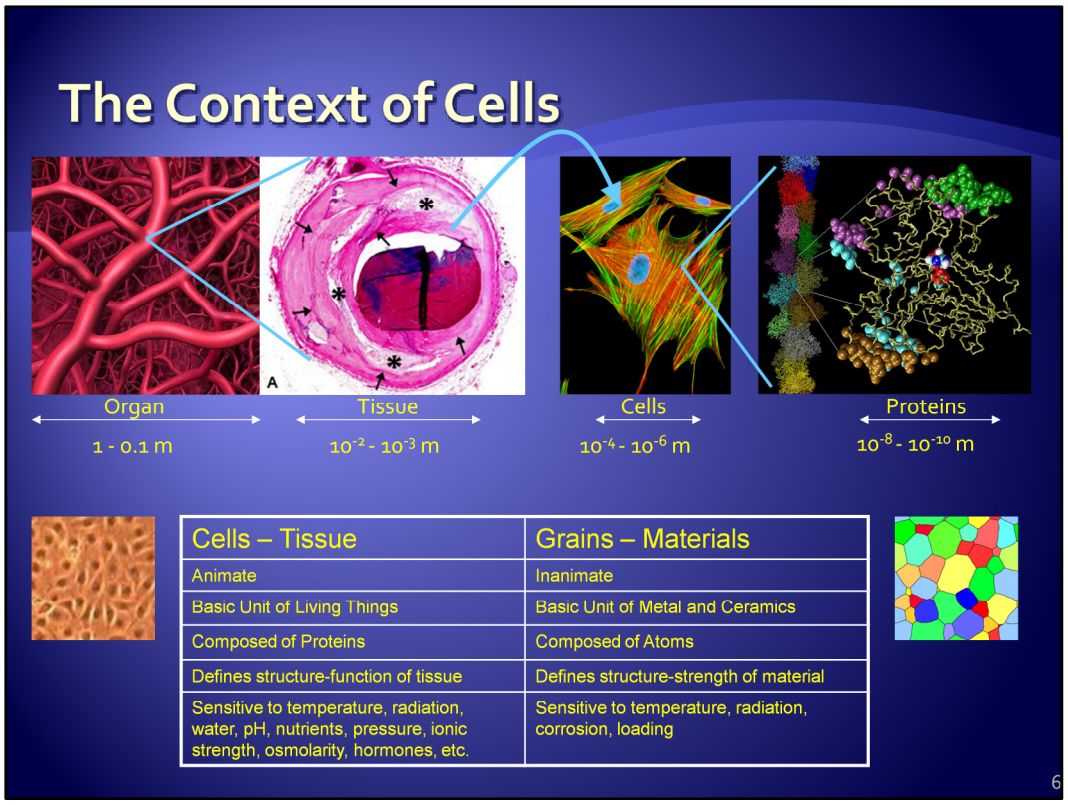
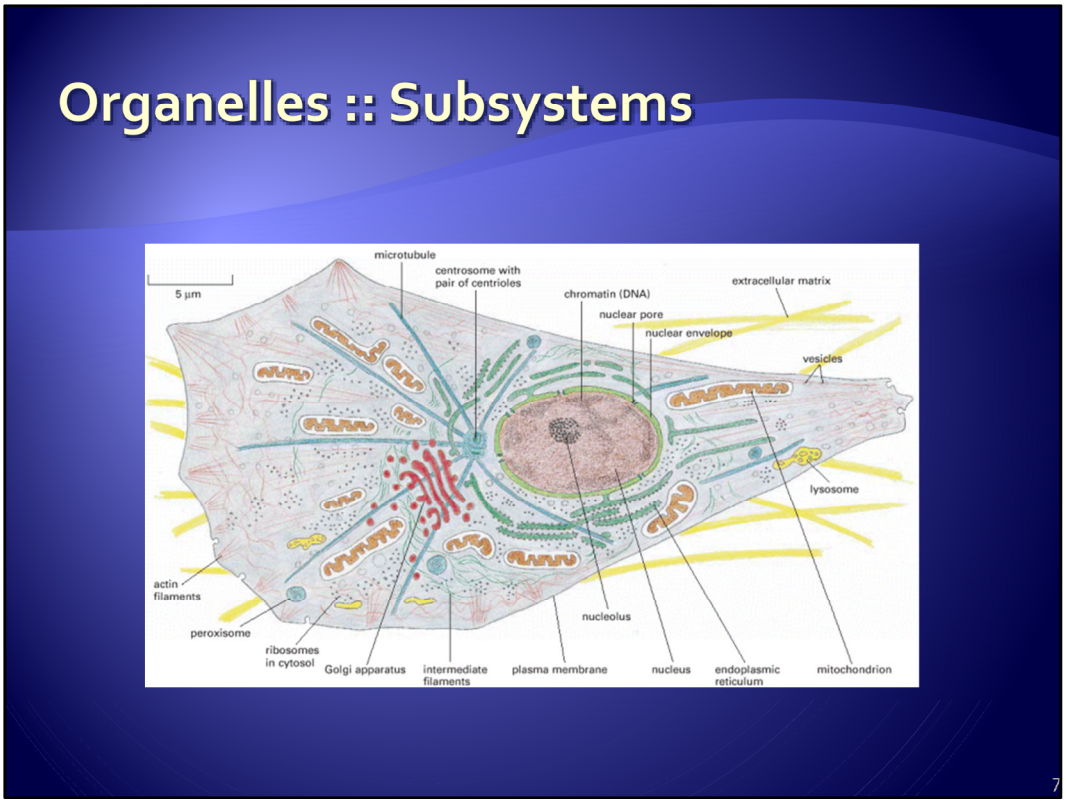
Cells are the basic units of life. We have 10 trillion cells and each one is unique in its structure and its function. For example, you have cells like osteoblasts that produce the hard bone matrix. You have highly flexible cells like red blood cells that have to squeeze through very narrow capillaries. And, you have muscle cells that are rich in proteins actin and myosin that generate motion in our bodies.

