Molecular, Cellular & Tissue Biomechanics

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Goal: Develop a *fundamental* understanding of biomechanics over a wide range of length scales.

MOLECULAR MECHANICS

I	Biomolecules and intermolecular forces
II	Single molecule biopolymer mechanics
III	Formation and dissolution of bonds
IV	Motion at the molecular/macromolecular level

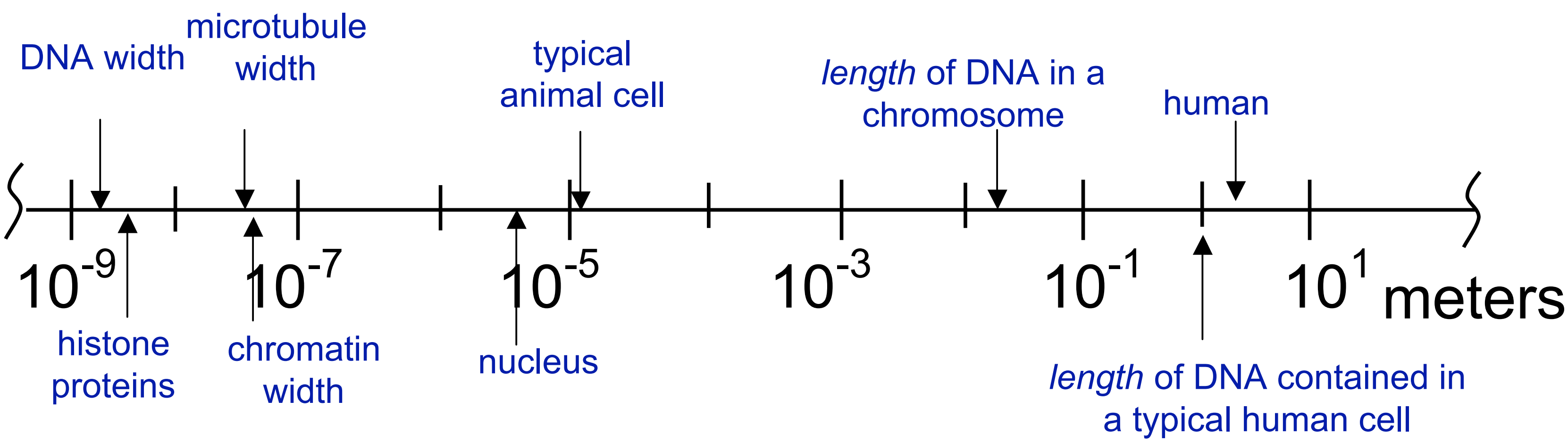
TISSUE MECHANICS

I	Molecular structure --> physical properties
II	Continuum, elastic models (stress, strain, constitutive laws)
III	Viscoelasticity
IV	Poroelasticity
V	Electrochemical effects on tissue properties

CELLULAR MECHANICS

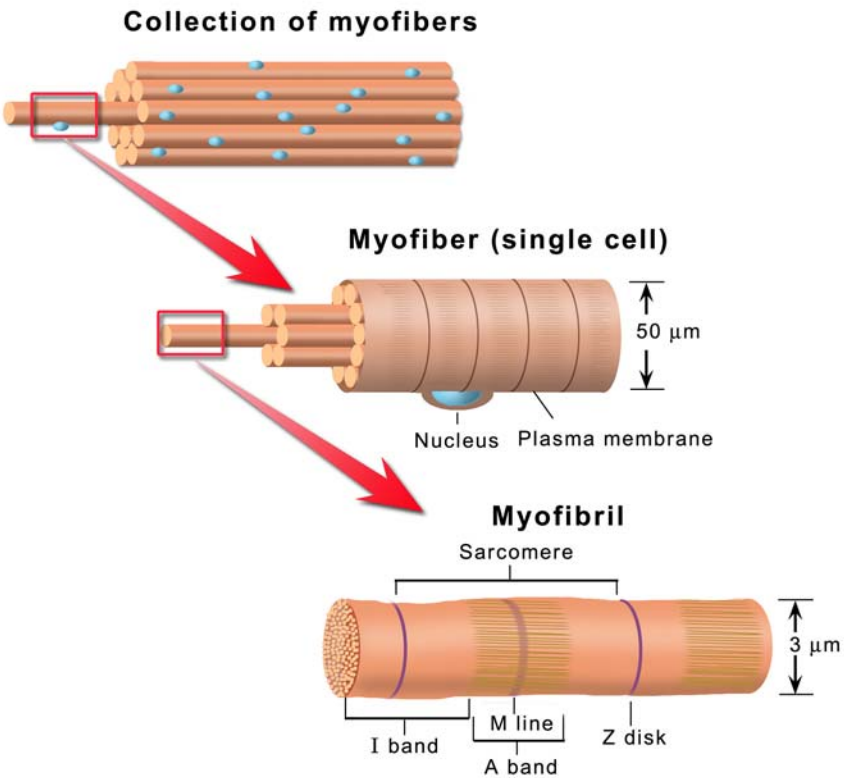
I	Structure/function/properties of the cell
II	Biomembranes
III	The cytoskeleton
IV	Cell adhesion and aggregation
V	Cell migration
VI	Mechanotransduction

