20.310J, 2.797J, 3.053J, 6.024J

MOLECULAR, CELLULAR, & TISSUE BIOMECHANICS

SPRING 2015

GENERAL COURSE INFORMATION

- **Textbooks and Reference Materials:**

Most of the material will come from journal articles and notes to be handed out by the instructors or available through the course website. There are no required textbooks.
Texts in the library that are used as sources for material distributed as PDFs include:

(a) A Grodzinsky, **Fields, Forces and Flows in Biological Systems,** 2011.
(b) D. Boal, **Mechanics of the Cell**, 2001.
(c) H. Lodish, D. Baltimore, L. Zipurksy, P. Matsudaira, **Molecular Cell Biology**, 2002.
(d) K. Dill and S. Bromberg, **Molecular Driving Forces**, 2003.
(e) J. Howard, **Mechanics of Motor Proteins and the Cytoskeleton**, 2001. ISBN-10: **0878933336**
(f) R. Phillips, J. Kondev, J. Theriot, **Physical Biology of the Cell**, 2008.
(g) Jackson, M.B. **Molecular and Cellular Biophysics**. Cambridge University Press (2006). ISBN-10: **0521624703**

Texts that may be useful as background material include:

(h) P. Nelson, **Biophysics**, 2008.
(i) M. Mofrad and R. Kamm, **Cytoskeletal Mechanics, Cambridge University Press**, 2006. ISBN 978-0-521-64828-9 (paperback).
(j) M. Mofrad and R. Kamm, **Cellular Mechanotransduction**, Cambridge University Press, 2009.
(k) Haynie, D. **Biological Thermodynamics**. Cambridge University Press (2008). ISBN-10: **0521711347**
(l) Wales, D.J. **Energy Landscapes**. With applications to clusters, biomolecules, and glasses. Cambridge University Press (2004). ISBN-10: **0521814154**
(m) Downarowicz, T. **Entropy in Dynamical Systems**. Cambridge University Press (2011).
(n) Ben-Naim, A. **Entropy Demystified**. World Scientific (2008).

- **Grading**

The term grade will be a weighted average of exams, term paper and homework grades. The general weighting distribution will be

- 60% for the three quizzes (two evening exams and one final exam; 20% each)
- 20% for the term paper (including written report and in-class presentation)
- 20% for the homework

Homework grading is intended to show you how well you are progressing in learning the course material. You are encouraged to seek advice or help from other students and/or to work in study groups. However, all of the work that is turned in must be your own. Please review MIT's academic honesty standards and policies at http://web.mit.edu/academicintegrity/. The homework exercise should be viewed as a learning experience, not a competition. Homework assignments are due in class at the beginning of the lecture on the assigned date.

Course Project and Term paper guidelines

Important dates:

Quiz #1	3/10 **evening**
Quiz #2	4/14 **evening**
Term paper	5/8
Group presentations	5/5, 5/7, ??
Quiz #3	Final exam week, TBA

20.310/2.797/3.053/6.024 Spring 2015 SYLLABUS
Lecture: Tue/Thurs 1-2:30pm, Room 4-270
MOLECULAR, CELLULAR, & TISSUE BIOMECHANICS

Molecular Mechanics

2/3 L#1: Length, Time, & Molecular-scale Forces in Biology (RDK)

