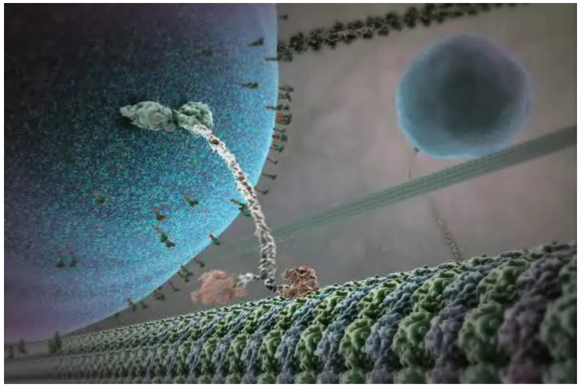
2. introduction to mechanics



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

me239 mechanics of the cell

1

mohammad mofrad, cal, today@4:15, 300-300

Peeking into the Rheology and Mechanics of the Cell
One Molecule at a Time

The cytoskeleton is the primary internal structure of the cell, providing its structural integrity. The rheology and mechanics of the cytoskeleton, therefore, are key to the cell's ability to accomplish its diverse functions in health and disease. Force-induced biological activities in the cell play a central role in development and in various disease processes that integrate mechanics and biology. How these mechanical and biochemical pathways interact remains largely unknown. Stresses transmitted through adhesion receptors are distributed throughout the cell, leading to conformational changes that occur in individual proteins which in turn lead to altered binding affinities. In this talk, I will first review some of the computational and phenomenological models as well as experimental techniques that have been proposed over the past two decades to describe the cytoskeletal rheology and mechanics. I will then present some of our computational models, ranging from molecular dynamics to coarse-grained and large-scale continuum simulations, developed toward understanding the response of the cell to mechanical stimuli. These quantitative models, predicated upon experimental measurements made across multiple length scales, will enable the coupling of continuum with meso- and molecular-level simulations for the study of mechanics of cell and tissue mechanotransduction in health and disease. I will conclude with some application examples from cardiovascular disease and developmental biology.

rheology & mechanics of the cell

2

markus buhler, MIT, thursday@4:15, thornton 110

Turning weakness into strength
How protein materials balance strength, robustness and adaptability

Biology exquisitely creates hierarchical structures, where initiated at nano scales, are exhibited in macro or physiological multifunctional materials to provide structural support, force generation, catalytic properties or energy conversion. This is exemplified in a wide range of biological materials such as hair, skin, bone, spider silk or cells, which play important roles in providing key functions to biological systems. This talk focuses on multiscale studies of deformation and failure of biological protein materials, used here to elucidate fundamental design concepts in order to understand physiological functions, disease mechanisms as well as to translate new material paradigms towards engineered materials. Based on a multiscale simulation approach validated through multiscale experiments, we explicitly consider the architecture of proteins across multiple scales, including the details of chemical bonding and explain how complex multifunctional properties of protein materials emerge. I will present a survey of recent studies of major classes of protein materials, including cellular protein networks, beta-sheet structures as found in spider silk and Alzheimer's disease, as well as collagenous tissues that form the structure of tendon and bone. Case studies will be presented that illustrate size effects in protein materials, flaw-tolerance mechanisms, and applications of materials science to genetic diseases, showing how structural defects at the molecular level can have profound effects at the material behavior at larger scales. Our work explains a universal materials design paradigm found in biology, where the formation of hierarchical structures at multiple scales is used to overcome the intrinsic limitations of inferior building blocks such as weak H-bonds. We show that through this paradigm, it is possible to create highly functional, tunable and changeable materials out of simple, abundant and inexpensive constituents.

turning weakness into strength

3

prokaryotic cells

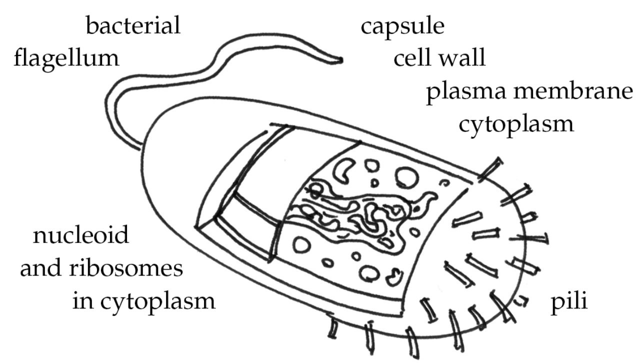


Figure 1.1 Prokaryotic cell. Cell without a nucleus.