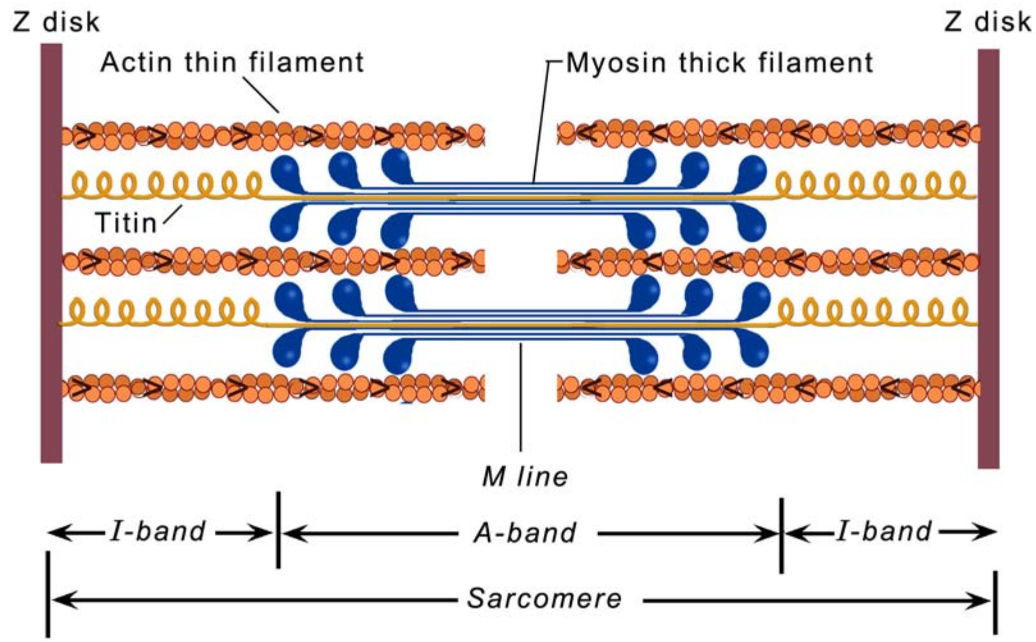
Typical Length Scales in Biology



Similar spectra exist in time scales or energy scales.

Muscles: Spanning from Macro to Nano





Actin: semiflexible polymer
Myosin: molecular motor
Titin: resting elasticity

Macro-scale applications

108 bpm

72 bpm

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Cardiovascular mechanics

Computational fluid mechanics used to study shear stresses in the carotid artery

Peak flow

Maximum deceleration

…or tissue stresses in the wall of a diseased vessel

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Computational mesh for finite element analysis

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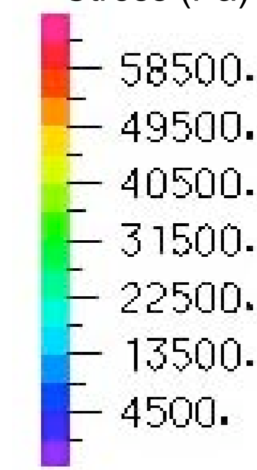
Stress (Pa)



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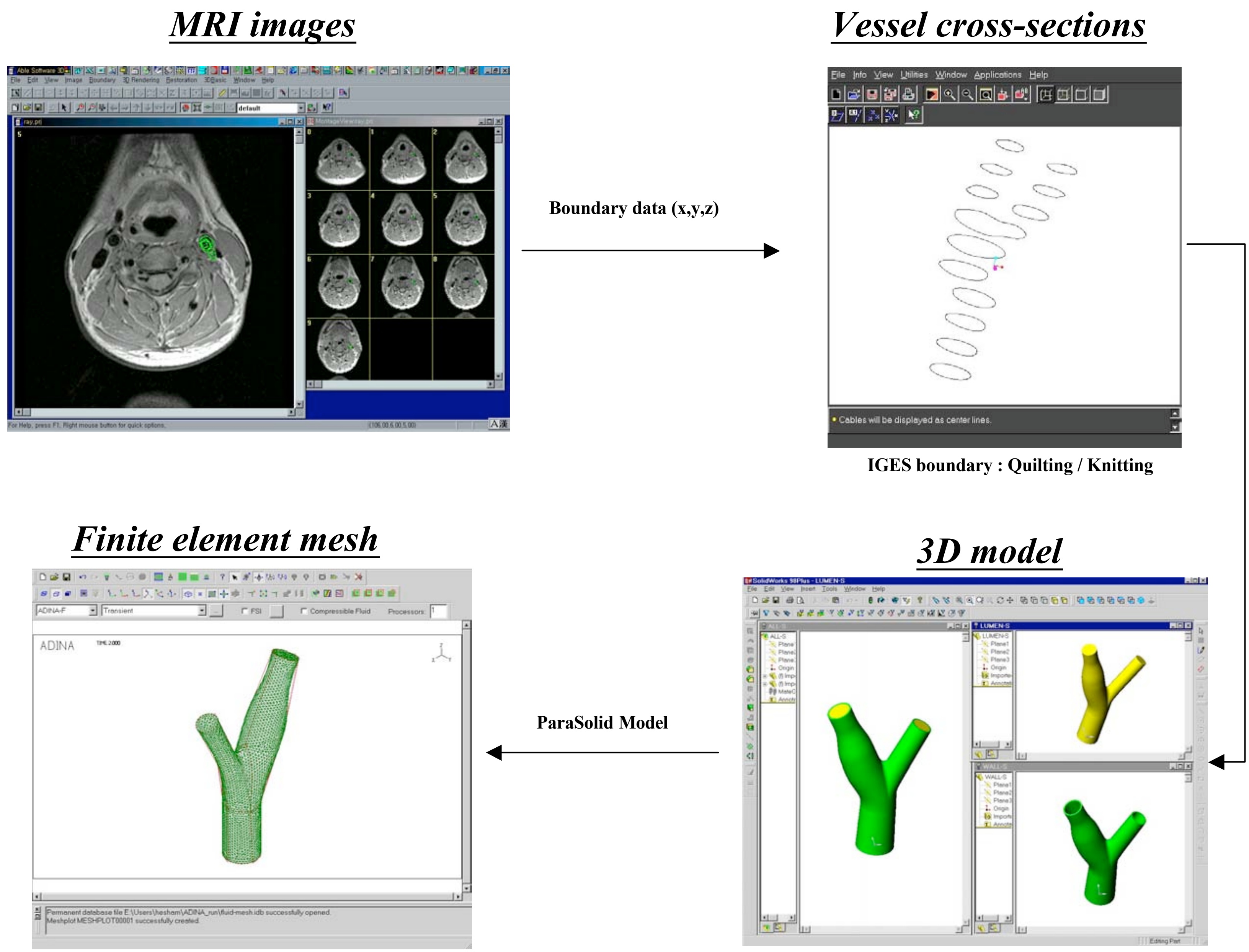
Histological section obtained from surgery


