1.021, 3.021, 10.333, 22.00 Introduction to Modeling and Simulation

Part I – Continuum and particle methods

Applications to biophysics and bionanomechanics (cont'd)

Lecture 11

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Content overview

I. Particle and continuum methods

Lectures 2-13

1. Atoms, molecules, chemistry
2. Continuum modeling approaches and solution approaches
3. Statistical mechanics
4. Molecular dynamics, Monte Carlo
5. Visualization and data analysis
6. Mechanical properties – application: how things fail (and how to prevent it)
7. Multi-scale modeling paradigm
8. Biological systems (simulation in biophysics) – how proteins work and how to model them

II. Quantum mechanical methods

Lectures 14-26

1. It’s A Quantum World: The Theory of Quantum Mechanics
2. Quantum Mechanics: Practice Makes Perfect
3. The Many-Body Problem: From Many-Body to Single-Particle
4. Quantum modeling of materials
5. From Atoms to Solids
6. Basic properties of materials
7. Advanced properties of materials
8. What else can we do?

Overview: Material covered so far…

- **Lecture 1: Broad introduction to IM/S**
- **Lecture 2**: **Introduction to atomistic and continuum modeling** (multi-scale modeling paradigm, difference between continuum and atomistic approach, case study: diffusion)
- **Lecture 3**: **Basic statistical mechanics – property calculation I** (property calculation: microscopic states vs. macroscopic properties, ensembles, probability density and partition function)
- **Lecture 4**: **Property calculation II** (Monte Carlo, advanced property calculation, introduction to chemical interactions)
- **Lecture 5: How to model chemical interactions I** (example: movie of copper deformation/dislocations, etc.)
- **Lecture 6: How to model chemical interactions II** (EAM, a bit of ReaxFF—chemical reactions)
- **Lecture 7: Application to modeling brittle materials I**
- **Lecture 8: Application to modeling brittle materials II**
- **Lecture 9: Application – Applications to materials failure**
- **Lecture 10: Applications to biophysics and bionanomechanics**
- **Lecture 11: Applications to biophysics and bionanomechanics (cont'd)**

Lecture 11: Applications to biophysics and bionanomechanics (cont’d)

Outline:

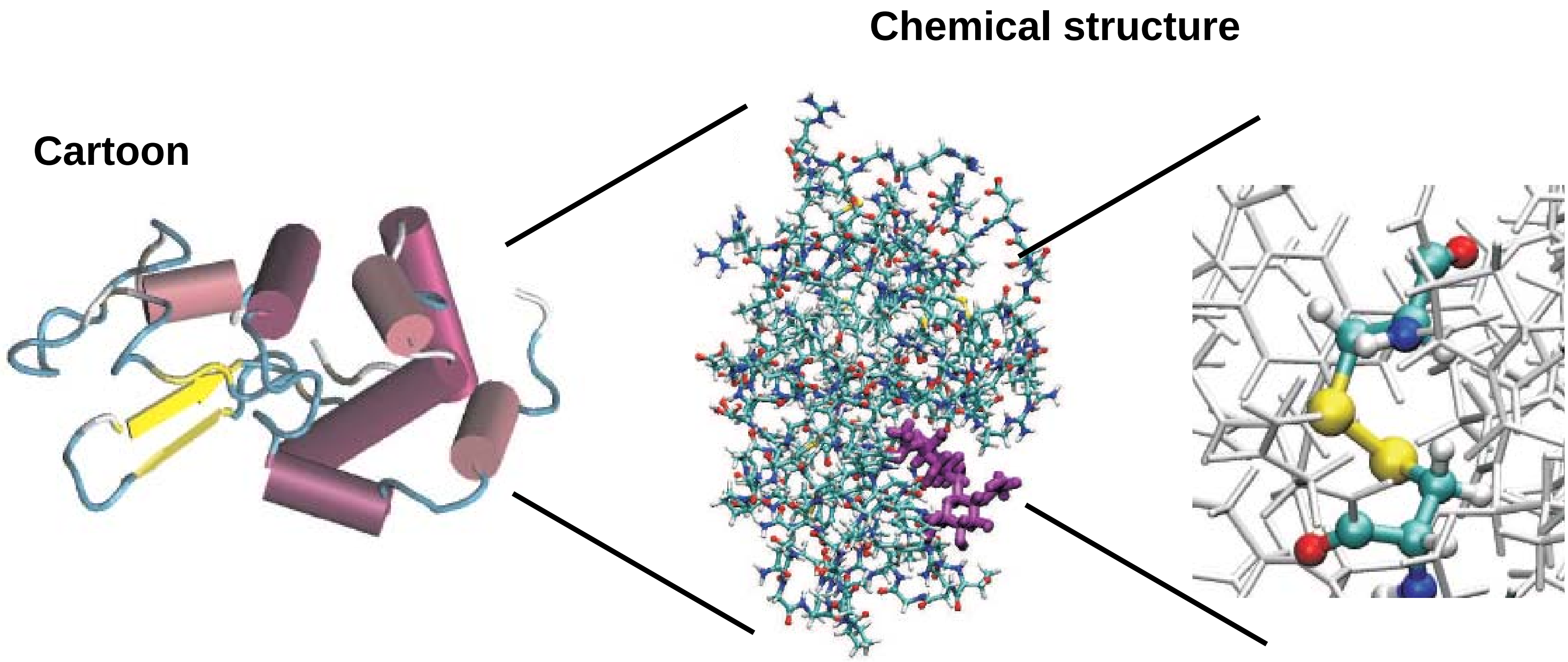
1. Force fields for proteins: (brief) review
2. Fracture of protein domains – Bell model
3. Examples – materials and applications

Goal of today’s lecture:

- Fracture model for protein domains: “Bell model”
- Method to apply loading in molecular dynamics simulation (nanomechanics of single molecules)
- Applications to disease and other aspects

1. Force fields for proteins: (brief) review

Chemistry, structure and properties are linked

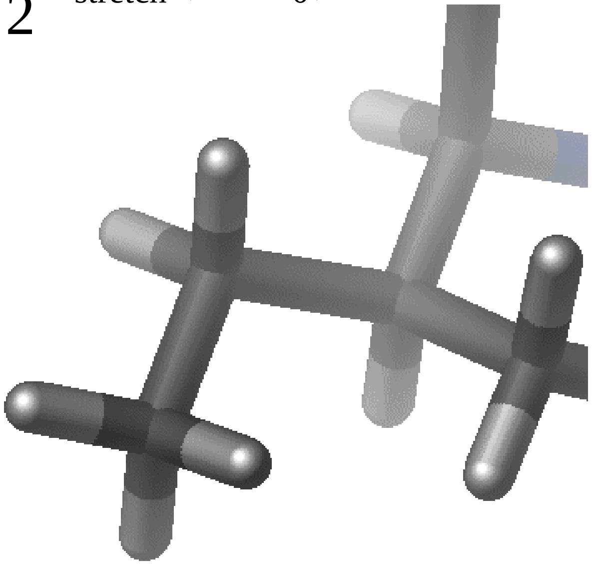


Presence of various chemical bonds:

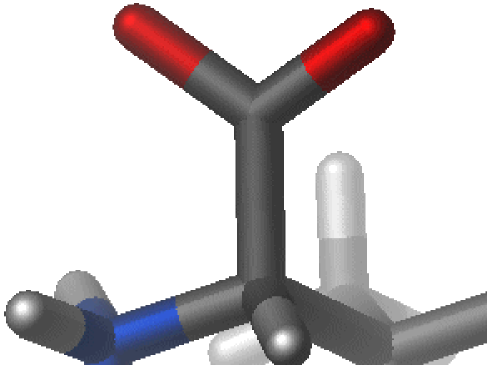
- Covalent bonds (C-C, C-O, C-H, C-N..)
- Electrostatic interactions (charged amino acid side chains)
- H-bonds (e.g. between H and O)
- vdW interactions (uncharged parts of molecules)

