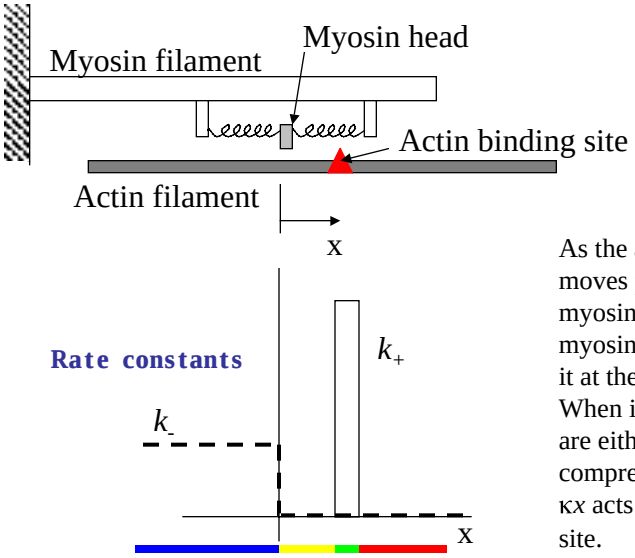
Sliding Filament Model



As the actin filament moves past the (fixed) myosin filament, the myosin head can bind to it at the red triangle. When it does, the springs are either stretched or compressed and a force κx acts at the binding site.

Equations governing the probability *n(x,t)* that a cross-bridge is attached

$$\frac{dn(x,t)}{dt} = \frac{\partial n(x,t)}{\partial t} - v\frac{\partial n(x,t)}{\partial x} = [1 - n(x,t)]k_+(x) - n(x,t)k_-(x)$$

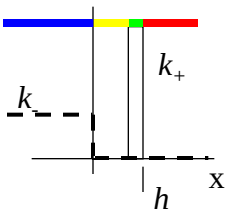
Formation of new bonds

Detachment of existing bonds

At steady state [$n = n(x)$]

$$-v\frac{dn(x)}{dx} = [1 - n(x)]k_+(x) - n(x)k_-(x)$$

k_+ = attachment rate; k_- = detachment rate; n = probability of attachment



The sliding filament model

x > h:

In this region the actin binding site is approaching the free myosin head, unoccupied. Since both k_+ and k_- are zero, no binding occurs:

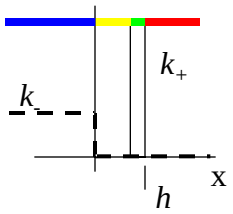
$$n(x) = n(h) = 0$$

h-x_0 < x <h:

If binding is to occur, it has to do so (according to this simple model) within this narrow region where the binding rate constant is large, described by the equation:

$$-v\frac{dn}{dx} = (1-n)k_+^0$$

$$n(h-x_0) = 1-\exp\left[-\frac{k_+^0 x_0}{v}\right]$$



0 < x < h-x_0

Both the attachment and detachment rate constants are zero, so the myosin head can neither bind to nor detach from an actin filament, and the probability of attachment remains constant:

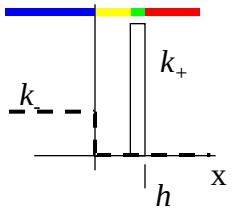
$$n(x) = n(h-x_0) = constant$$

x < 0

As the complex moves into the region *x < 0*, the force of interaction sustained at the actin-myosin bond changes sign and its probability of attachment begins to fall, as described by the equation:

$$-v\frac{dn}{dx} = -k_-^0 n$$

$$n(x) = n(0)\exp\left[\frac{k_-^0 x}{v}\right] = \left[1-\exp\left[-\frac{k_+^0 x_0}{v}\right]\right]\exp\left[\frac{k_-^0 x}{v}\right]$$



Work done by a single cross-bridge that attaches at $x=a$ and detaches at $x=-b$:

$$W = \int_{-b}^{a} \kappa x dx = \frac{\kappa}{2}\left(a^2 - b^2\right) \qquad \sigma lA = \int_{-\infty}^{\infty} \left[n(x)\rho_s As/2\right]\kappa x dx$$