MRI images
Boundary data (x,y,z)
Vessel cross-sections
IGES boundary : Quilting / Knitting
3D model
ParaSolid Model
Finite element mesh
ADINA

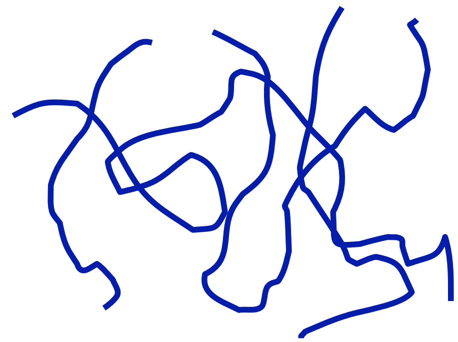
Modeling Complex Material Properties

Continuum

Microstructural

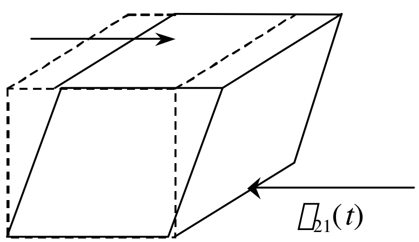
bending plate

entangled polymer

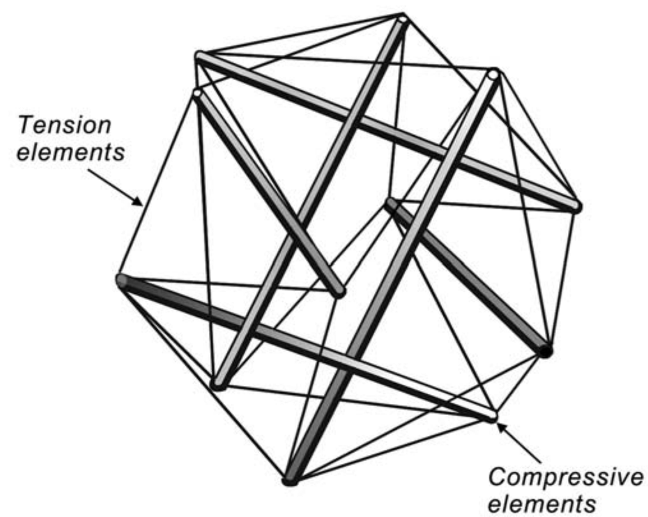


Constitutive relations and force balance

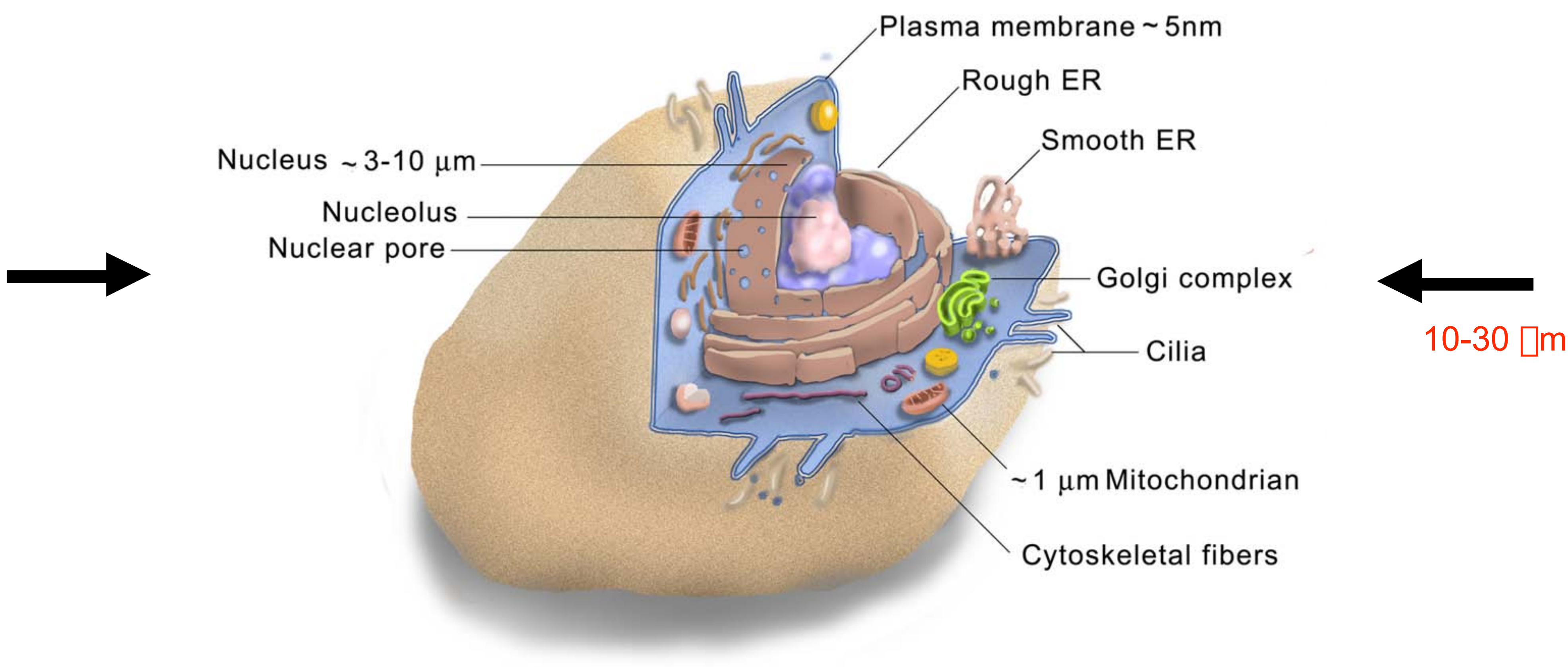
Viscoelastic or poroelastic solid



strut model



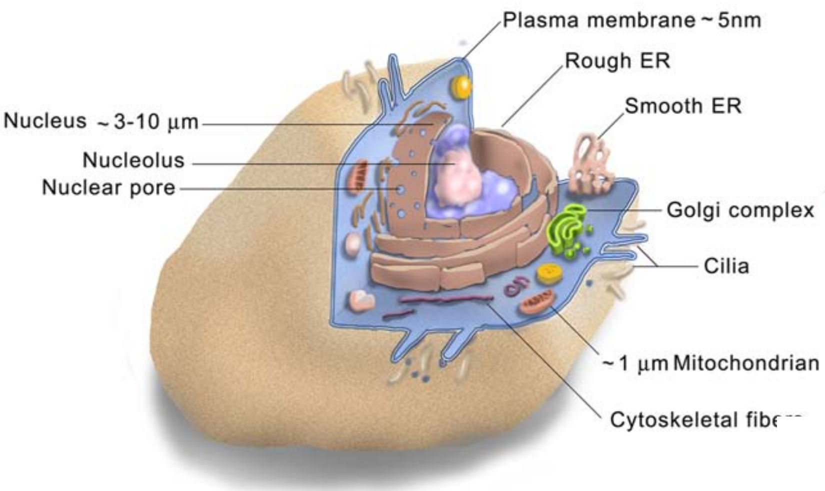
Typical Eukaryotic Cell



1 µm = 10^{-6} m
1 nm = 10^{-9} m
1 Å = 10^{-10} m

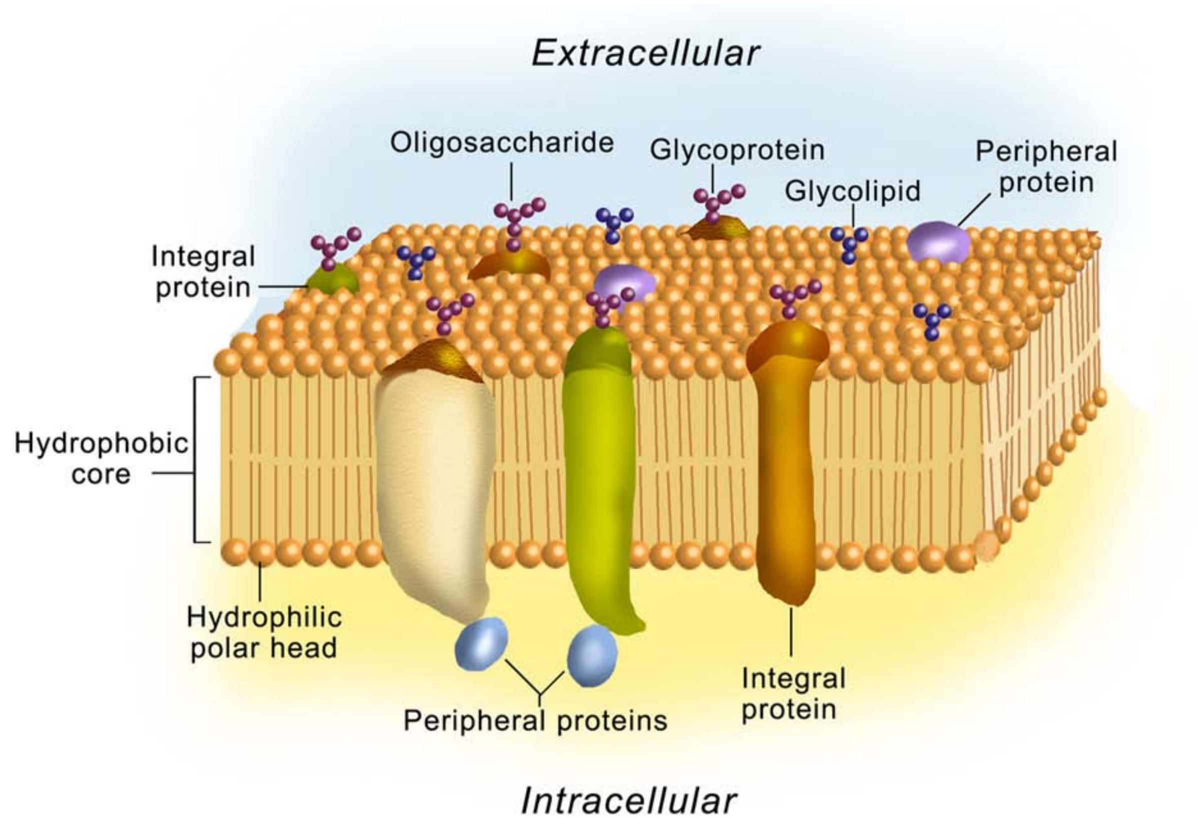