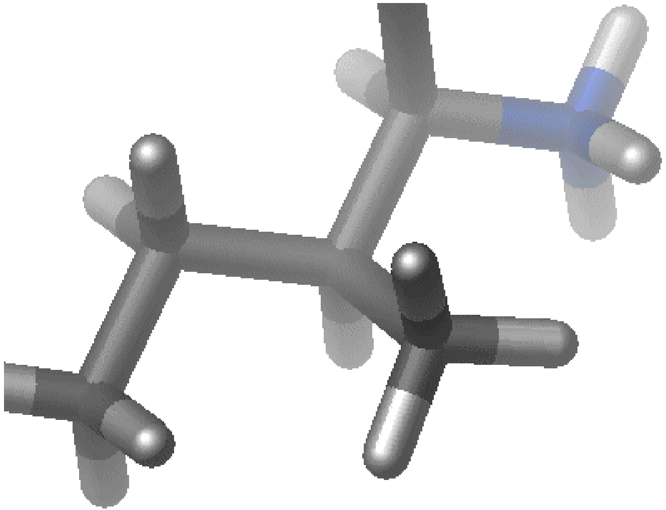
Model for covalent bonds

$$\phi_{\text{stretch}} = \frac{1}{2} k_{\text{stretch}} (r - r_0)^2$$



$$\phi_{\text{bend}} = \frac{1}{2} k_{\text{bend}} (\theta - \theta_0)^2$$





$$\phi_{\text{rot}} = \frac{1}{2} k_{\text{rot}} (1 - \cos(\vartheta))$$

Courtesy of the EMBnet Education & Training Committee. Used with permission.
Images created for the CHARMM tutorial by Dr. Dmitry Kuznetsov (Swiss Institute of Bioinformatics) for the EMBnet Education & Training committee (http://www.embnet.org)

http://www.ch.embnet.org/MD_tutorial/pages/MD.Part2.html

Summary: CHARMM potential (pset #3)

$$U_{total} = \overset{\checkmark}{U_{\mathrm{Elec}}} + \overset{\checkmark}{U_{\mathrm{Covalent}}} + \overset{=0 \text{ for proteins}}{\cancel{U_{\mathrm{Metallic}}}} + \overset{\checkmark}{U_{\mathrm{vdW}}} + \overset{\checkmark}{U_{\mathrm{H-bond}}}$$

U_{Elec} : Coulomb potential $\phi(r_{ij}) = \dfrac{q_i q_j}{\varepsilon_1 r_{ij}}$

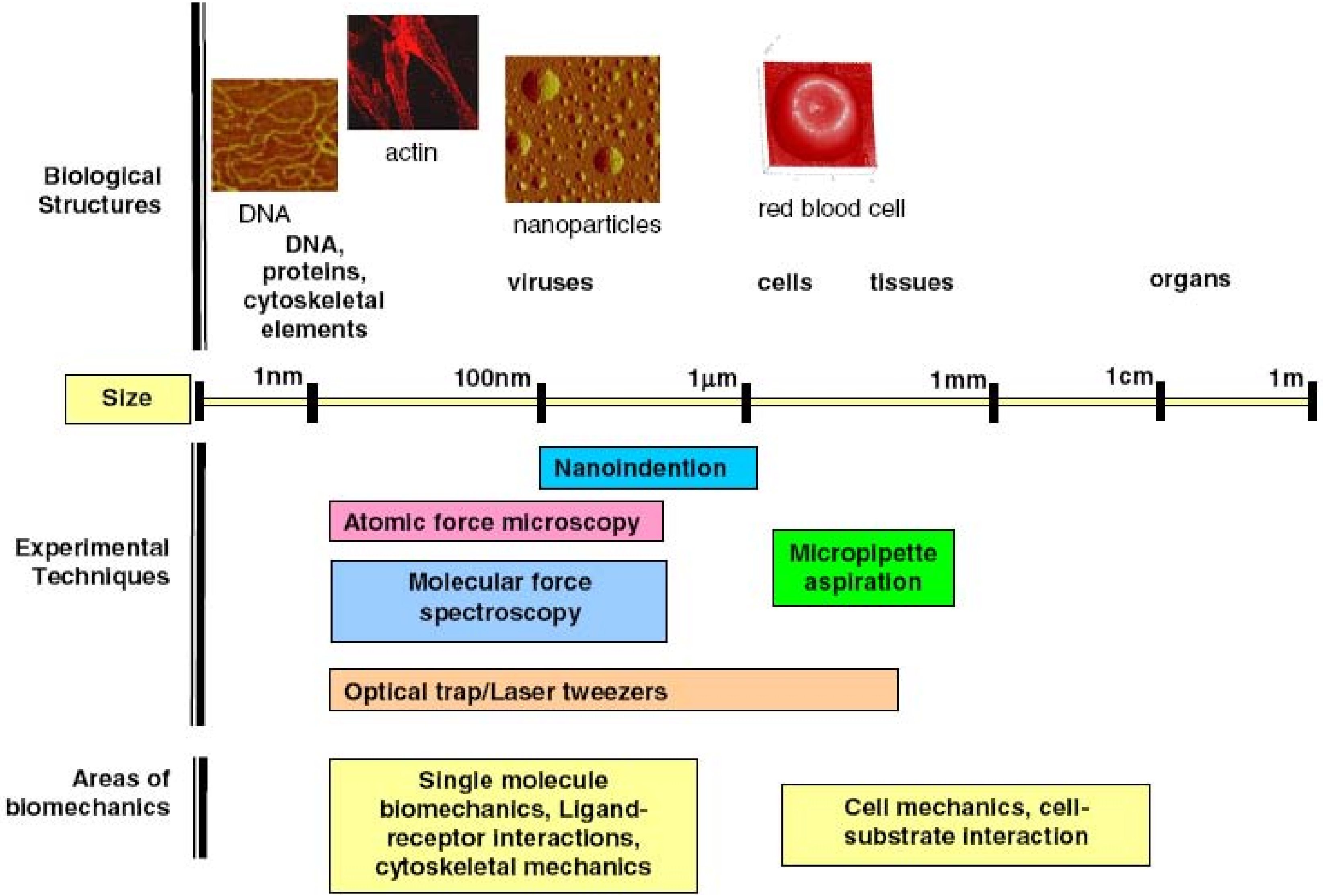
$$U_{\mathrm{Covalent}} = U_{\mathrm{stretch}} + U_{\mathrm{bend}} + U_{\mathrm{rot}} \quad \begin{cases} \phi_{\mathrm{stretch}} = \dfrac{1}{2} k_{\mathrm{stretch}} (r - r_0)^2 \\ \phi_{\mathrm{bend}} = \dfrac{1}{2} k_{\mathrm{bend}} (\theta - \theta_0)^2 \\ \phi_{\mathrm{rot}} = \dfrac{1}{2} k_{\mathrm{rot}} (1 - \cos(\vartheta)) \end{cases}$$

U_{vdW} : LJ potential $\phi(r_{ij}) = 4\varepsilon \left[\left(\dfrac{\sigma}{r_{ij}} \right)^{12} - \left(\dfrac{\sigma}{r_{ij}} \right)^{6} \right]$

$U_{\mathrm{H-bond}}$: $\phi(r_{ij}) = D_{\mathrm{H-bond}} \left[5 \left(\dfrac{R_{\mathrm{H-bond}}}{r_{ij}} \right)^{12} - 6 \left(\dfrac{R_{\mathrm{H-bond}}}{r_{ij}} \right)^{10} \right] \cos^4(\theta_{\mathrm{DHA}})$

2. Fracture of protein domains – Bell model

Experimental techniques



Biological Structures

DNA

actin

nanoparticles

red blood cell

DNA, proteins, cytoskeletal elements

viruses

cells

tissues

organs

Size

1nm

100nm

1µm

1mm

1cm

1m

Experimental Techniques

Nanoindention

Atomic force microscopy

Molecular force spectroscopy

Micropipette aspiration

Optical trap/Laser tweezers

Areas of biomechanics

Single molecule biomechanics, Ligand-receptor interactions, cytoskeletal mechanics