What is very interesting is that we all start from one cell, the fertilized egg. This is true for diverse organisms like sea urchins, mice, or vegetation. It is through cell division where we end up with a steady state of 10^13 cells and it is through differentiation that each cell becomes specialized in its function.



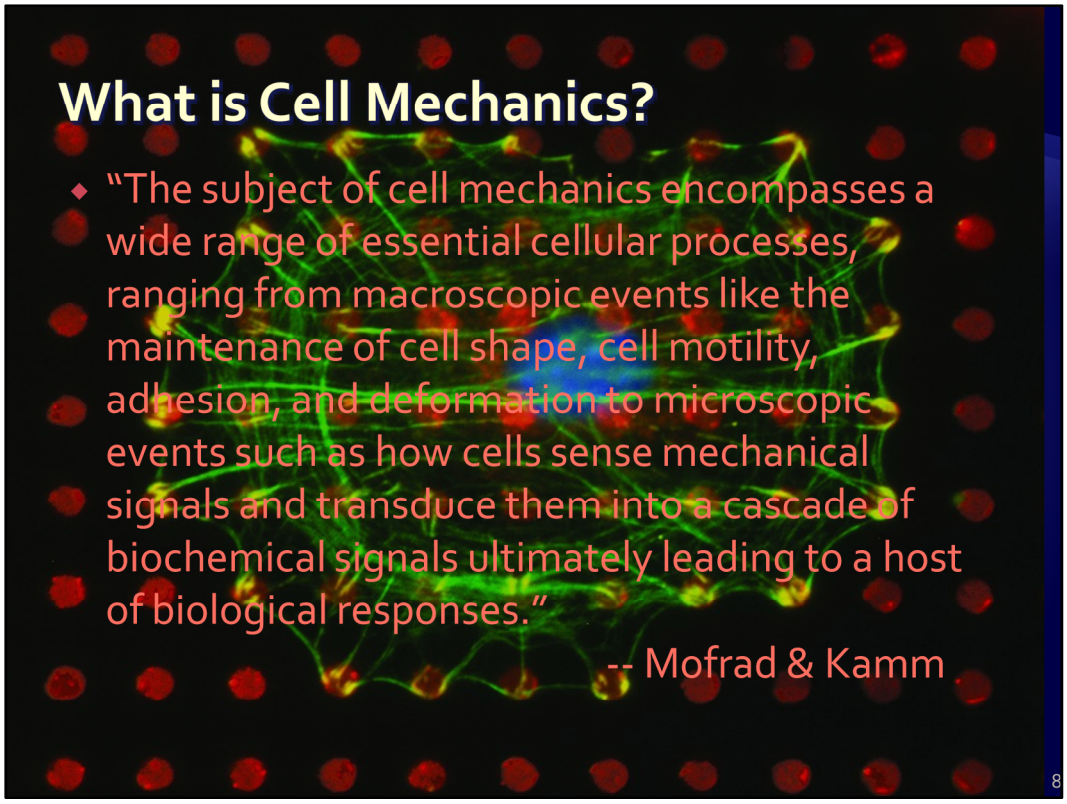
Cells are integral to the biological hierarchy of our bodies. Each organs are made up of different tissues, which in turn are made up of different types of cells, often in layers of multiple cells. A single cell is approximately 10 -100 microns in diameter. Cells like RBC or muscle are different by the proteins they produce.