Plasma Membrane

Plasma Membrane

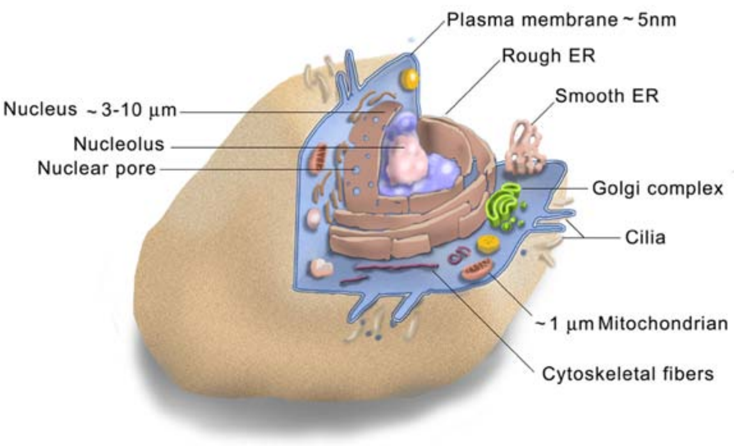


2-D Elastic Plate

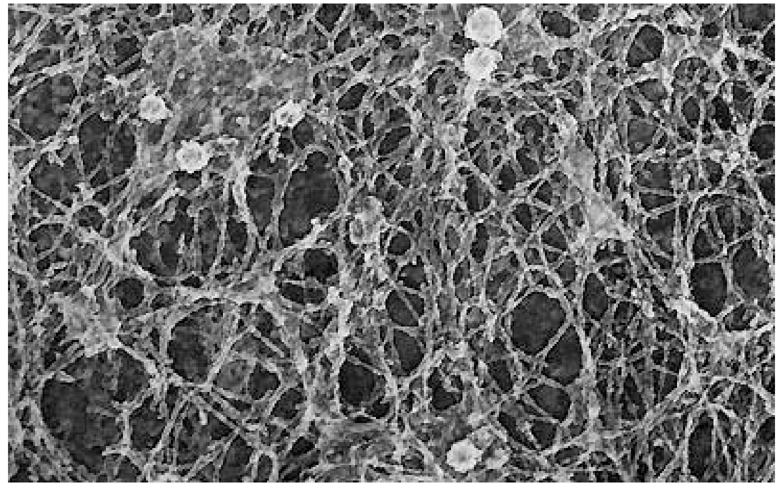
~5 nm



Cytoskeleton



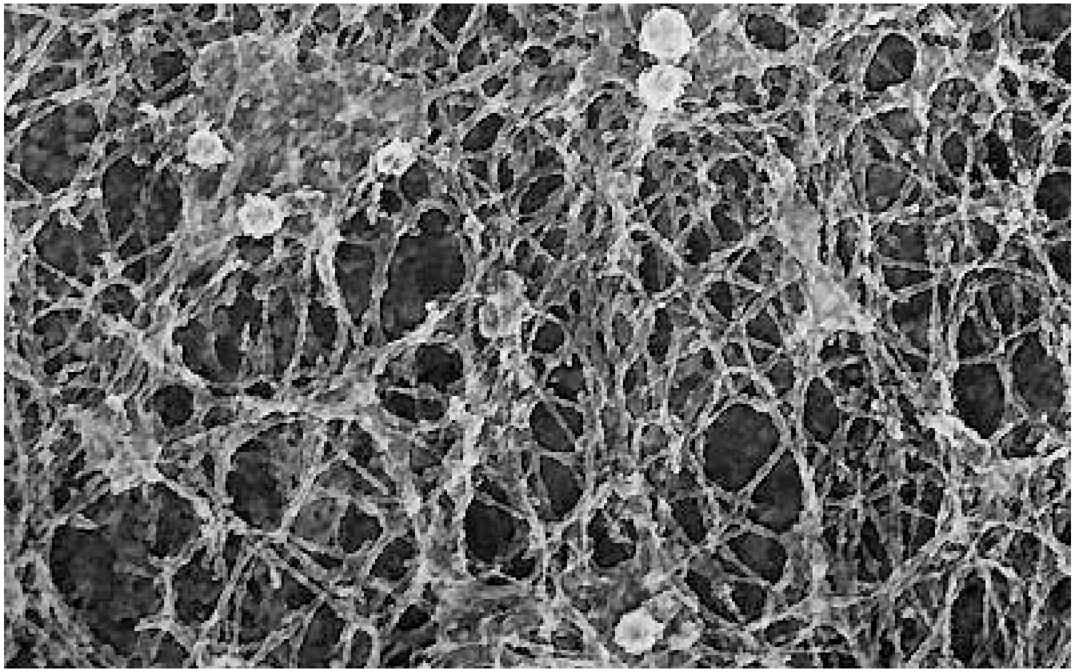
Cytoskeletal fibers



TEM cytoskeleton photograph, J. Hartwig, Harvard University. Courtesy of J. Hartwig. Used with permission.