Cell mechanics, cell-substrate interaction

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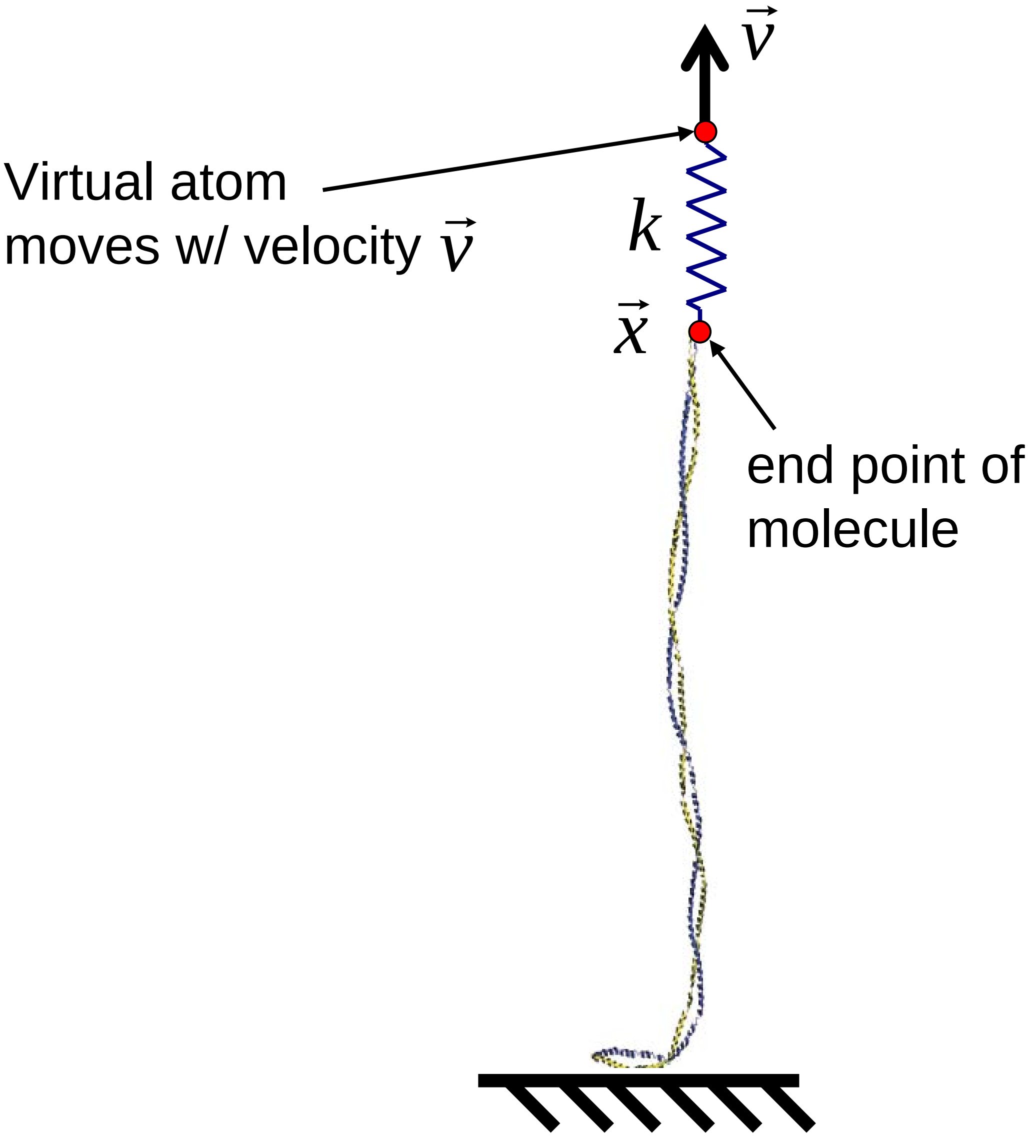
How to apply load to a molecule

(in molecular dynamics simulations)

Steered molecular dynamics (SMD)

Steered molecular dynamics used to apply forces to protein structures



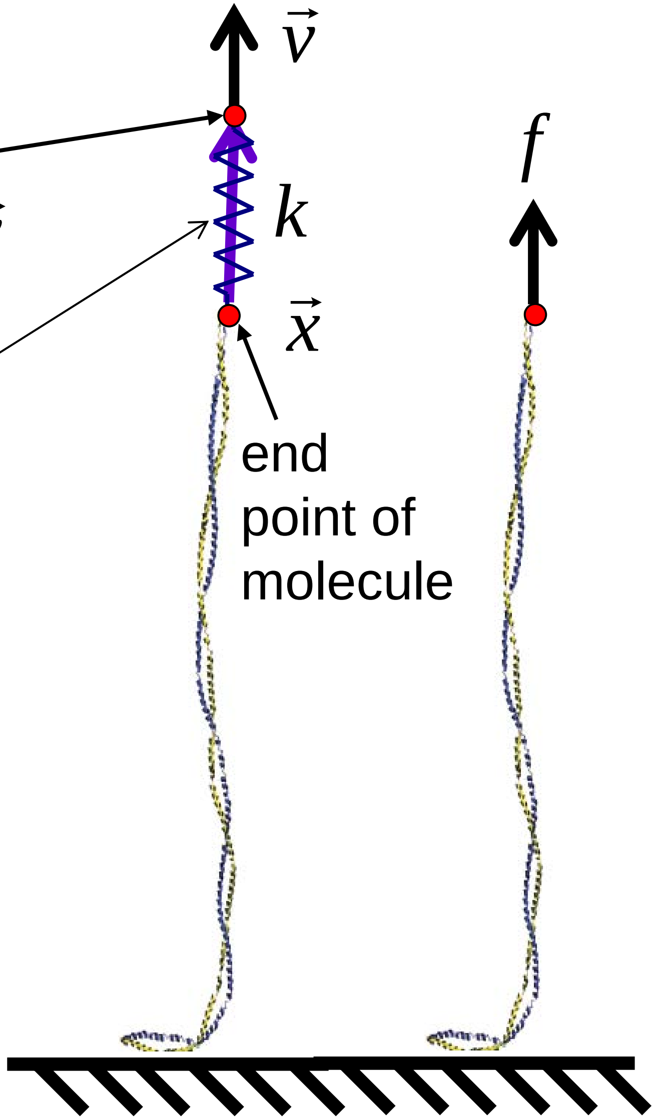
Virtual atom moves w/ velocity $\vec{v}$

end point of molecule

Steered molecular dynamics (SMD)