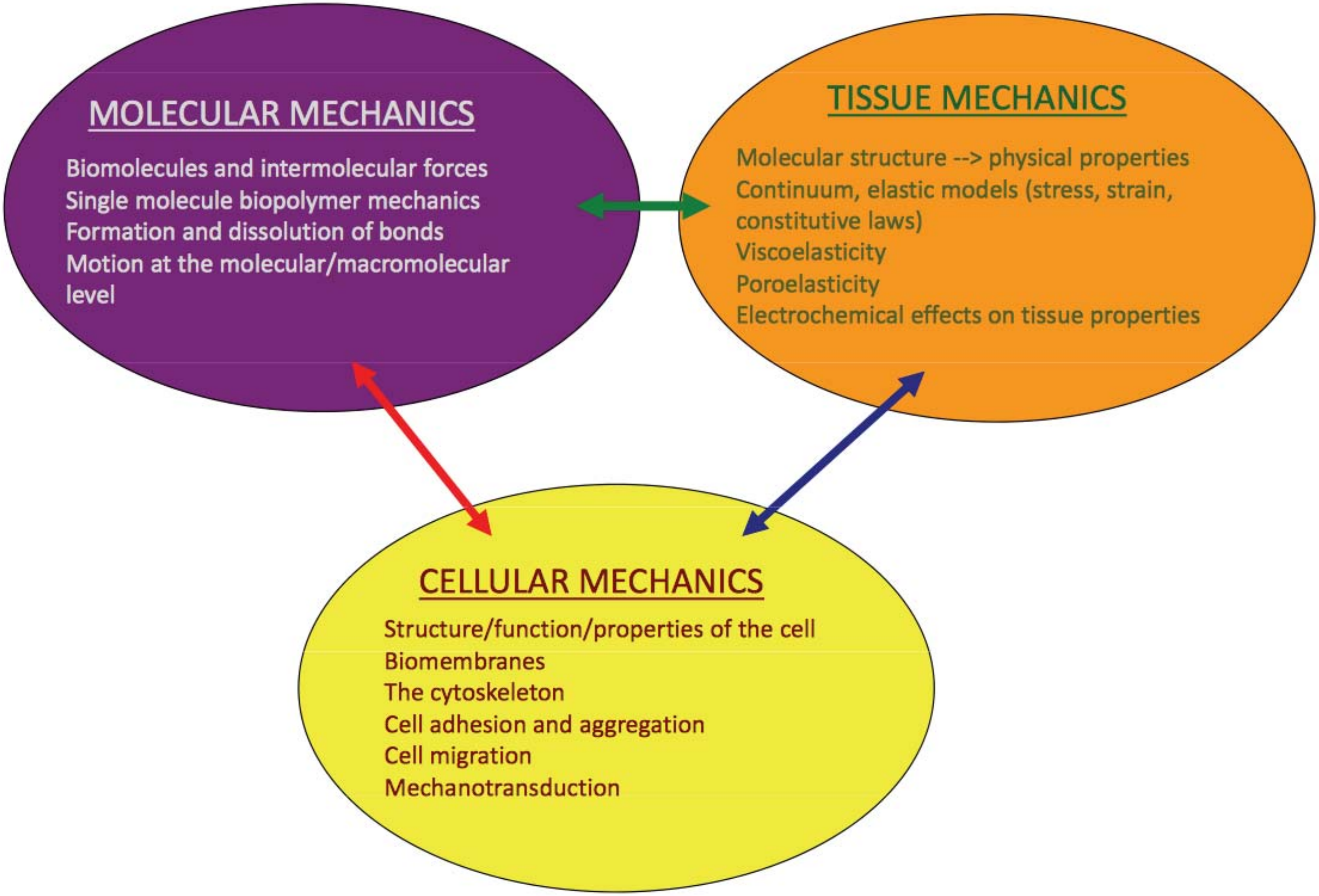
Overview of mechanics across all scales. Learning objectives for the term. Scales of force, displacement, time, and energy relevant to biological structures. Molecular forces and bond energies; kT as an energy ruler. Examples drawn from DNA folding, peptide assembly, protein binding, cytoskeletal strain, and tissue compliance.

Readings: Mahadevan Chapter, Phillips 1.2, 2.1 – 2.3, 3.1, 3.4

2/5 L#2: Single molecule mechanics (RDK)

Thermal forces and Brownian motion. Diffusion, viscous drag, shear forces at low Reynolds numbers. Statistical mechanics and entropy; rubber elasticity and freely jointed chain; Applications to Intracellular Cytoskeleton: rigidity of actin and microtubules.

Readings: Dill & Bromberg 17, Howard 4, 6


MOLECULAR MECHANICS
Biomolecules and intermolecular forces
Single molecule biopolymer mechanics
Formation and dissolution of bonds
Motion at the molecular/macromolecular level
TISSUE MECHANICS
Molecular structure --> physical properties
Continuum, elastic models (stress, strain, constitutive laws)
Viscoelasticity
Poroelasticity
Electrochemical effects on tissue properties
CELLULAR MECHANICS
Structure/function/properties of the cell
Biomembranes
The cytoskeleton
Cell adhesion and aggregation
Cell migration
Mechanotransduction