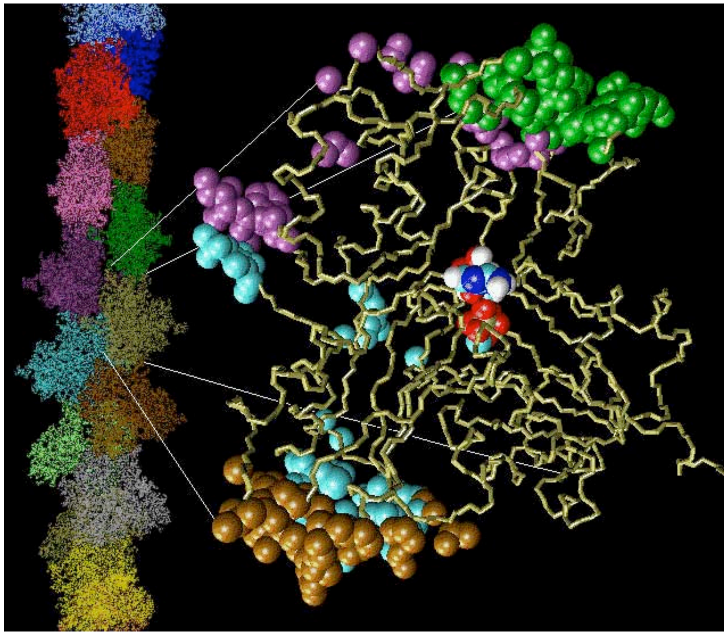
"rigidity"

	Diameter (nm)	Persistence Length (μm)
actin	6-8	15
microtubule	10	60,000
intermediate filament	20-25	1-3



TEM cytoskeleton photograph, J. Hartwig, Harvard University.
Courtesy of John Hartwig. Used with permission.

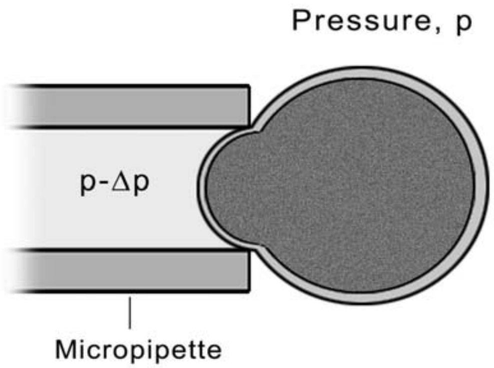
When stressed, cells form stress fibers, mediated by a variety of **actin-binding proteins**.



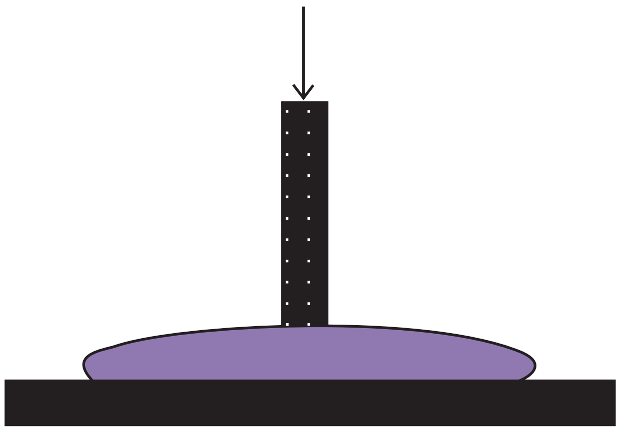
Structure of actin.
Image courtesy of Dr. Willy Wriggers.
Used with permission.

Measuring Complex Material Properties

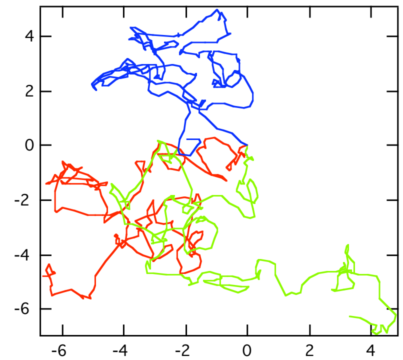
Aspiration



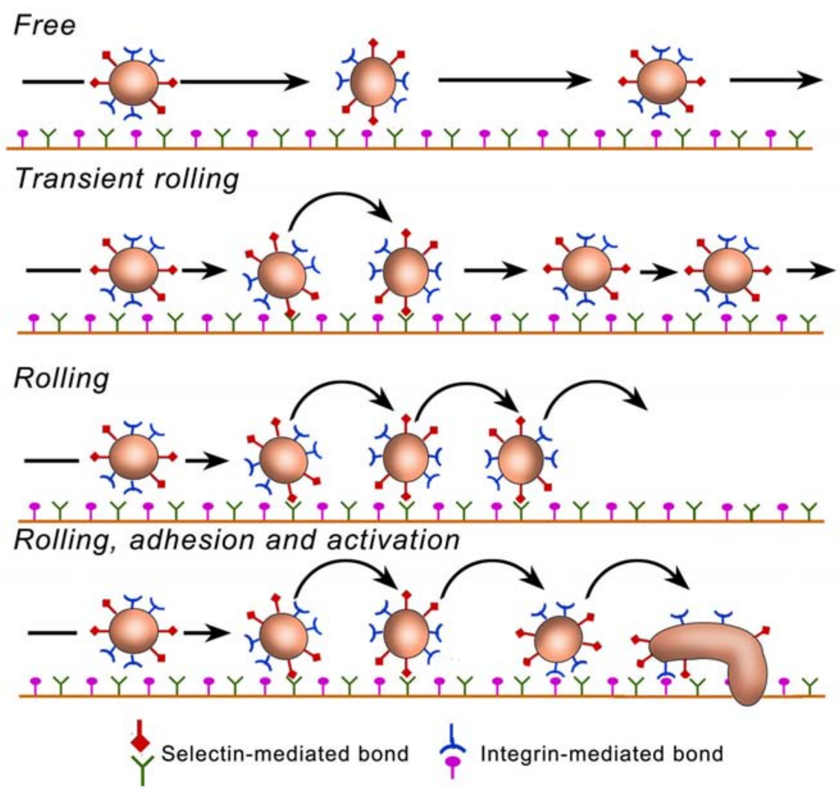
Cell Poking



Thermal tracers



Cell Adhesion



After Orsello, Lauffenburger and Hammer, 2001.