So let's compare cells and tissue to what we know about grains and materials from material science.



Let's play a game…

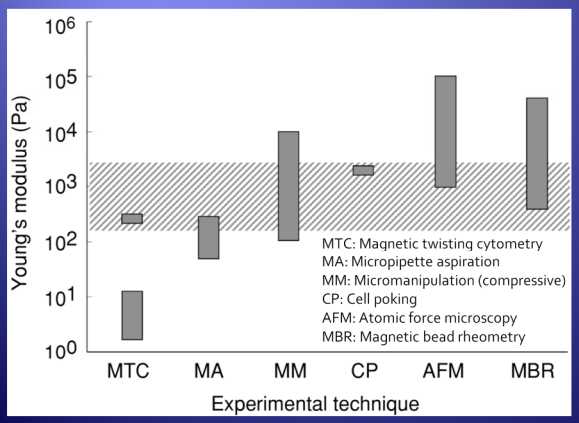
A. Walls :: Plasma Membrane – barrier made up of lipids in a bilayer arrangment and augmented by specialize proteins that separates the components in the cytosol from the extracellular environment (matrix or solubles). Cell death is likely if membrane is ruptured. Ion gradients exists across membranes needed for ATP synthesis, transmembrane transport of select ions, or produce and transmit electrical signals. Contains sensors of extracellular cues known as receptors that transfer information across the cell membrane rather than ions or molecules.
B. Building Framework :: Cytoskeleton – three filamentous proteins. 1) Actin, 2) Microtubules, 3) Intermediate Filaments
C. Power Engines :: Mitochondria
D. Command Center :: Nucleus
E. Assembly Workers :: Ribosomes – two types. 1) Membrane-bound ribosomes attach to the cytosolic side of the ER membrane and synthesize proteins from mRNA. 2) Free ribosomes are unattached to any membrane and synthesize all other proteins encoded by the nuclear genome.
F. Assembly Line :: Endoplasmic reticulum – consists of half the total membrane of a cells. Highly convoluted space of branching tubules and flattened sacs formed from a continuous membrane sheet that interconnects in the cytosol. Both proteins (ribosomes) and lipids (enzymes) are synthesized here. Takes advantage of hydrophobic regions for fatty acids and hydrophilic for cytosolic proteins. Smooth ER is where lipid membrane buds off for transport to the Golgi apparatus.
G. Processing and packaging department (Golgi apparatus) – not all proteins are ready for prime time. Need to undergo folding steps and post-translational modifications before they have biological activity
H. Transport system (vesicles, vacuoles, lysosomes) – Vesciles contains proteins to be secreted to the extracellular space. Lysosomes contain enzymes which act to break down metabolic by-products, misfolded proteins, ingested extracellular material, and other unwanted substances.

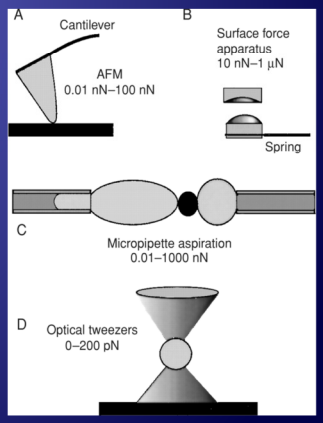


This is a great definition of cell mechanics.

Cell Mechanical Analysis

- Diameter: 30-50 μm (~3 μm for bacteria)
- Mass: 2-6 x 10^{-8} g
- Young's modulus: 1 – 10^5 Pa (CSK: ~ 10^{-9} Pa)