Steered molecular dynamics used to apply forces to protein structures

Virtual atom moves w/ velocity $\vec{v}$



$$f = k(v \cdot t - x)$$

$$\vec{v} \cdot t - \vec{x}$$

SMD spring constant

$$\vec{f} = k(\vec{v} \cdot t - \vec{x})$$

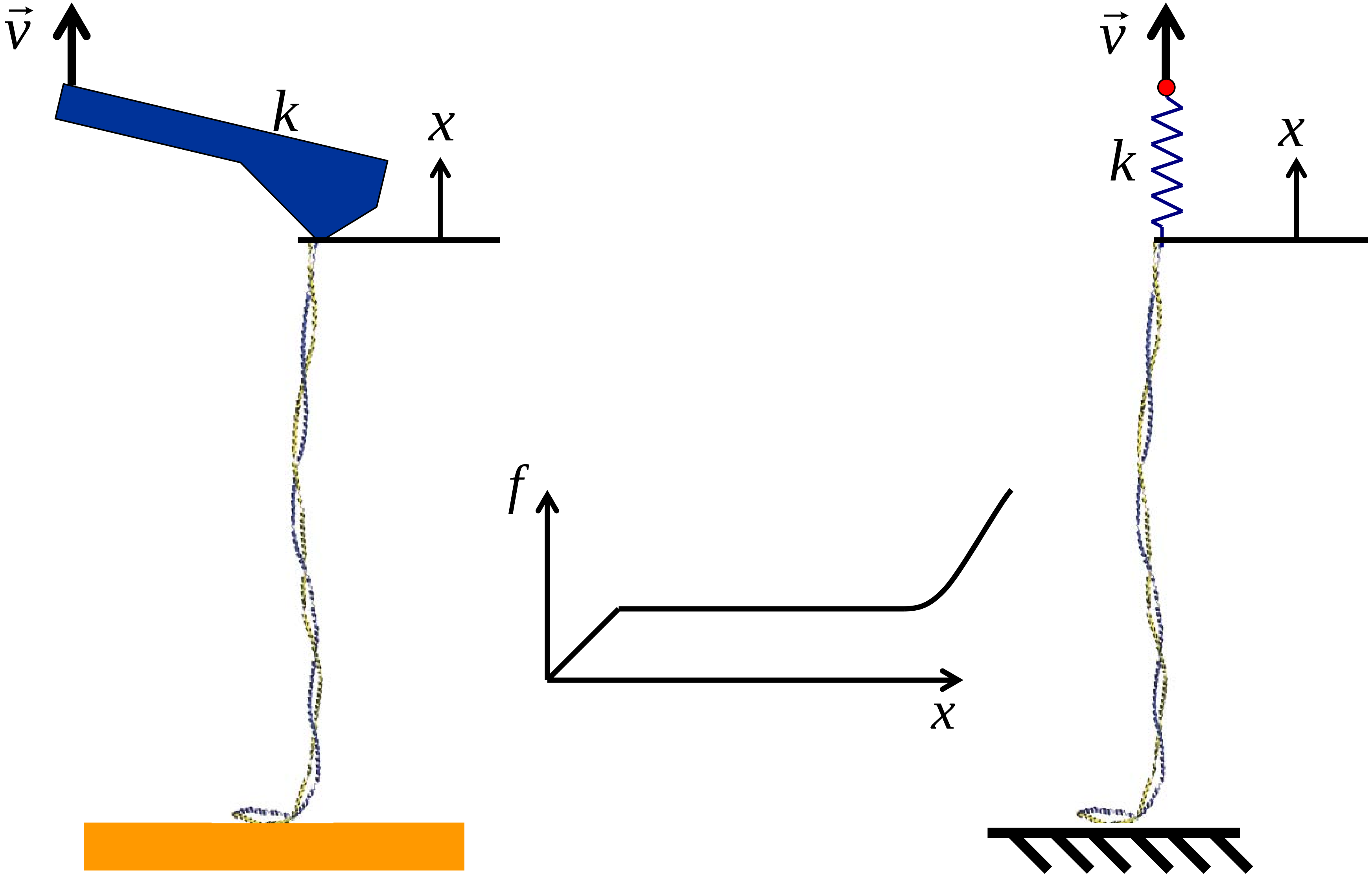
SMD deformation speed vector

time

Distance between end point of molecule and virtual atom

SMD mimics AFM single molecule experiments

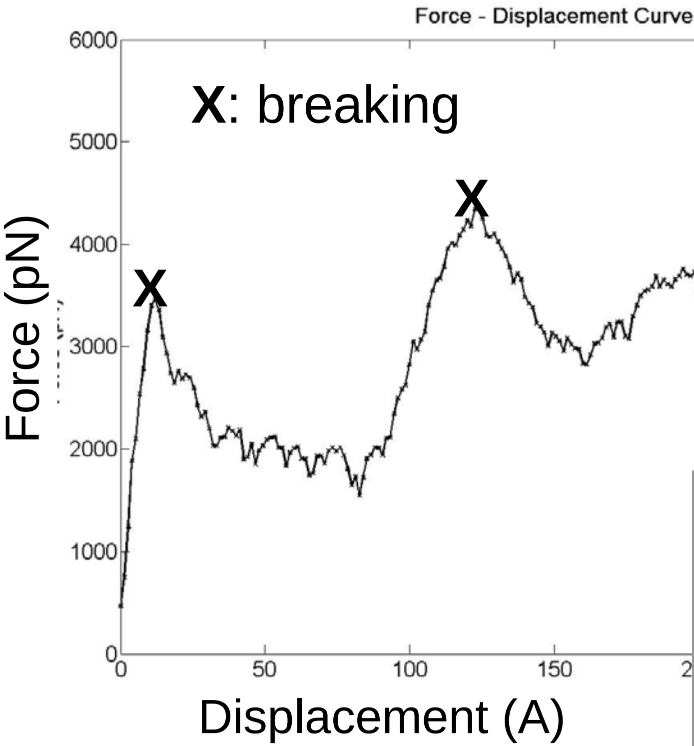
Atomic force microscope



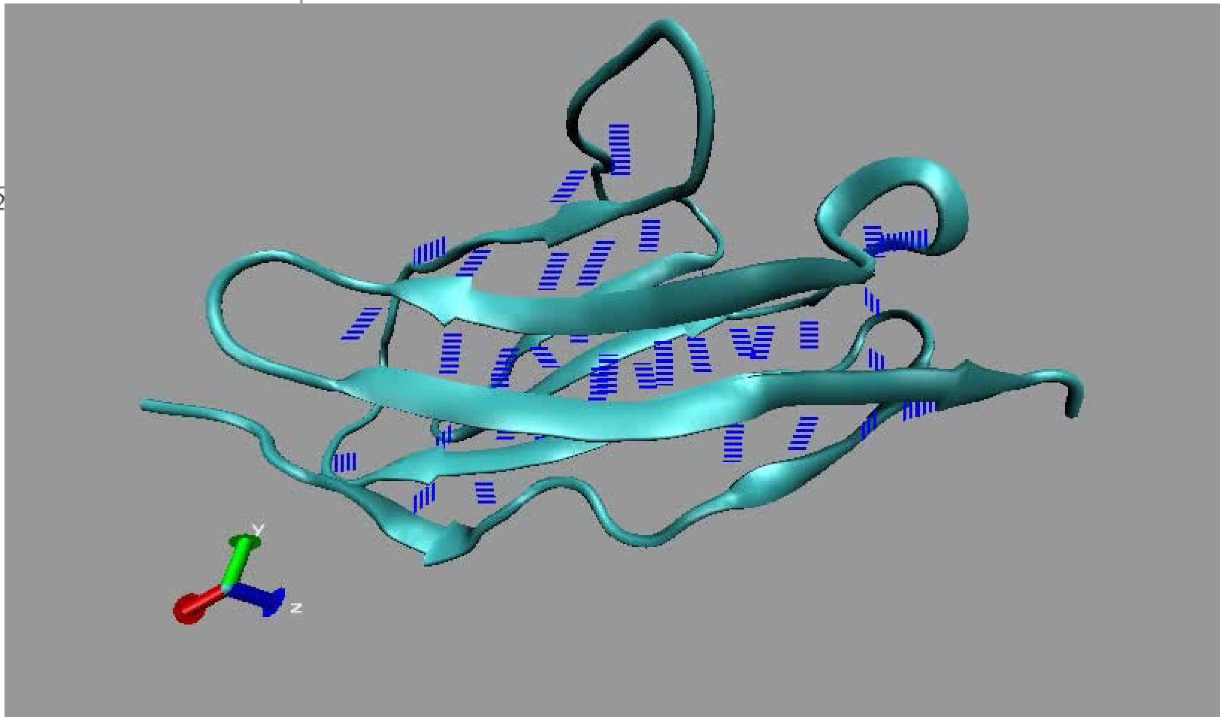
SMD is a useful approach to probe the nanomechanics of proteins (elastic deformation, “plastic” – permanent deformation, etc.)

Example: titin unfolding (CHARMM force field)