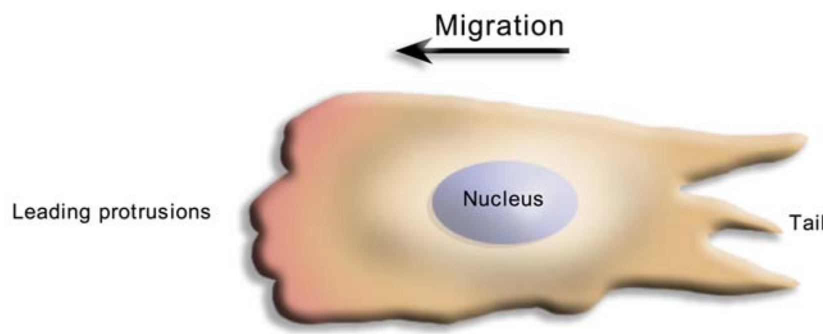
Physical forces effect bond association/dissociation

Finite contact times

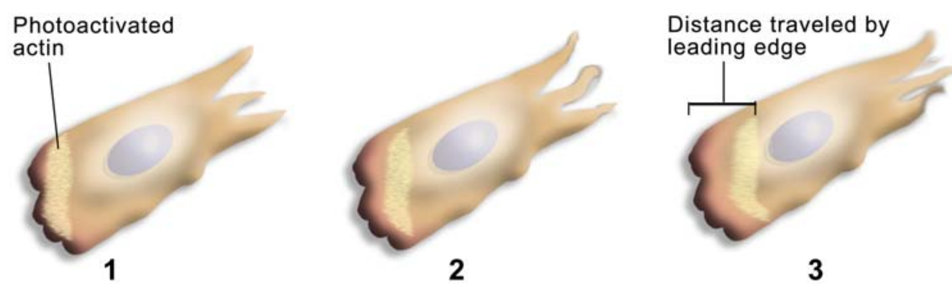
Cell deformation

Dynamic Processes: Cell Migration

Cell Motility



Fluorescently marked actin



- Actin is a polymer
- The cytoskeleton is active
- Coordinated processes: adhesion, (de-) polymerization

Active Cell Contraction

Cardiac myocyte (Jan Lammerding)

Courtesy of Jan Lammerding, Harvard Medical School. Used with permission.

Cytoskeletal Mechanics Probed by External Force

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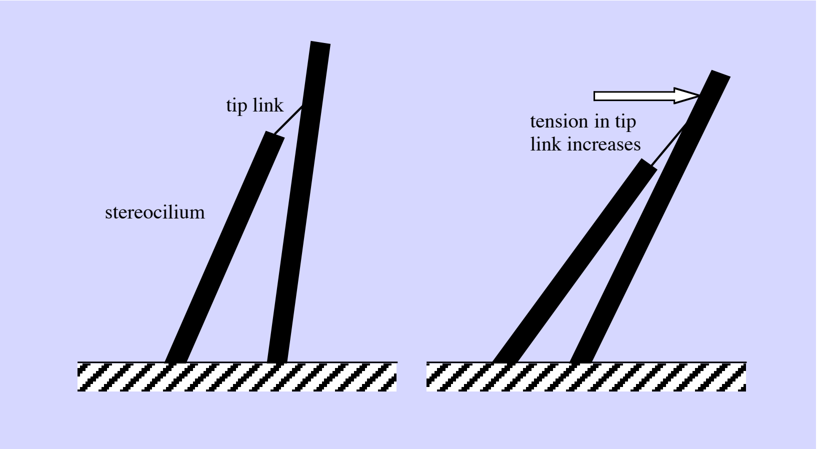
Fibroblast with fluorescent mitochondria forced by a magnetic bead

D. Ingber, P. LeDuc

Mechanotransduction: Hair cell stimulation



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SEM of the stereocilia on the surface of a single hair cell (Hudspeth)

Image removed due to copyright considerations.

Tension in the tip link activates a stretch-activated ion channel, leading to intracellular calcium ion fluctuations.

Molecular dynamics simulation of channel regulation by membrane tension

Images removed due to copyright considerations.
See Figures 1 and 9 in Gullingsrud, Justin, Dorina Kosztin, and Klaus Schulten.
"Structural Determinants of MscL Gating Studied by Molecular Dynamics Simulations."
Biophys J, Vol. 80, No. 5 (May 2001), p. 2074-2081.
http://www.biophysj.org/cgi/content/full/80/5/2074

But other evidence suggests that the pore increases to >20 angstroms!

Steered molecular dynamics of fibronectin

Images removed due to copyright considerations.
See Figures 2 and 3 in Gao, Mu, David Craig, Viola Vogel, and Klaus Schulten.
"Identifying unfolding intermediates of FN-III10 by steered molecular dynamics."
Journal of Molecular Biology, 323:939-950 (2002).

Constant applied force = 500 pN

Unfolding has been thought to be important in exposing buried cryptic binding sites.

The Orders of Magnitude in DNA Organization

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Diagram showing range of size magnitudes,
from metaphase chromosome (1400 nm) down to
short region of DNA double-helix (2 nm).

Compaction of a stretched DNA after histones are introduced.