Biomechanics at all length scales

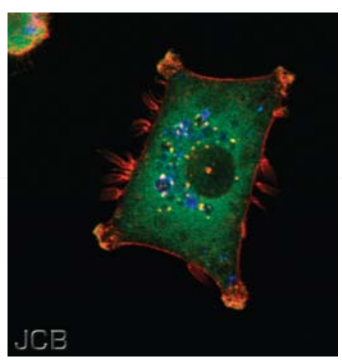
← Traditional domain of biomechanics →

Quantum mechanics	Molecular dynamics	Networks and Brownian dynamics	Continuum mechanics	Large-scale, discrete or lumped systems
	Molecular motors Mechanotransduction	Migration Cytoskeletal rheology	Bone Cartilage Cardiovascular system	Flight Swimming Gain analysis

atoms — proteins — organelles — cells — organs — organisms

10^{-10} — 10^{-9} — 10^{-6} — 10^{-2} — 10^{0} meters

Courtesy of Wenqing Xu and RCSB Protein Data Bank. Used with permission.



Courtesy of The Journal of Cell Biology. License: CC BY-NC-SA.

Courtesy of Eugene Archer on Flickr. License CC BY-NC.

Biomechanics at all length scales

20.310

Quantum mechanics	Molecular dynamics	Networks and Brownian dynamics	Continuum mechanics	Large-scale, discrete or lumped systems
	Molecular motors	Migration	Bone	Flight
	Mechanotransduction	Cytoskeletal rheology	Cartilage	Swimming
			Cardiovascular system	Gain analysis

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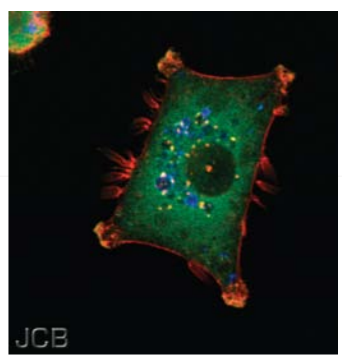

Biomechanics in the news

Question of the day

ARTICLE

doi:10.1038/nature12968

Stimulus-triggered fate conversion of somatic cells into pluripotency

Haruko Obokata[1,2,3], Teruhiko Wakayama[3]†, Yoshiki Sasai[4], Koji Kojima[1], Martin P. Vacanti[1,5], Hitoshi Niwa[6], Masayuki Yamato[7] & Charles A. Vacanti[1]

Nature, 2014

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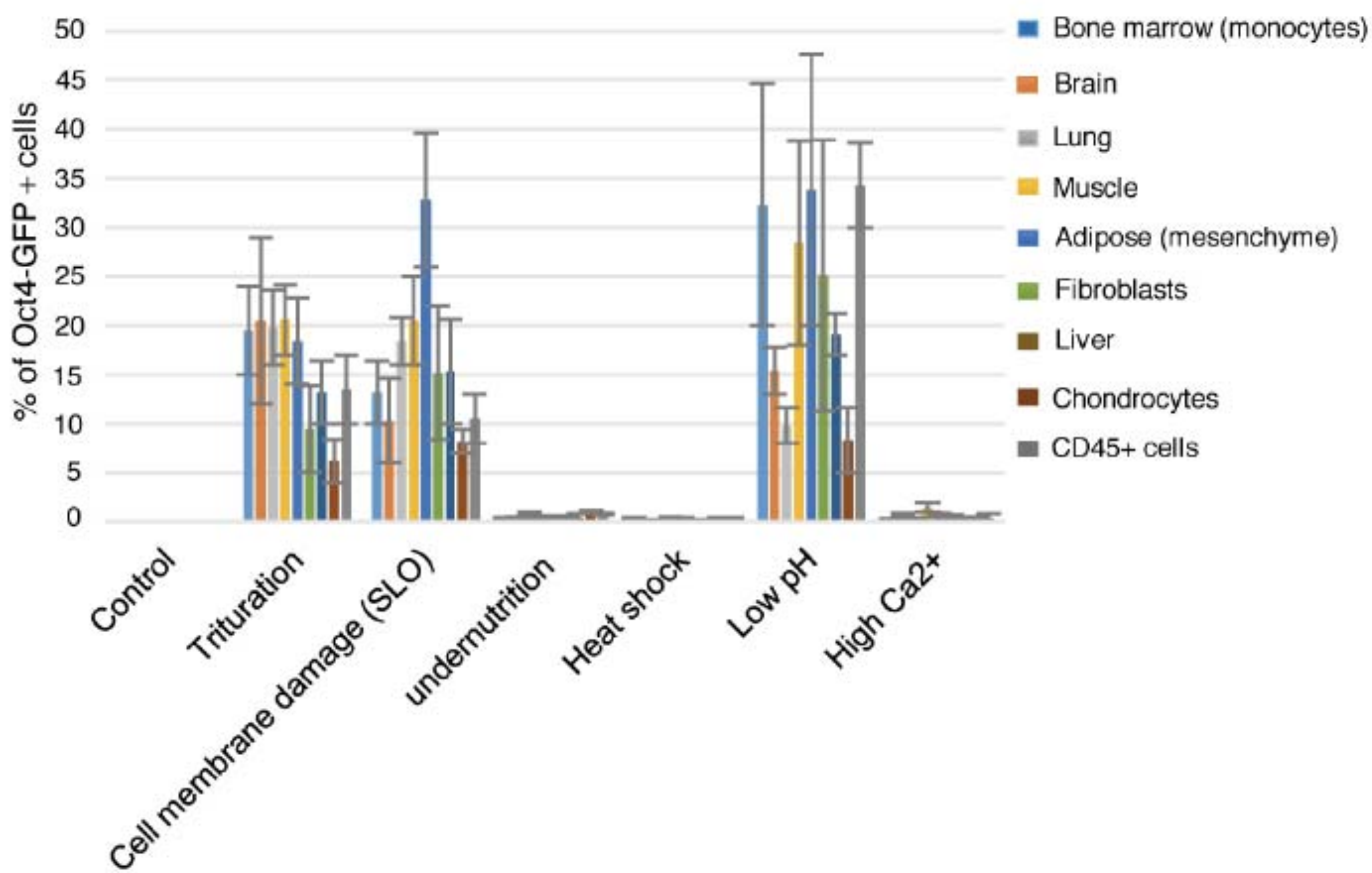