Unfolding of titin molecule

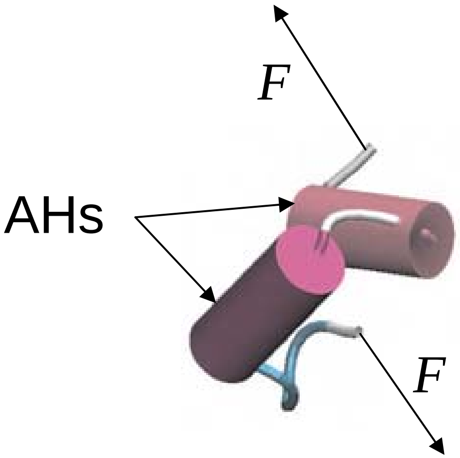


Titin I27 domain: Very resistant to unfolding due to parallel H-bonded strands

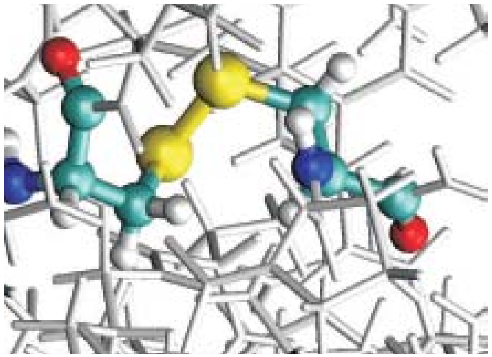


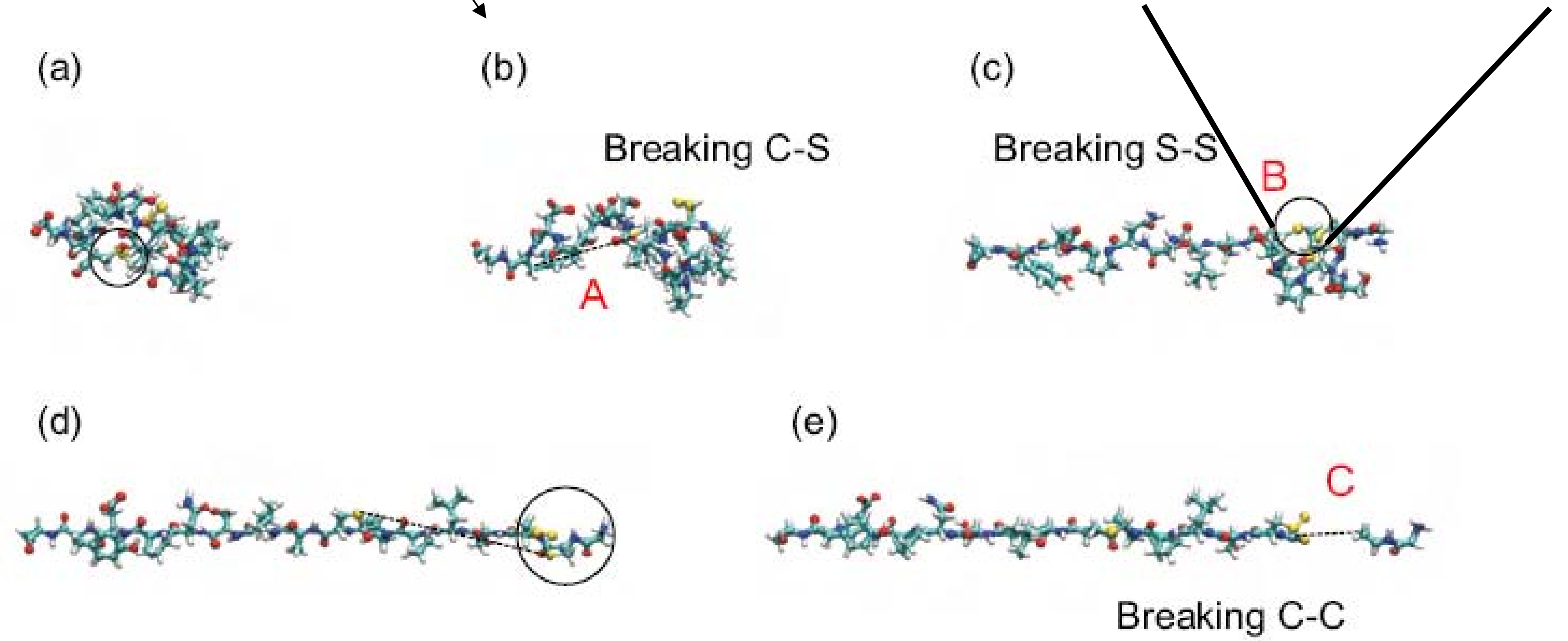
Keten and Buehler, 2007

Protein unfolding - ReaxFF



PnIB 1AKG

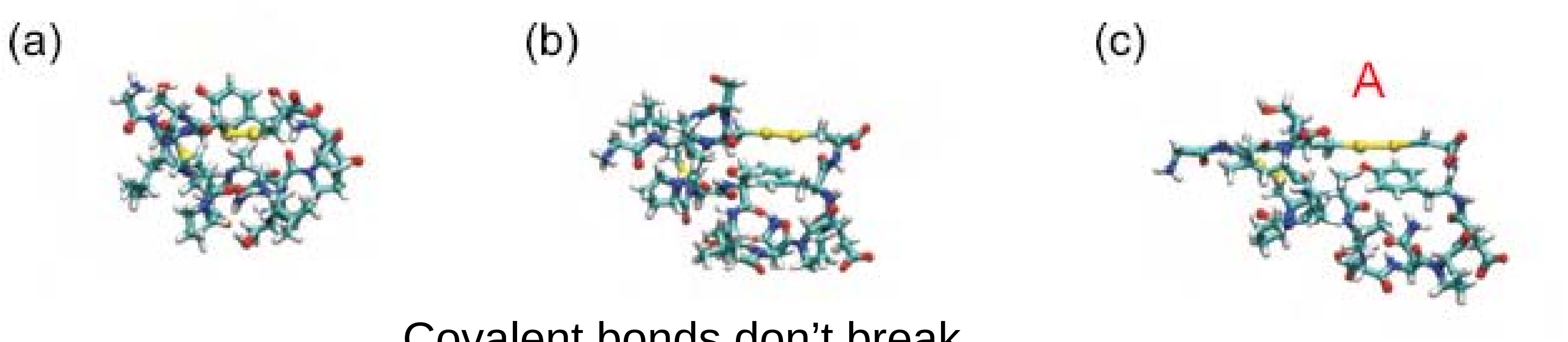




ReaxFF modeling

M. Buehler, JoMMS, 2007

Protein unfolding - CHARMM

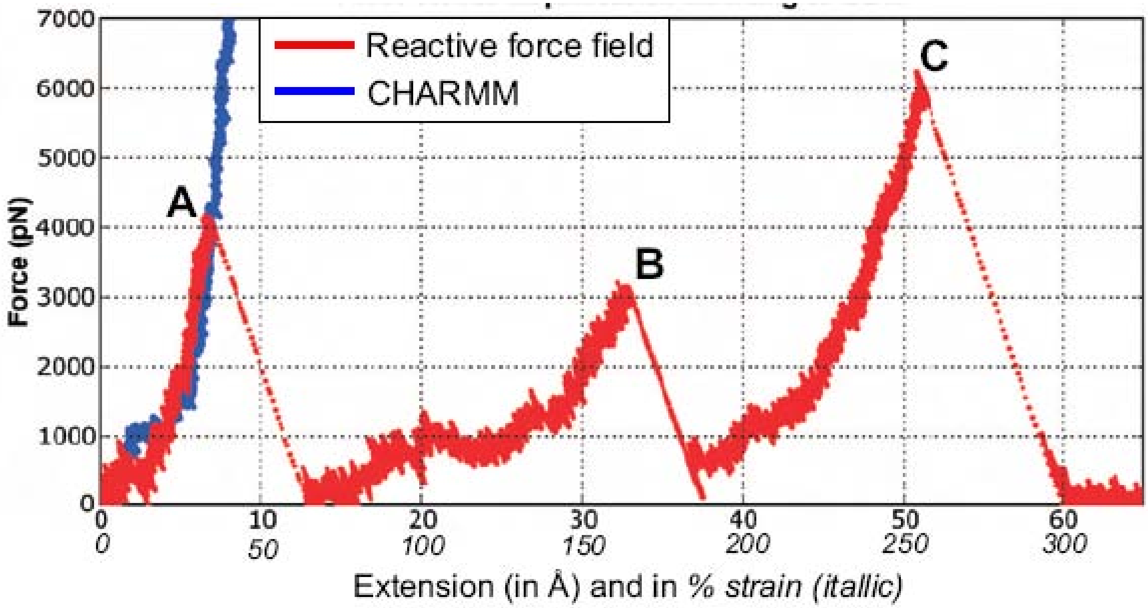


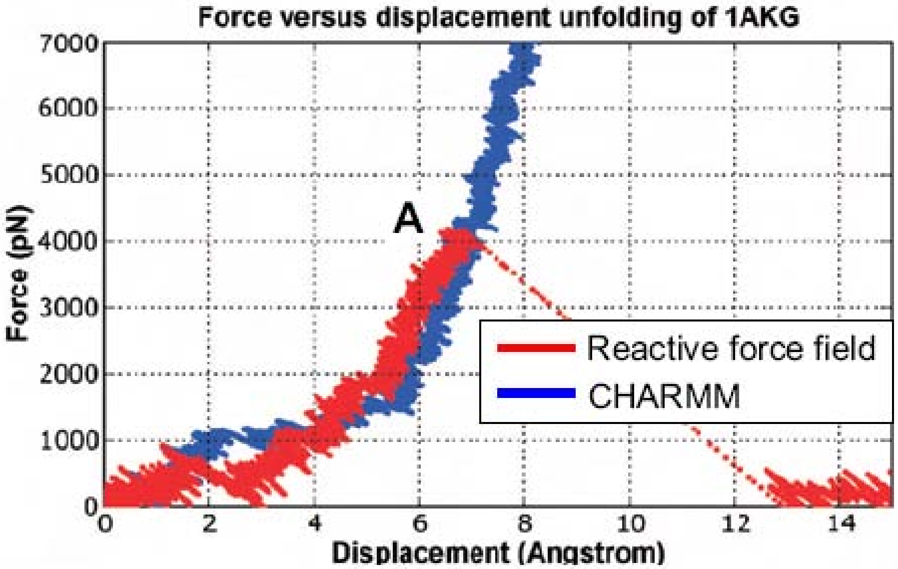
Covalent bonds don't break

CHARMM modeling

M. Buehler, JoMMS, 2007

Comparison – CHARMM vs. ReaxFF

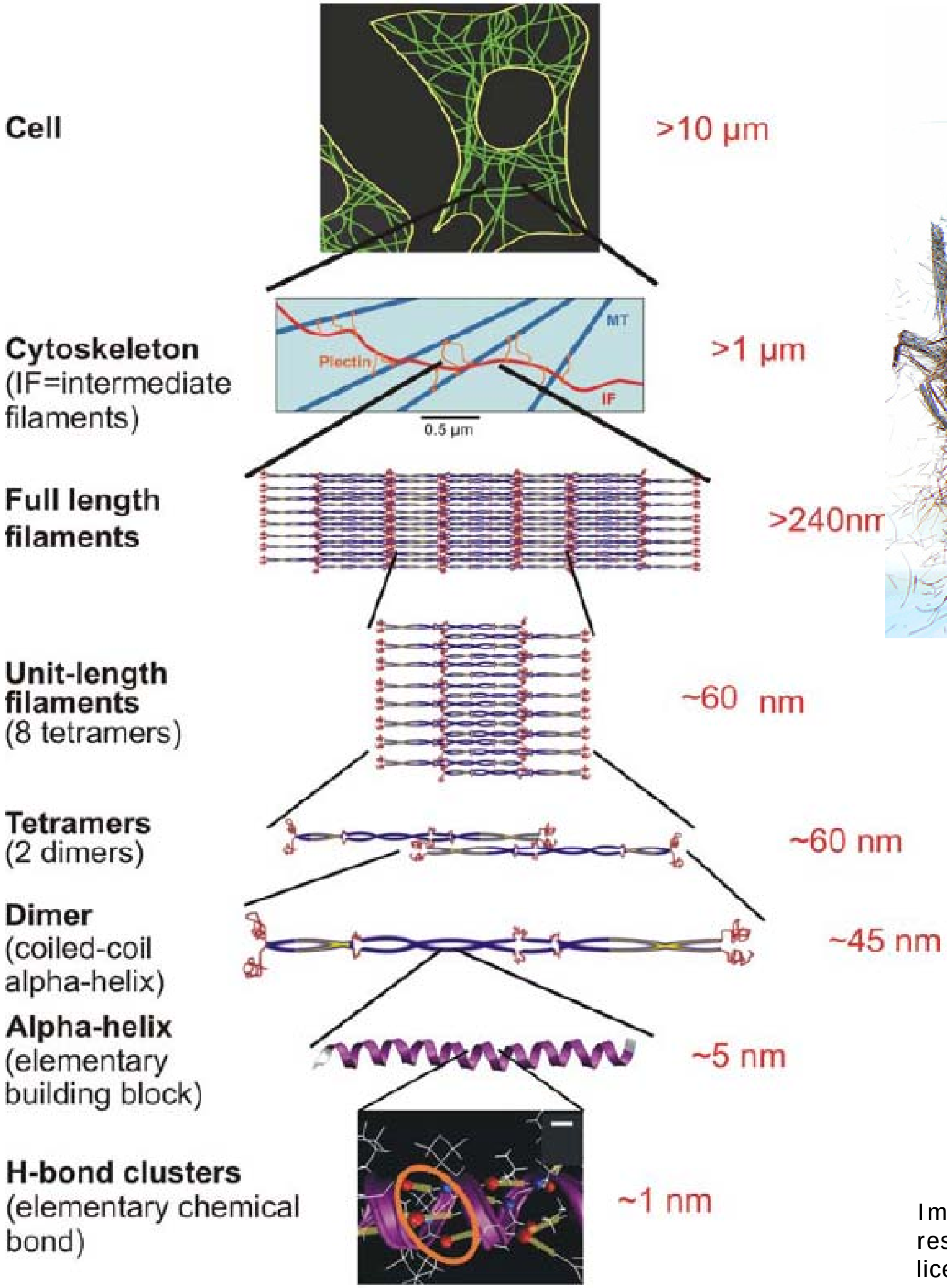




M. Buehler, JoMMS, 2007

Application to alpha-helical proteins