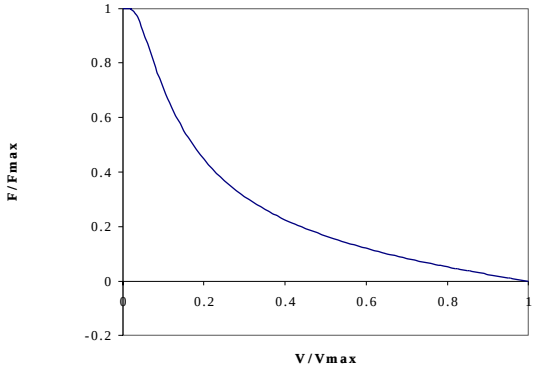
$$\sigma = \frac{\rho_s A s \kappa}{2lA}\int_{-\infty}^{\infty} n(x)x dx = \frac{\rho_s A s \kappa}{2lA}\left[\int_{-\infty}^{0} n(0)x \exp\left(\frac{k_-^0 x}{v}\right)dx + \int_{0}^{h} n(0)x dx\right]$$

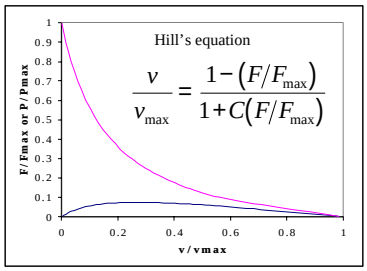
$$\sigma = \frac{\rho_s s \kappa h^2}{4l}\left[1 - 2\left(\frac{v}{hk_-^0}\right)^2\left(1 - \exp\left(-\frac{k_+^0 x_0}{v}\right)\right)\right]$$

$$\frac{\sigma}{\sigma_{\max}} = \left[1 - \left(\frac{v}{v_{\max}}\right)^2\left(1 - \exp\left(-\frac{k_+^0 x_0}{v}\right)\right)\right] \qquad \sigma_{\max} = \frac{\rho_s s \kappa h^2}{4l}$$

$$v_{\max} = \frac{hk_-^0}{\sqrt{2}}$$

Predicted force-velocity curve from cross-bridge model





$$\frac{F}{F_{\max}} = \left[1 - \left(\frac{v}{v_{\max}}\right)^2\left(1 - \exp\left(-\frac{k_+^0 x_0}{v}\right)\right)\right]$$

Introduction to Cellular Biomechanics

References: R.D. Kamm Chapters 2.1, 2.2 (handed out)
Molecular Cell Biology, Lodish et al.

Goals for today:

- Why is cell mechanics important ?
- Important structural components of the cell.
- Plasma Membrane.

Models

Length scales and details

Lumped parameters (Kelvin, Voight, Maxwell..)

Coarse Grained Continuum Mechanics

Statistical Mechanical Models

Single Molecule

Why is cell mechanics important ?

Critical to function: red blood cells

Migration

Cell-Cell/Cell-Matrix Adhesion

Division

Mechanotransduction- respond to mechanical stimuli
- cell differentiation
- gene expression
-diseases (arthritis)

Single Cell Mechanics: Aspiration by Micropipette

What mechanical properties can we measure ?

During blood clotting, platelets change shape due to changes in the actin cytoskeleton

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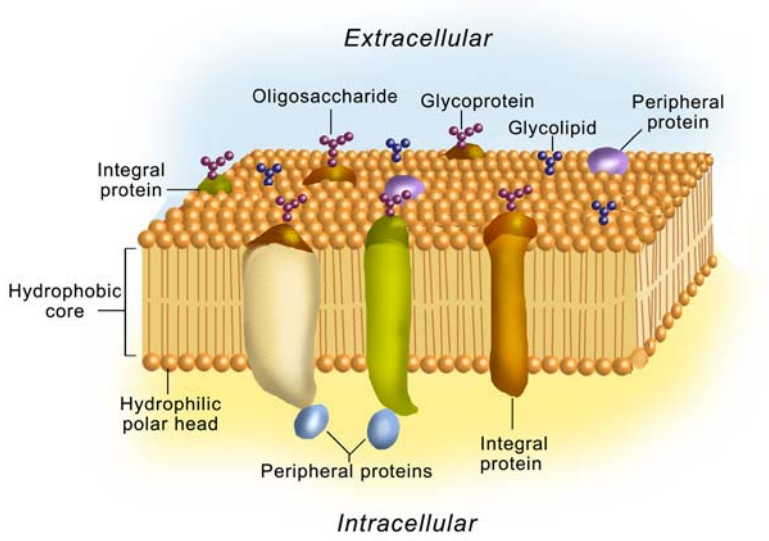
Important Structural Components in Cells