Source: Obokata, Haruko, Teruhiko Wakayama, et al. "Stimulus-triggered Fate Conversion of Somatic Cells into Pluripotency." *Nature* 505, no. 7485 (2014): 641-7.

Martin Karplus
2013 Nobel Prize in Chemistry

The Nobel website said the prize was awarded for the researchers' work in "the development of multiscale models for complex chemical systems."

Some Learning Objectives

1. To understand the fundamental concepts of mechanics and be able to apply them to simple problems in the deformation of continuous media
2. To understand the underlying basis for the mechanical properties of molecules, cells and tissues
3. To be able to model biological materials using methods appropriate over diverse length scales
4. To be familiar with the wide spectrum of measurement techniques that are currently used to determine mechanical properties
5. To appreciate the close interconnections between mechanics and biology/chemistry of living systems

Length scale bars (10^{-10} m to 10^{7} m):

Human hair diameter	C. elegans worm length	Eukaryotic cell nucleus diameter
DNA basepair length	Red blood cell diameter	Microtubule diameter
E. coli width	HIV diameter	Human genome length
Human height	Average protein radius	Lipid bilayer thickness

Time scale bars (1 fs to 4 billion years):

Human lifespan	Stem cell replication	Protein side chain rotation
Earth age	Covalent bond vibration	Fly lifespan
Protein folding	Cell crawls 50 um	Sequoia lifetime

Energy scale bars (1 kT to 10^{31} kT):

AA battery	Sugar (1 g)	Covalent bond
H-bond	Food you eat today	E. coli replication (1 cell)
Lightning bolt	Human heart beat (1)	Gasoline (1 gal)