Vimentin intermediate filaments



Cell >10 µm

Cytoskeleton (IF=intermediate filaments) >1 µm

Full length filaments >240nm

Unit-length filaments (8 tetramers) ~60 nm

Tetramers (2 dimers) ~60 nm

Dimer (coiled-coil alpha-helix) ~45 nm

Alpha-helix (elementary building block) ~5 nm

H-bond clusters (elementary chemical bond) ~1 nm

Source: Qin, Z., L. Kreplak, and M. Buehler. "Hierarchical Structure Controls Nanomechanical Properties of Vimentin Intermediate Filaments." *PLoSONE* 4, no. 10 (2009). doi:10.1371/journal.pone.0007294. License CC BY.

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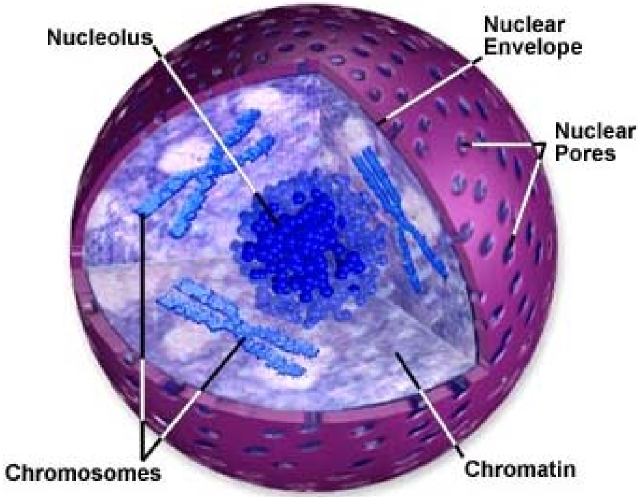
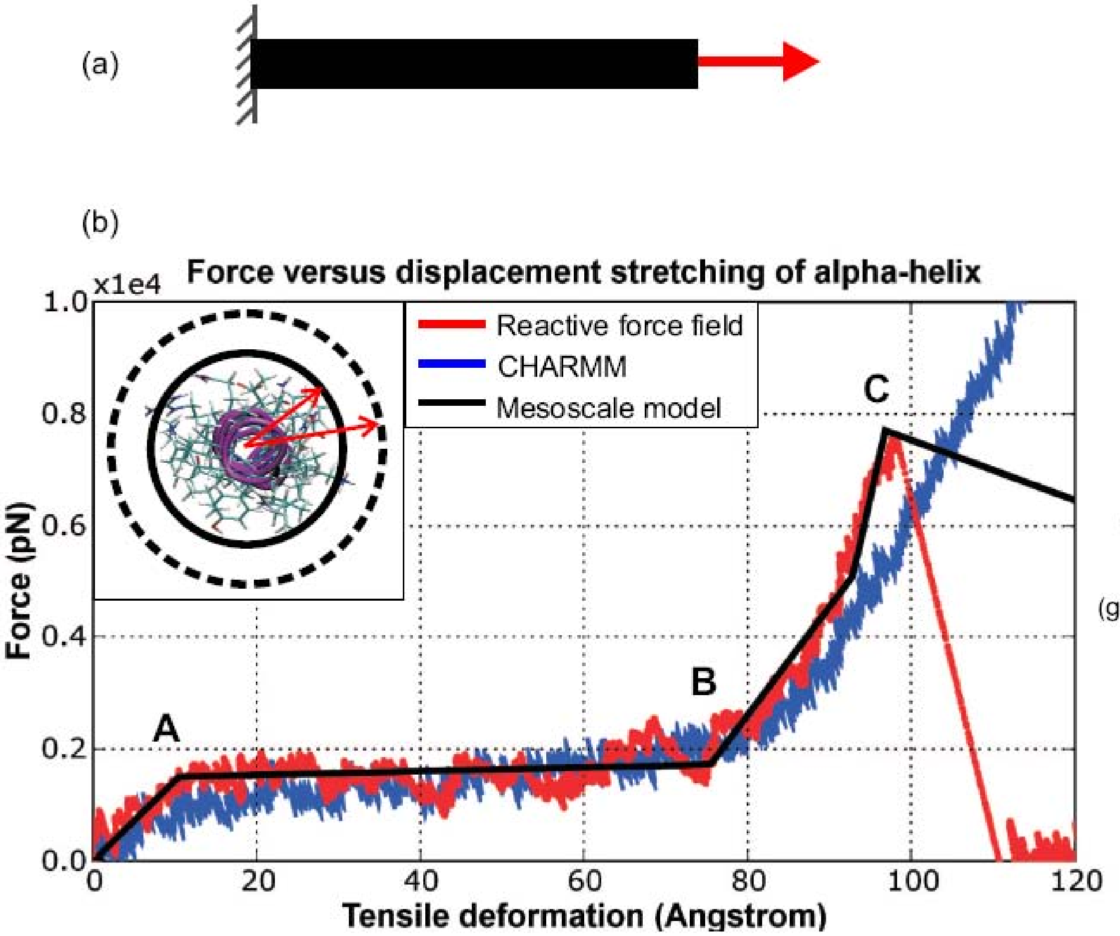
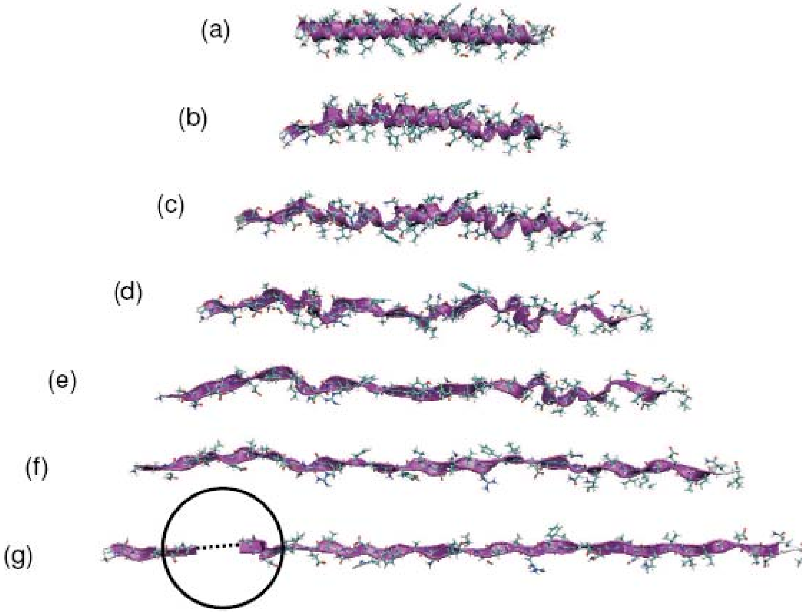