1.2 introduction to the cell

4

eukaryotic cells

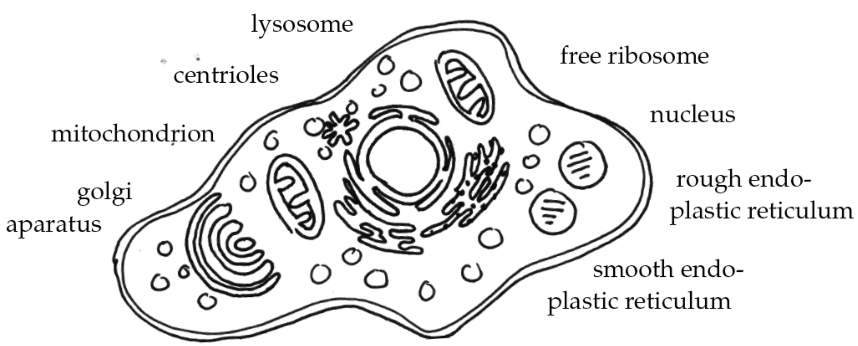


Figure 1.2 Eukaryotic cell. Cell without a distinct nucleus.

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?

biopolymers

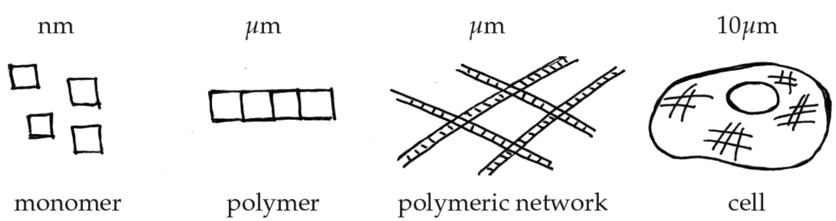


Figure 3.1. Biopolymers. Characteristic length scales on the cellular and sucellular level..

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**.

the cytoskeleton

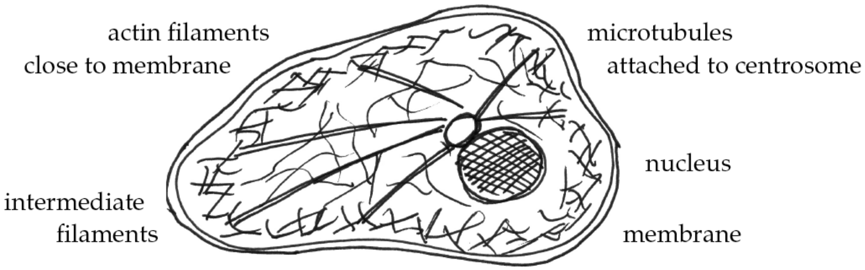


Figure 1.3. Eukaryotic cytoskeleton. The cytoskeleton provides structural stability and is responsible for force transmission during cell locomotion. Microtubules are thick hollow cylinders reaching out from the nucleus to the membrane, intermediate filaments can be found anywhere in the cytosol, and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

the cell membrane

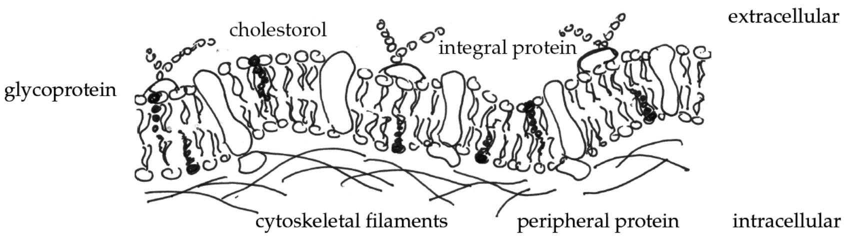


Figure 1.3. Cell membrane. Phospholipic bilayer with hydrophobic water-avoiding tails and hydrophilic water-loving heads.