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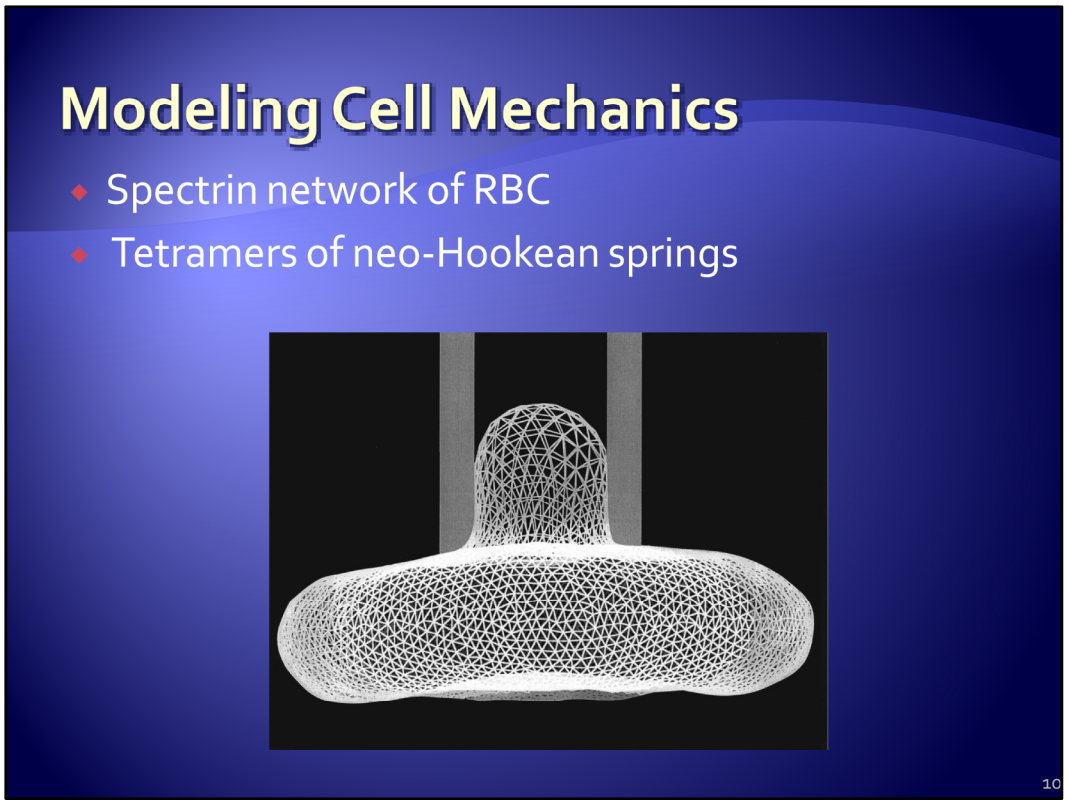
Cells are very small and if we assume that it has a similar density to water, then its mass is very small. As a result, momentum and gravity are less of a factor than surface forces like viscous drag or surface tension.

In this class we will talk about the different techniques that we can use to measure cell mechanical properties. Because cells are so small, we have to use mechanical analysis techniques that are at the micro and nano scale. However, we will see that how you measure a cell, what techniques, at what time, and at what spatial locations can give you measurements that are greatly different.



At the level of the cell, for example, one finds tensegrity models, which emphasize the importance of pre-stress in a cell and the
possibility of mechanical stresses acting at a distance, cortical membrane models that emphasize the importance of the actin sub-membrane in maintaining cell shape during migration, cell spreading, and deformation, percolation theories that emphasize dynamic changes in cytoskeletal inter-connectiveness, soft glassy rheological models that suggest that the cytoskeleton is metastable, able to transform instantaneously from more solid-like to more fluid-like behaviors, and continuum models, based on cells as inclusions in a matrix, that allow study of cell-matrix interactions.

Although one is quickly tempted to argue that one approach is better than another, it is essential to recognize that mathematical models do not describe a material – they only seek to address the responses of a material under particular conditions. Multiple models are thus to be expected given the diverse empirical observations extant at the different scales. Moreover, multiple models offer and emphasize different insights – they describe different phenomenon. It is often through the consideration of such diversity that salient commonalities surface, ones that lead to the desired unification of theories. Such is needed for a model to be integrative; it must address common mechanisms or processes at different scales and within different contexts.

Role of Cell Mechanics

- Conflicting mindsets:
  - Mechanics treats cells as a material with properties that are time invariant
  - Mechanotransduction illustrates that cells are living, changing entities that alter themselves in response to mechanical stimuli
- Conceptual Framework:
  - *The mechanics of cells and their altered biological functions are intrinsically linked.*
  - *What are the central structure-function relationships?*

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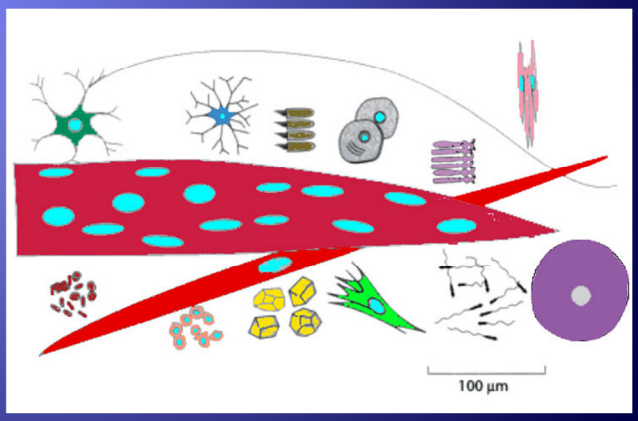
Maintenance of Cell Shape