Alpha-helical protein: stretching





ReaxFF modeling of AH stretching

A: First H-bonds break (turns open)
B: Stretch covalent backbone
C: Backbone breaks

M. Buehler, JoMMS, 2007

Coarse-graining approach

Describe interaction between “beads” and not “atoms”

Same concept as force fields for atoms

$$U\left(\vec{R}\right) = U_T + U_B,$$

$$U_T = \sum_{pairs} \phi_T(r) \quad \text{and} \quad U_B = \sum_{angles} \phi_B(\varphi).$$

$$\phi_B(\varphi) = \frac{1}{2} K_B (\varphi - \varphi_0)^2$$

$$\frac{\partial \phi_T}{\partial r}(r) = H(r_{break} - r) \begin{cases} k_T^{(1)}(r - r_0) & r_1 > r \\ R_1 + k_T^{(2)}(r - r_1) & r_1 \leq r < r_2 \\ R_2 + R_1 + k_T^{(3)}(r - r_2) & r_2 \leq r < r_3 \\ R_3 + R_2 + R_1 + k_T^{(4)}(r - r_3) & r_3 \leq r \end{cases}.$$

See also: http://dx.doi.org/10.1371/journal.pone.0006015

Case study: From nanoscale filaments to micrometer meshworks

Movie: MD simulation of AH coiled coil

Image removed due to copyright restrictions. Please see
http://dx.doi.org/10.1103/PhysRevLett.104.198304.

See also: Z. Qin, ACS Nano, 2011, and Z. Qin BioNanoScience, 2010.

What about varying pulling speeds?

Changing the time-scale of observation of fracture

Variation of pulling speed

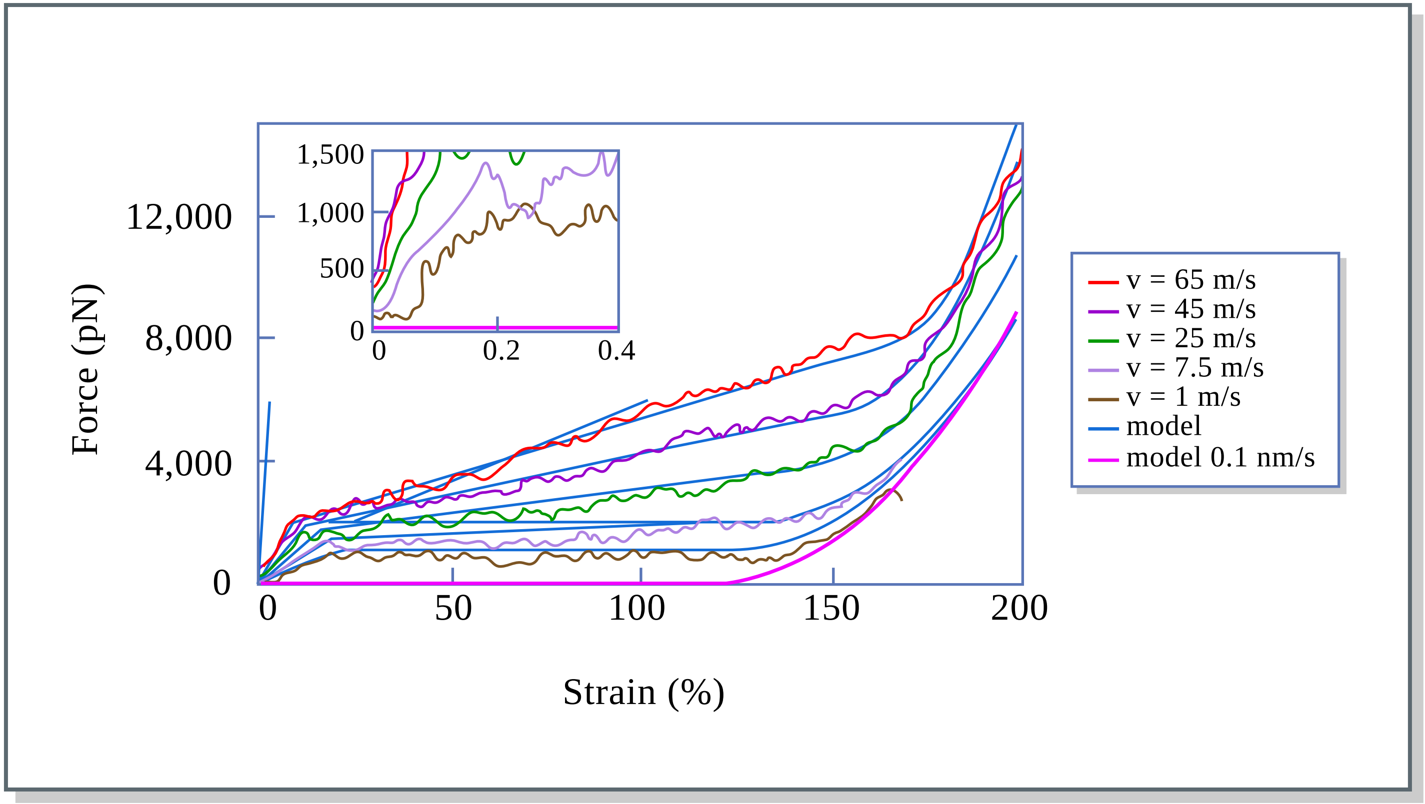
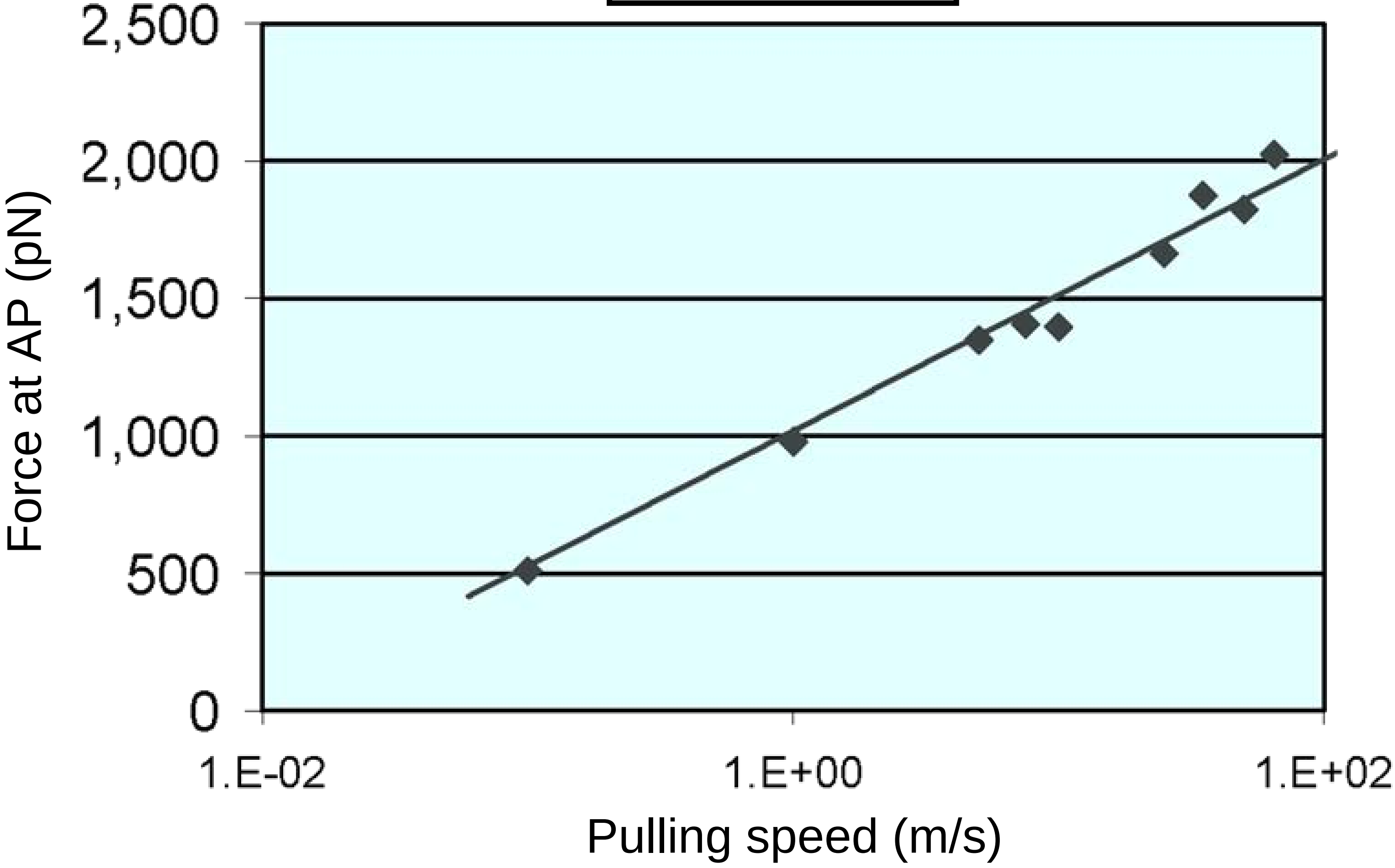


Image by MIT OCW. After Ackbarow and Buehler, 2007.