Image removed due to copyright considerations.
See Figure 1 in Ladoux, B., P. Doyle et al.
"Fast kinetics of chromatin assembly revealed by single-molecule videomicroscopy and scanning force microscopy."
Proc Natl Acad Sci U S A. 97(26):14251-6 (2000 Dec 19).

Dynamic Processes: Molecules

Single T4-phage
DNA in solution

Doyle Group

Stretching a Single DNA

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copyright considerations.

Bustmante 1996

- Thermal forces are important (kT/ 1 nm ~ 4 x 10^{-12} N)
- Entropic & enthalpic effects
- Generic/specific mechanical responses
- Single molecule experiments are possible

Motor Proteins

Mechanochemical (Enzyme) *Engines*

ATP hydrolysis->conformation change

Rotary Motor (F_0F_1)

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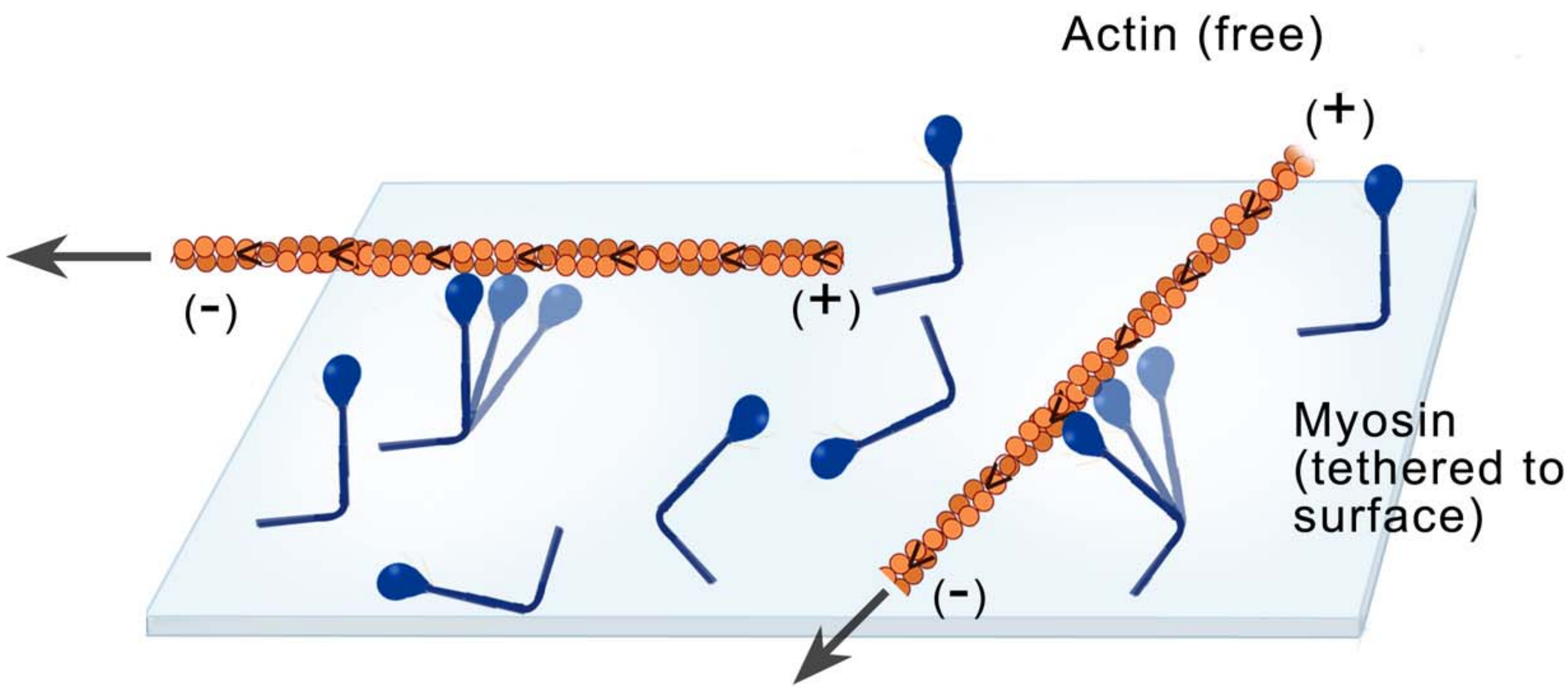
Yanagida 1999

Linear Motor Myosin II

Image removed due to copyright considerations.

Actin filament

Motor Proteins



Reoccurring Themes in Biomechanics

- Multiple length/time/energy scales
- Polymers play an important role
- Thermal energy is important
- Interplay of chemical, electrical, mechanical interactions
- Quantitative (single molecule) experiments

Molecular, Cellular & Tissue Biomechanics

Biology is soft, wet & dynamic

Using Engineering/Physics to Unravel & Manipulate Biology

- Scaling arguments
- Mechanical models (polymer physics)
- Experimental techniques
- Importance of the stochastic nature of biology

Readings

There is no single text which covers all of this material !

Texts:

Y. C. Fung, **Biomechanics: Mechanical Properties of Living Tissues**, 2nd Edition, Springer -Verlag, 1993R. Nossal and L. Lecar, **Molecular and Cellular Biophysics,** Wiley, 1990.H. Lodish, D. Baltimore, L. Zipurksy, P. Matsudaira, **Molecular Cell Biology**, 1996. K. Dill and S. Bromberg, **Molecular Driving Forces**, 2003

Manuscript Drafts:

P.C. Nelson, Biological Physics: Energy, Information Life

A. Grodzinksy, R. Kamm, L. Mahadevan: BEH 410

Research Articles:

Posted/linked on the web

Notes:

Periodically posted