- Cell function follows form
- Cell types:
  - motor neuron
  - osteocyte
  - hair cell
  - adipocyte
  - rods and cones
  - endothelials
  - skeletal muscle
  - smooth muscle
  - RBC
  - lymphocyte
  - epithelial (separated)
  - fibroblasts
  - sperm and egg cells



(Drawn to scale)

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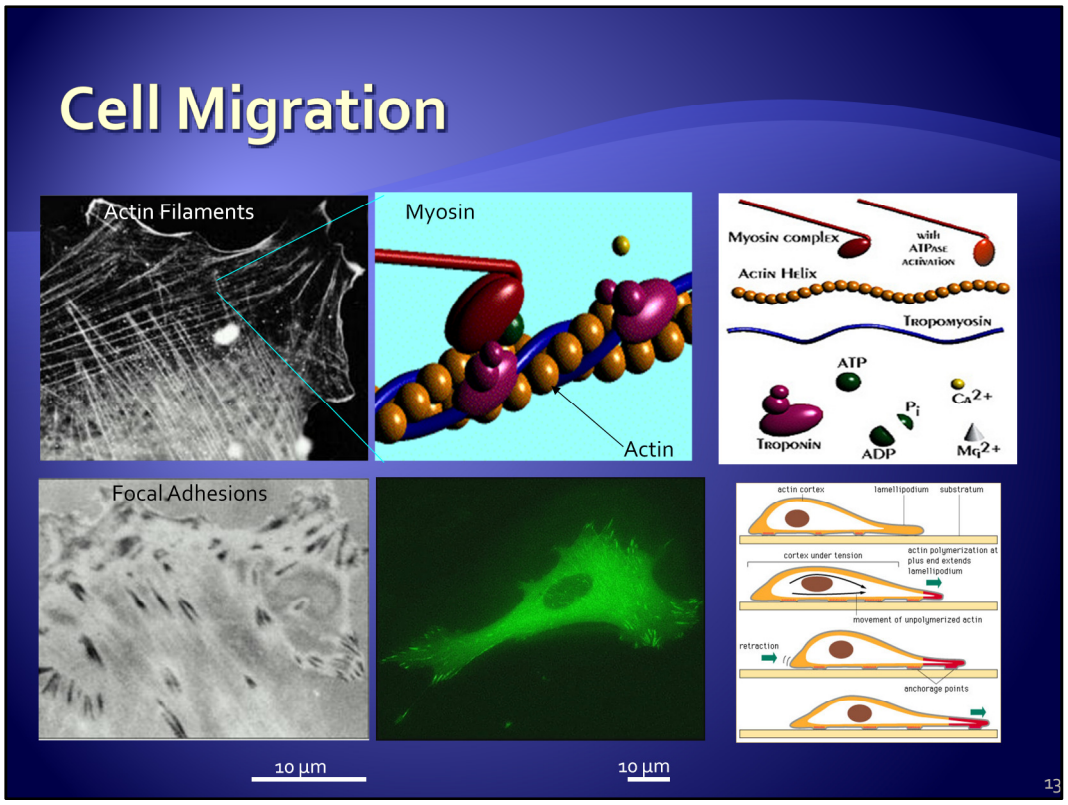
Soft, deformable surface of tissue cells allow them to take up a much wider variety of shapes than those of plants, fungi, and bacteria. Cells in the human body vary enormously in size and shape, often reflecting their function in their form. Examples: RBCs and WBCs are tiny, round, and flexible to squeeze through capillaries or migrate through tissue. Adipocytes have bellies swollen with lipids. Endothelial and epithelial cells have form tightly packed layer to be a tissue barrier. Muscle cells are long, strong, and grow thicker with exercise (hypertrophy).