12

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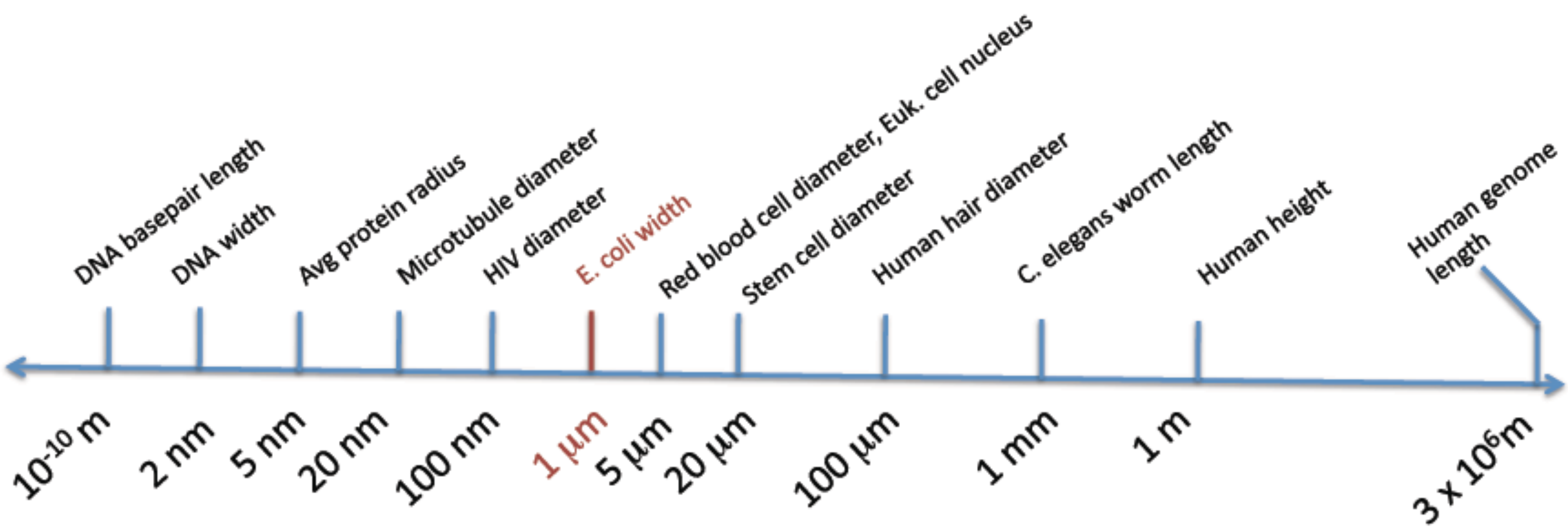

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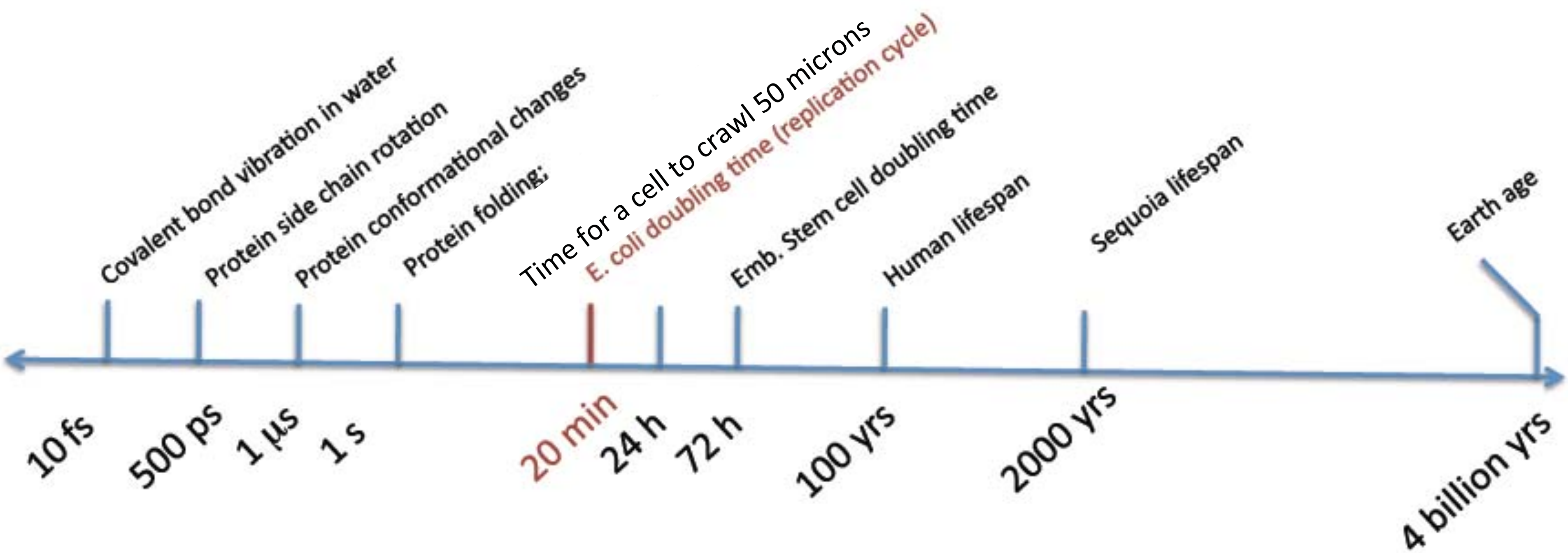