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 lipid bilayer

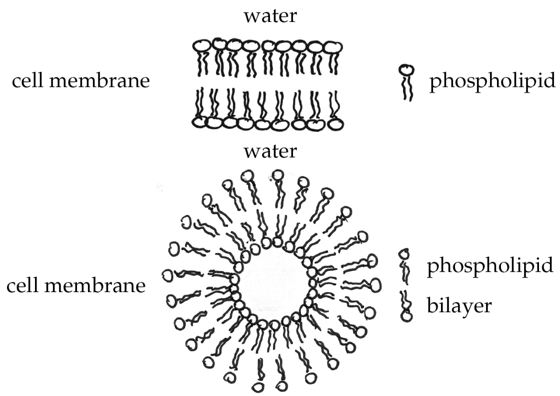


Figure 5.16. Lipid bilayer of the cell membrane. Characteristic arrangement of phospholipid molecules with hydrophilic polar head group being oriented towards the aqueous phase while the hydrophilic tails are oriented towards the non-polar inside.

your three most important equations of mechanics

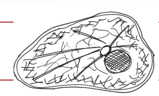
constitutive equations • the stress strain relations, which are sometimes also referred to as material model • their one dimensional version in the form of Hooke's law $\sigma = E\,\varepsilon$ • Hooke's law for a linear spring $F = k\ x$ • its version for torsion $T = L\theta$ • its three dimensional version $\varepsilon_x = 1/E\,[\sigma_x - \nu\,\sigma_y - \nu\,\sigma_z]$ • the definition of Poisson's ratio $\nu = -\,\varepsilon_{trans} / \varepsilon_{long}$ • the strain energy of a Hooke'an material $W = 1/2\ \sigma\ \varepsilon$.

equilibrium equations • which are sometimes as referred to as momentum balance • their one dimensional form for rigid bodies $F=m\ a$ • their form for a deformable continuum $\mathrm{div}\boldsymbol{\sigma} + \rho\mathbf{b} = \rho d_t^2\mathbf{u}$.

kinematic equations • for a one-dimensional bar $\varepsilon = \Delta l / l$ • for a continuum $\boldsymbol{\varepsilon} = d\,\mathbf{u}/d\,\mathbf{x}$.

other • relation between stress and stress resultants $\sigma = N / A$ • the differential equation for beam bending $y'' = M / [\,EI\,]$ which actually is a result of the combination of the three sets of equations discussed above

one-dimensional bar



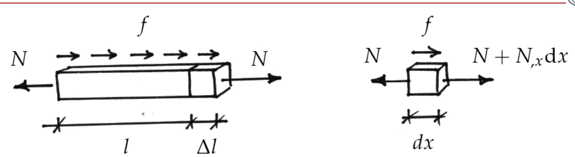
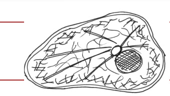
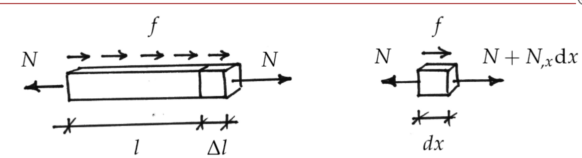


Figure 2.1: One dimensional truss of initial length l subject to axial force f which stretches it by the amount Δl (left) and infinitesimal truss element of length $\mathrm{d}x$ with resultant forces N on the negative and $N + N_{,x}\,\mathrm{d}x$ on the positive side

one-dimensional bar





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- kinematics $\quad \varepsilon = \lim_{x \to 0} \dfrac{u}{x} = \dfrac{\mathrm{d}u}{\mathrm{d}x} = u_{,x} \quad$ homogeneous $\quad \varepsilon = \dfrac{\Delta l}{l}$
- constitutive equation $\quad \sigma = \sigma(\varepsilon) \quad$ linear elastic $\quad \sigma = E\,\varepsilon$
- stress resultant $\quad N = \iint \sigma\,\mathrm{d}y\mathrm{d}z \quad$ homogeneous $\quad \sigma = \dfrac{N}{A}$
- equilibrium $\quad \sum f \doteq 0 \quad$ in axial direction $\quad N_{,x} + f = 0$