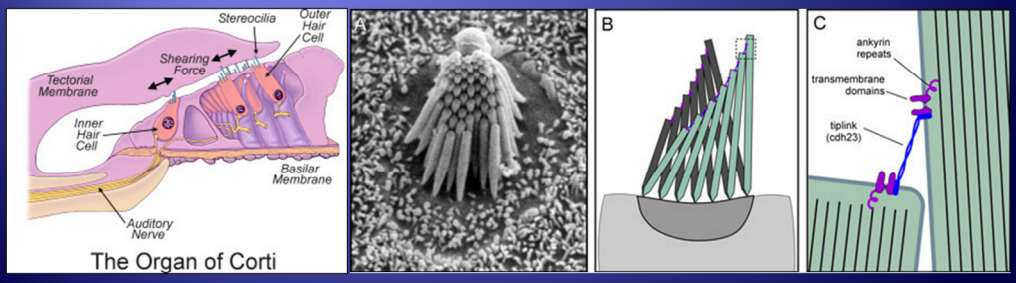


Cells migrate during development, wound repair, immune response, cancer metasis, angiogenesis

Stages: protrusion, contraction, release. Produces projection structures known as lamellapodia ("sheet-like") and filopodia ("finger-like").

Mechanosensing

- Mechanosensation: Hair cells, touch-sensitive sensory neurons
- Mechanotransduction: mechanical stimuli that cause a biochemical response



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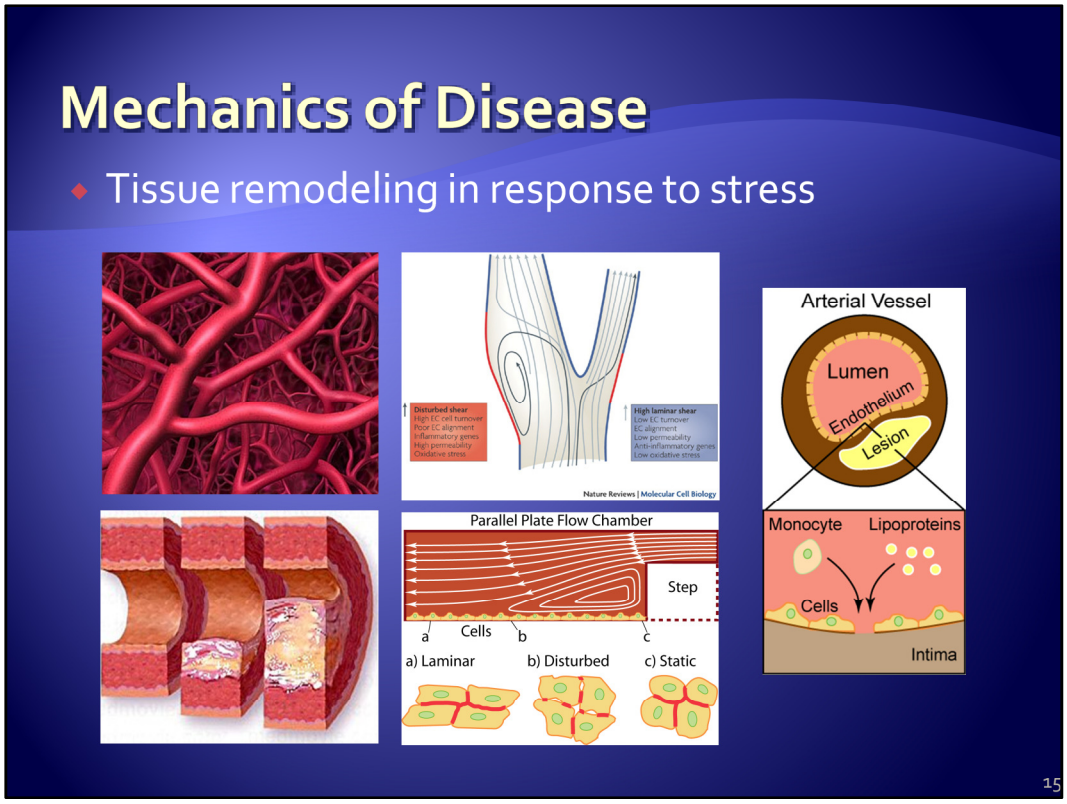
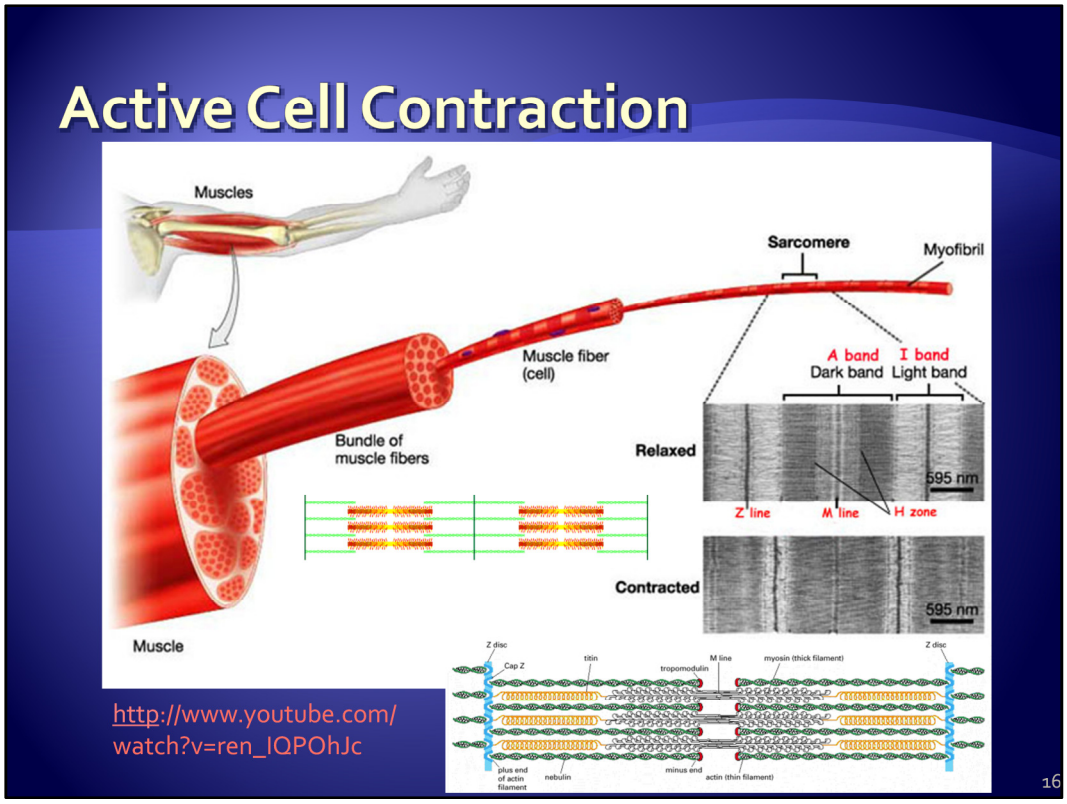
Mechanical stimili produced by sound transduced into electrical signal. Sound bends the hair cell's stereocilia on the apical surface that cause an ion influx through mechanically-gated ion channels. The flow on ions changes the electrical charge on the cell membrane and controls the release of nerotransmitters at the cells basal end where the cell synapses with a nerve ending