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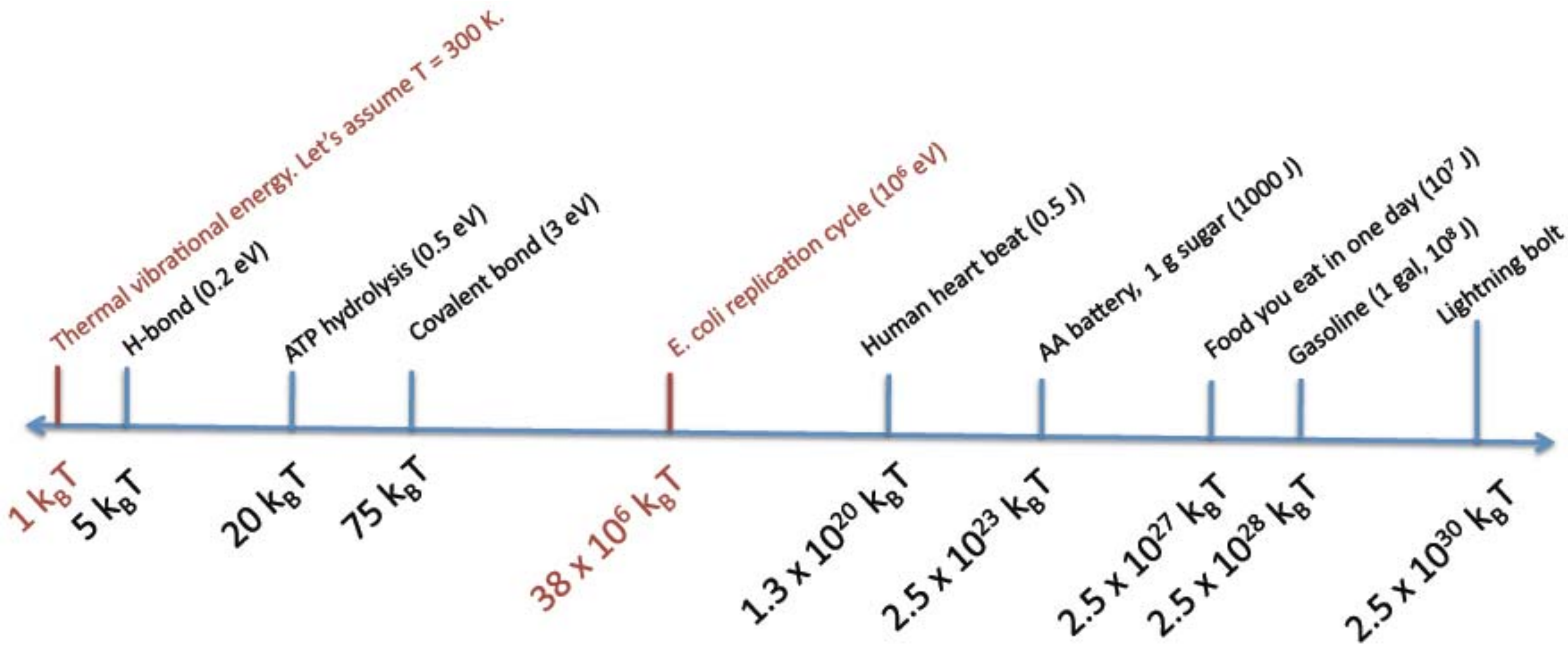


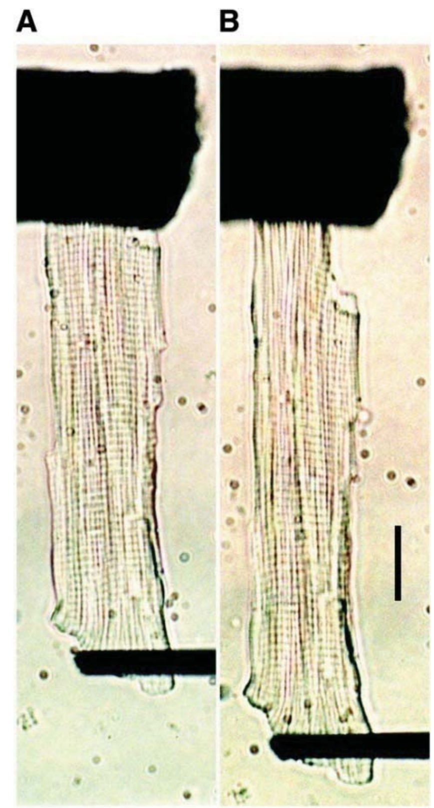
How much force does a heart muscle cell generate?