one-dimensional bar

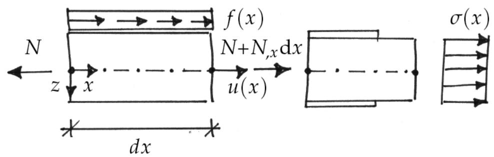


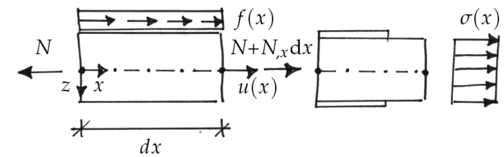
Figure 3.1: Axial loading of one dimensional structure ∘ Stresses σ are constant across the cross section

$$N_{,x} + f \;=\; A\,\sigma_{,x} + f \;=\; EA\,\varepsilon_{,x} + f \;=\; EA\,u_{,xx} + f \;=\; 0$$

∘ differential equation $\quad EA\,u_{,xx} + f = 0 \quad$ or $\quad EA\,\Delta u + f = 0$

homogeneous $\quad u \;=\; N\,L\,/\,[\,EA\,]$

one-dimensional bar



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	r	A	E	EA
microtubule	12.5 nm	491 nm^2	$1.9{\cdot}10^9$ N/m^2	$93{\cdot}10^{-8}$ N
intermediate filament	5.0 nm	79 nm^2	$2.0{\cdot}10^9$ N/m^2	$15{\cdot}10^{-8}$ N
actin filament	3.5 nm	39 nm^2	$1.9{\cdot}10^9$ N/m^2	$7{\cdot}10^{-8}$ N

Table 3.1: Axial stiffness EA of major consituents of cytoskeleton: microtubules, intermediate filaments and actin filaments

the strain displacement relation

normal strains

$$\varepsilon_{xx} = \lim_{x\to 0}\frac{u}{x} = \frac{\mathrm{d}u}{\mathrm{d}x} \qquad \varepsilon_{xx} = u_{,x}$$

$$\varepsilon_{yy} = \lim_{y\to 0}\frac{v}{y} = \frac{\mathrm{d}v}{\mathrm{d}y} \qquad \varepsilon_{yy} = v_{,y}$$

$$\varepsilon_{zz} = \lim_{z\to 0}\frac{w}{z} = \frac{\mathrm{d}w}{\mathrm{d}z} \qquad \varepsilon_{zz} = w_{,z}$$

shear strains

$$\varepsilon_{xy} = \frac{1}{2}\left[\frac{\mathrm{d}u}{\mathrm{d}y} + \frac{\mathrm{d}v}{\mathrm{d}x}\right] \qquad \varepsilon_{xy} = \tfrac{1}{2}\,[\,u_{,y} + v_{,x}\,] \;=\; \varepsilon_{yx}$$

$$\varepsilon_{yz} = \frac{1}{2}\left[\frac{\mathrm{d}v}{\mathrm{d}z} + \frac{\mathrm{d}w}{\mathrm{d}y}\right] \qquad \varepsilon_{yz} = \tfrac{1}{2}\,[\,v_{,z} + w_{,y}\,] \;=\; \varepsilon_{zy}$$

$$\varepsilon_{zx} = \frac{1}{2}\left[\frac{\mathrm{d}w}{\mathrm{d}x} + \frac{\mathrm{d}u}{\mathrm{d}z}\right] \qquad \varepsilon_{zx} = \tfrac{1}{2}\,[\,w_{,x} + u_{,z}\,] \;=\; \varepsilon_{xz}$$

the stress strain relation

generalized 3d hooke's law

$$\sigma_{xx} = \frac{E}{1-\nu^2}\,[\,\varepsilon_{xx} + \nu\,\varepsilon_{yy} + \nu\,\varepsilon_{zz}\,] \qquad \sigma_{xy} = \frac{E}{1+\nu}\,\varepsilon_{xy} = \sigma_{yx}$$

$$\sigma_{yy} = \frac{E}{1-\nu^2}\,[\,\varepsilon_{yy} + \nu\,\varepsilon_{xx} + \nu\,\varepsilon_{zz}\,] \qquad \sigma_{yz} = \frac{E}{1+\nu}\,\varepsilon_{yz} = \sigma_{zy}$$

$$\sigma_{zz} = \frac{E}{1-\nu^2}\,[\,\varepsilon_{zz} + \nu\,\varepsilon_{xx} + \nu\,\varepsilon_{yy}\,] \qquad \sigma_{zx} = \frac{E}{1+\nu}\,\varepsilon_{zx} = \sigma_{xz}$$