Ankyrin – soft spring
Cadherin 23 (cdh23) – stiff string. Hereditary deafness



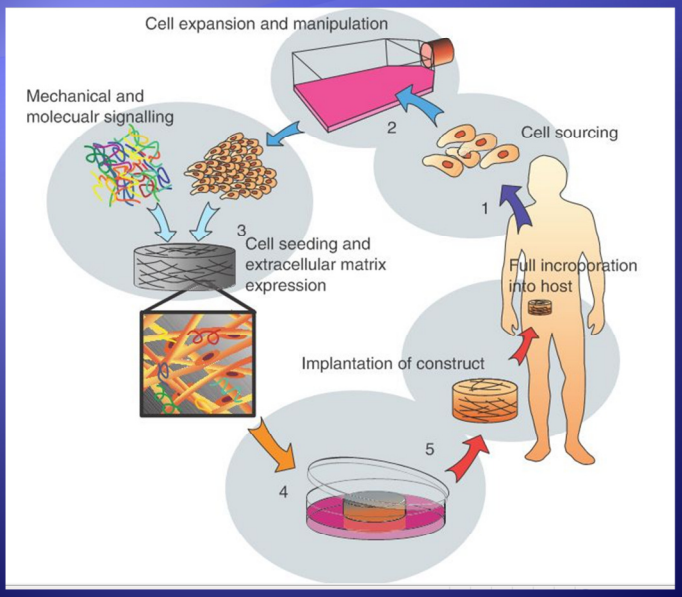
How cells response to external forces can lead to mechanical changes that adversely affect our health. A classic topic of interest in mechanotransduction is how endothelial cells response to shear flow. Where ever there are bends or birfurcations in the vasculature, this leads to unsteady flow from its normal laminar state. If you compare these locations of recirculation or disturbed flow from bends or bifurcations, you will find that the arterial tissue at these locations are more prone to the onset of atherosclerosis, which is the formation of fatty streaks that occlude the lumen of the artery and is due to the accumulation of monocytes and lipoproteins in the underlying intima of the blood vessel. Several cell mechanics researchers like Shu Chien or Peter Davies have studied this pathological phenomena by recreating these flow conditions in vitro by subjecting endothelial cells to shear flow. What they have found is that cells subjected to laminar flow are tighly knitted together with low permeability and have elongate cell shape in the direction of the flow. The well-formed adhesions is also seen for cells grown under static conditions but without the elongated shape. However, cells under the disturbed regions have gaps or discontinuities in the cell-cell adhesions with their neighbors which makes it more likely for oxidized LDL or monocytes to get into the underlying tissue and form a fatty streak.