Peak twitch force/cell:

$F_{max} = 1.06 \pm 0.20\ \mu N$

Force per cross-sectional area:

$\sigma = 2.91 \pm 0.65\ mN/mm^2$



Source: Yasuda, So-Ichiro, et al. "A Novel Method to Study Contraction Characteristics of a Single Cardiac Myocyte using Carbon Fibers." *American Journal of Physiology-Heart and Circulatory Physiology* 281, no. 3 (2001): H1442-6.

Yasuda, S.-I. et al. *Am J Physiol Heart Circ Physiol* 2001

How much does a cell weigh?

$F_{weight} = \rho \times V \times g$

(neglecting the buoyancy force!)

Assume for cell:

- ρ ~ (1.1x) density of water, 1100 kg/m^3
- $V \sim 20 \times 20 \times 20$ µm = $(20 \times 10^{-6}$ m$)^3$
- $g = 9.81$ m/s^2

=> $F \sim 100 \times 10^{-12}$ N = 100 pN

Forces at the molecular level

Type of Force	Example	Rupture Force*	Length	Energy
Breaking of a covalent bond	C-C	~1600 pN	0.1-0.5 nm	~ 1.6×10^{-19} J ~ 90-350 kT
Breaking of a noncovalent bond.	Biotin/streptavidin	~5-160 pN	~ 1 nm	~ 1.6×10^{-19} J ~40 kT
Breaking of a weak bond.	Hydrogen bond	~4-20 pN	~ 0.3nm	~ $4\text{-}8 \times 10^{-21}$ J ~ 1 kT
Developed by molecular motor	Kinesin walking on microtubule	~5 pN	8 nm (step size)	~ 40×10^{-21} Nm ~10 kT

1 nm = 10^{-9} m
1pN = 1×10^{-12} N
[Energy] = F L = [N m] or [J]
$k_B = 1.38 \times 10^{-23}$ J/K
$k_B T = 4.14 \times 10^{-21}$ J = 4.14 pN * 1 nm

* Rupture forces generally depend on the rate of force application! Faster force application requires higher rupture forces!

Relevant molecules in biology

What's inside a cell?

A lot of water, ions (*e.g.* Ca^{2+}, Mg^{2+}), and lots of small carbon-containing molecules from these four major classes of biological molecules.

Carbohydrate	Lipid	Protein	Nucleic acid

Entropic forces

Entropy:

$S = k_B \ln (W)$

k_B = Boltzmann constant

W = multiplicity, i.e. number of microstates

vs.

Review (and a look ahead)

- Random walks and diffusion (see, e.g., Dill & Bromberg)
- Boltzmann statistics

$$P_i = \frac{1}{Q}\exp\left(\frac{-G_i}{k_B T}\right) \qquad Q = \sum_i \exp\left(\frac{-G_i}{k_B T}\right)$$

(note use of free energy, *G*, as opposed to internal energy, *U*, corresponding to an ensemble of states, taking entropy into account; G = H - TS)

- Thermal energy, $k_B T$ = 4 pN·nm = 0.6 kcal/mole (for T = 300K)
- Persistence length (thermal energy ⟺ bending stiffness)

$$l_p = \frac{K_b}{k_B T} \qquad K_b = EI$$

More on this later!

RESEARCH

RESEARCH ARTICLE

CELL ADHESION

The minimal cadherin-catenin complex binds to actin filaments under force

Craig D. Buckley,[1]* Jiongyi Tan,[2]* Karen L. Anderson,[3] Dorit Hanein,[3] Niels Volkmann,[3] William I. Weis,[2,4,5]† W. James Nelson,[5,6]† Alexander R. Dunn[1,2,7]†

Figures removed due to copyright restrictions. See figure in the research article summary, and figures 2A and 5C in the research article Buckley, Craig D. "The Minimal Cadherin-catenin Complex Binds to Actin Filaments Under Force." *6FLHQFH* 346, no. 6209 (2014): 1254211.