1. Membrane
2. Cytoskeleton
3. Nucleus and other organelles
4. Cytosol (excluding the cytoskeleton)
5. Adhesion sites

Plasma Membrane



Cytoskeleton

1. Actin
2. Microtubules
3. Intermediate Filaments

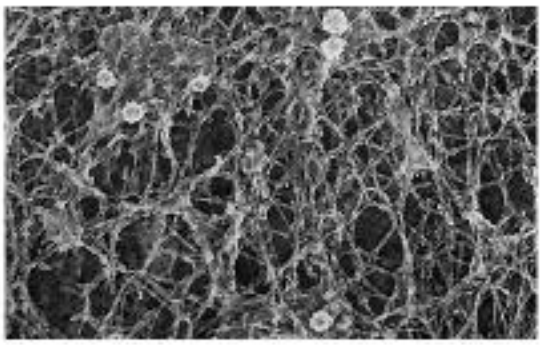


Image courtesy of J. Hartwig. Used with permission.

Motility and the Cytoskeleton

- Actin filaments (or microfilaments) are one of the three protein filament systems that comprise the cytoskeleton
- Eukaryotic cells contain abundant amounts of highly conserved actin

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See Figure 18-1 in [Lodish].

Figure 18-1

Organelles of the eukaryotic cell

- Lysosomes
- Peroxisomes
- Mitochondria
- Chloroplasts
- the Endoplasmic Reticulum
- the Golgi complex
- the Nucleus
- the Cytosol

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Cytosol (excluding the cytoskeleton)

- Inclusion bodies
- Proteins (actin monomers)
- Ions
- Water

Viscosity=50-10^4 cp
(water : 1 cp)

Valentine and Weitz 2003

Image removed due to copyright considerations.

Image removed due to copyright considerations.

Xenopus egg extracts: microrheology

Glycocalyx: 'Cell Coat', 'Furry Coat'

Image removed due to copyright considerations.
See Holland, N.B., et al. Biomimetic engineering of non-adhesive glycocalyx-like surfaces using oligosaccharide surfactant polymers. *Nature* 392(6678):799-801 (1998 Apr 23).

In endothelial cells- compressible barrier from blood cells

Case Study:

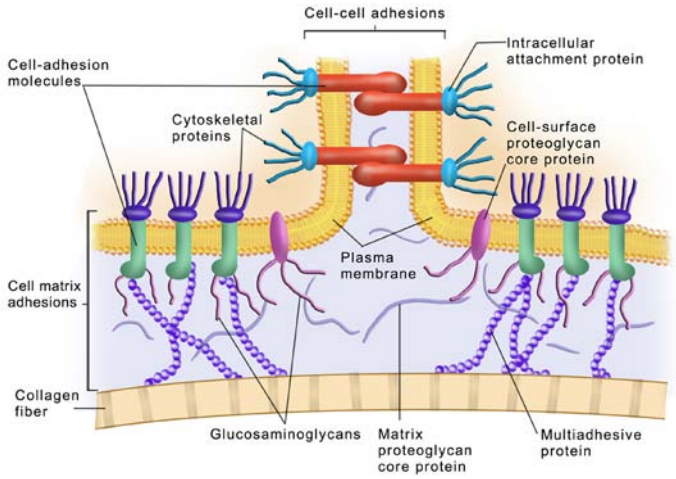
Bacteria- 2 Primary Roles:

1) resisting phagocytosis

2) adhering to and colonizing environmental surfaces (rocks, hair, teeth…)

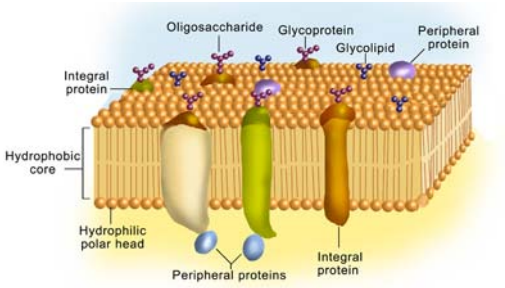
Adhesion sites

- Coupling to tissue
- Sensing
- Migration
- Communication



Plasma Membranes

~5nm



Main components:

1) Lipid bilayer
2) Plasma proteins
3) Carbohydrates

Plasma Protein Classes: Integral membrane proteins
Peripheral proteins → Associated
Peripheral proteins → Skeletal (spectrin)

Functions of the Plasma Membrane

- Regulate transport of nutrients into the cell
- Regulate transport of waste out of the cell
- Maintain "proper" chemical conditions in the cell
- Provide a site for chemical reactions not likely to occur in an aqueous environment
- Detect signals in the extracellular environment
- Interact with other cells or the extracellular matrix (in multicellular organisms)

Lipid Membrane Permeability

Image removed due to copyright considerations.

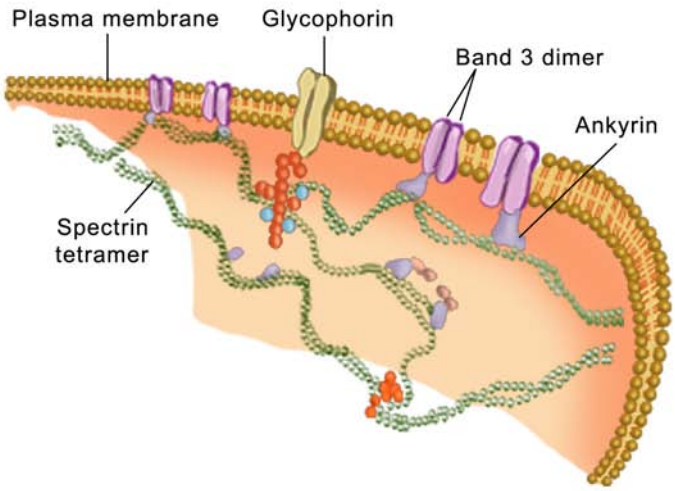
Patch Clamp permit measurement of ion movements through channels

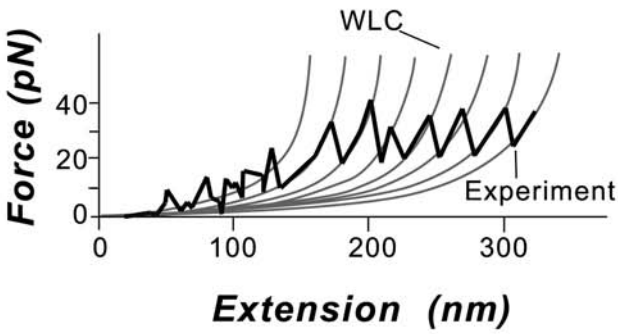
E. Neher and B. Sakmann 1976 (Nobel Prize 1991)

Image removed due to copyright considerations.
See Figure 21-19 in [Lodish].
Fig. 21-19a is available online via PubMed Bookshelf at
http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mcb.figgrp.6162.

Molecular Cell Biology
Lodish et al., Chapter 21

Cortical networks in erythrocytes





Lipid Bilayers

Phospholipids are the main (lipid) constituents of most biomembranes.

Due to the amphiphilic nature and structure (2 tails) of phospholipids, these molecules spontaneously assemble to form closed bilayers.

Image removed due to copyright considerations.

Liposomes: Drug delivery systems

Phospholipid structure

Some common head groups

tails

heads

Images removed due to copyright considerations.

Source: Molecular cell biology, Lodish et al.