There are a lot of educational videos on YouTube about sarcomeres and muscle contraction . This one is particularly amusing and intelligent. Be careful with videos because they often give you a false impression about the biophysics that is occuring. A lot of the mechanics is left up for interpretation and these video designers take liberties.

Here is a schematic of what we know about muscle contraction. Muscle is a hierarchal tissue. Each muscle in composed of bundled muscle fibers that are multinucleated cells containing myofibrils. A myofibril is composed of sarcomeres in a series. Each sacromere is the primary contractile apparatus of a muscle. The dark bands are formed from myosin thick filaments. The light bands are actin thin filaments. The sarcomere is a highly organized grouping of different proteins that active 2-4 pN of force per myosin head.

Tissue Engineering



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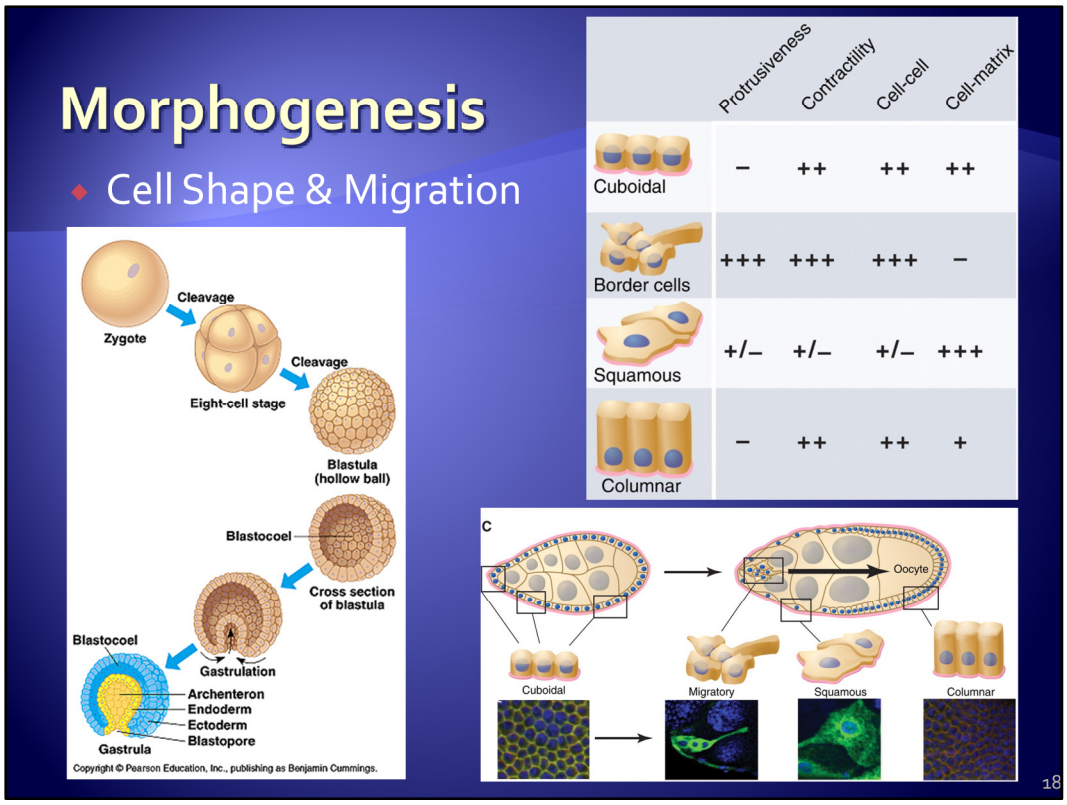
Cell mechanics is important for tissue engineeirng. If we are going to grow new or replacement tissue, we want the provide the right chemical and mechanical signals to the cells to encourage them to differentiation into their proper functional form.



During development, there is a host of mechanical activity that leads to the shape and structure of our final forms. We all start out as a mass of a few hundred cells, but then the cells become migratory and gastrulate to form the key systems of our body. The endoderm become the digestive system, the ectoderm becomes the neuronal and skin tissue, and the mesoderm between the endoderm and ectoderm becomes the musculoskeletal system and the cardiovascular system.

Different cell shape help to guide the morphological changes that occur during cell migration as shown for the Drosophila embryo.