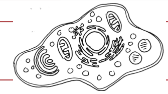
inverse hooke's law

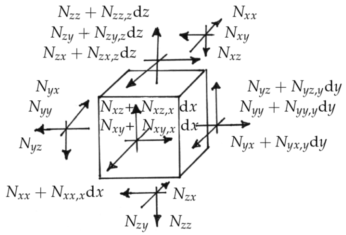
$$\varepsilon_{xx} = \frac{1}{E}\,[\,\sigma_{xx} - \nu\,\sigma_{yy} - \nu\,\sigma_{zz}\,] \qquad \varepsilon_{xy} = \frac{1+\nu}{E}\,\sigma_{yx} = \varepsilon_{xy}$$

$$\varepsilon_{yy} = \frac{1}{E}\,[\,\sigma_{yy} - \nu\,\sigma_{xx} - \nu\,\sigma_{zz}\,] \qquad \varepsilon_{yz} = \frac{1+\nu}{E}\,\sigma_{yz} = \varepsilon_{yz}$$

$$\varepsilon_{zz} = \frac{1}{E}\,[\,\sigma_{zz} - \nu\,\sigma_{xx} - \nu\,\sigma_{yy}\,] \qquad \varepsilon_{zx} = \frac{1+\nu}{E}\,\sigma_{zx} = \varepsilon_{xz}$$

the stress force relation





$$\sum f_x \doteq 0 \qquad [-N_{xx} + N_{xx} + N_{xx,x}\,\mathrm{dx}\,] + [-N_{yx} + N_{yx} + N_{yx,y}\,\mathrm{dy}\,] + [-N_{zx} + N_{zx} + N_{zx,z}\,\mathrm{dz}\,] + f_x = 0$$

$$\sum f_x \doteq 0 \qquad \sigma_{xx,x} + \sigma_{yx,y} + \sigma_{zx,z} + f_x = 0$$

$$\sigma_{ij,i} + f_i = 0_i \qquad \mathrm{div}(\boldsymbol{\sigma}^{\mathrm{t}}) + \boldsymbol{f} = \boldsymbol{0}$$

trusses, beams, walls, plates, membranes, shells

	dimension	geometry	loading	deformation	gov eqn
truss	1d straight	$w,h \ll l$	axial	tension	2^{nd} order
beam	1d straight	$w,h \ll l$	transverse	bending	4^{th} order
wall	2d flat	$h \ll w,l$	in plane	tension/shear	2^{nd} order
plate	2d flat	$h \ll w,l$	transverse	bending	4^{th} order
membrane	3d curved	$h \ll w,l$	in plane	tension/shear	2^{nd} order
shell	3d curved	$h \ll w,l$	transverse	bending	4^{th} order

Table 2.1: Classification of structural elements based on dimension, geometry and loading

typical example - the cell membrane

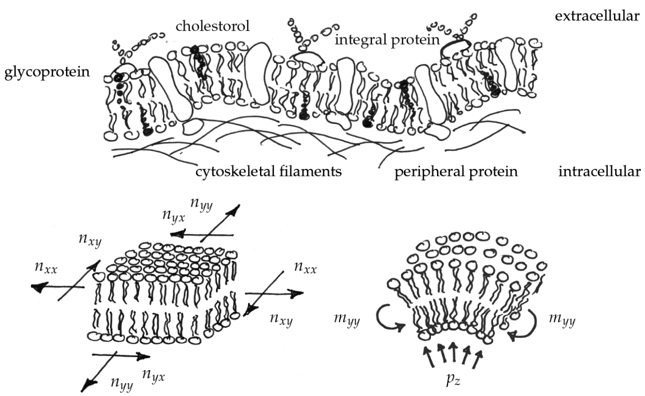


Figure 5.3: Infinitesimal element of the cell membrane subject to tension causing in plane deformation and shear (left) and bending causing out of plane deformation (right)

mohammad mofrad, cal, today@4:15, 300-300

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