Force at angular point f_{AP}=fracture force

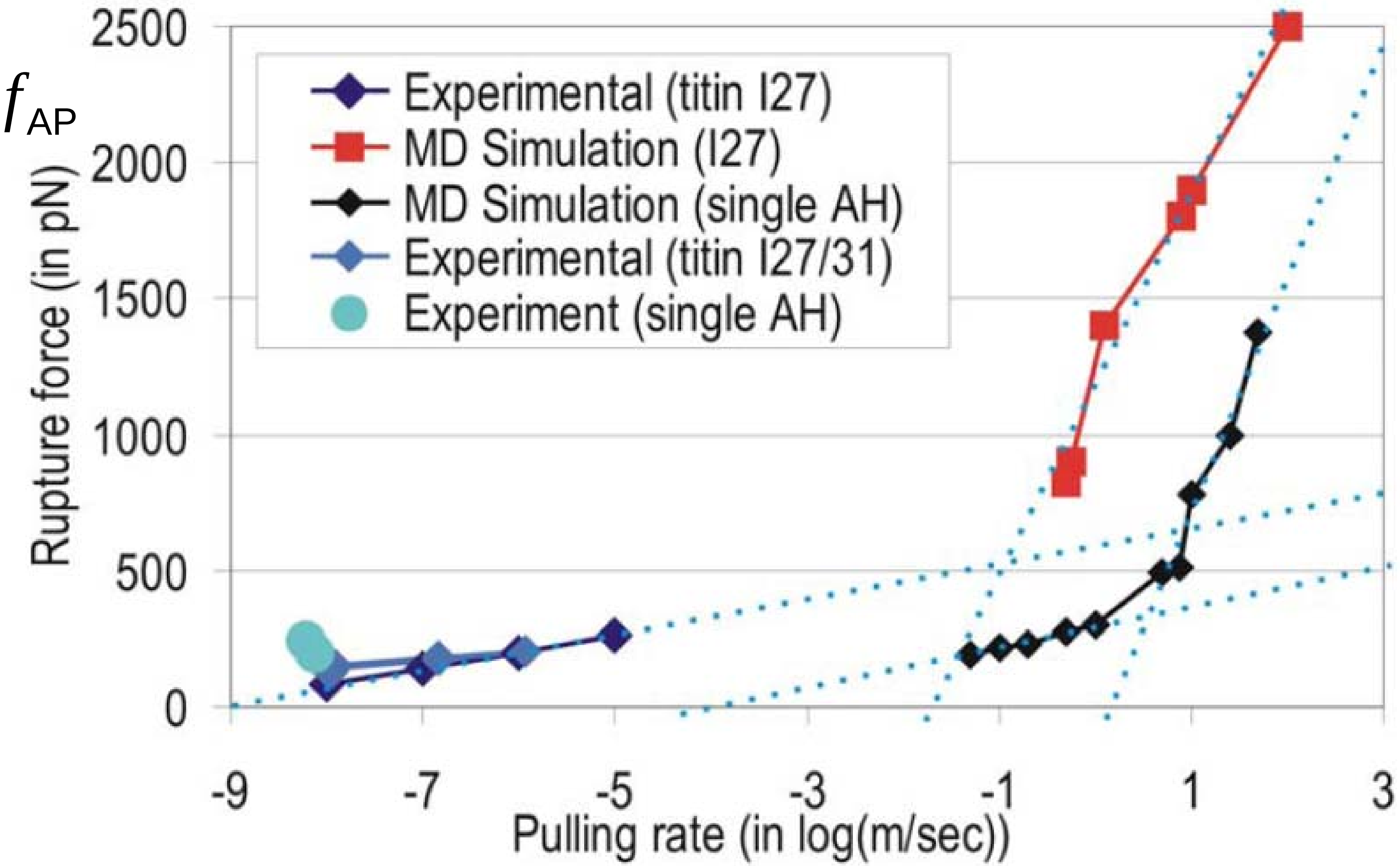
$$\boxed{f_{\mathrm{AP}} \sim \ln v}$$



See also Ackbarow and Buehler, *J. Mat. Sci.*, 2007

General results…

Rupture force vs. pulling speed



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Source: Buehler, M. ,and Yung, Y. "Chemomechanical Behaviour of Protein Constituents." *Nature Materials* 8, no. 3 (2009): 175-88. © 2009.

Buehler *et al*., *Nature Materials*, 2009

How to make sense of these results?

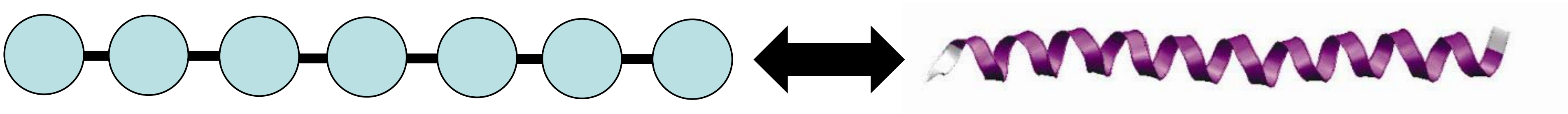
A few fundamental properties of bonds

- Bonds have a “bond energy” (energy barrier to break)

- Arrhenius relationship gives probability for energy barrier to be overcome, given a temperature

$$p = \exp\left(-\frac{E_b}{k_B T}\right)$$

- All bonds vibrate at frequency ω



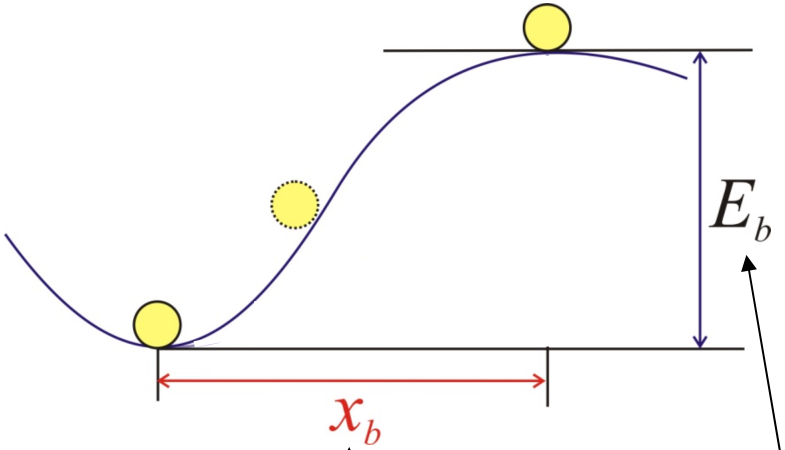
Bell model

Probability for bond rupture (Arrhenius relation)

$$p = \exp\left(-\frac{E_b}{k_B T}\right)$$

Boltzmann constant

temperature



distance to energy barrier

height of energy barrier

“bond”

Bell model

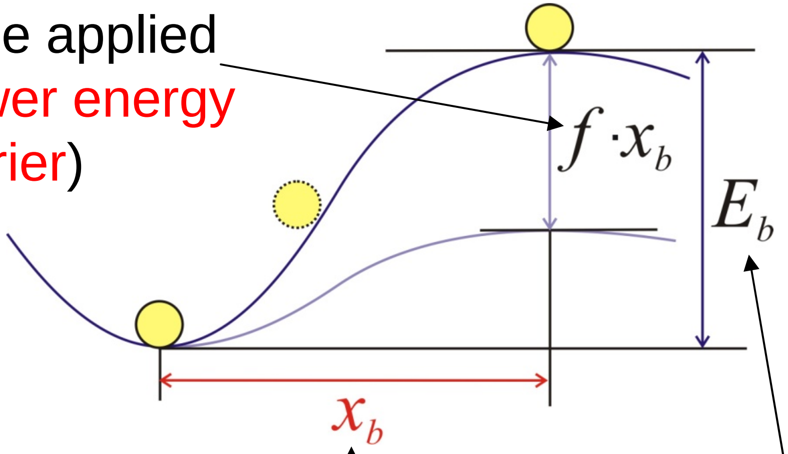
Probability for bond rupture (Arrhenius relation) $f = f_{\text{AP}}$

$$p = \exp\left(-\frac{E_b - f \cdot x_B}{k_B T}\right)$$

Boltzmann constant

temperature

force applied (lower energy barrier)



distance to energy barrier

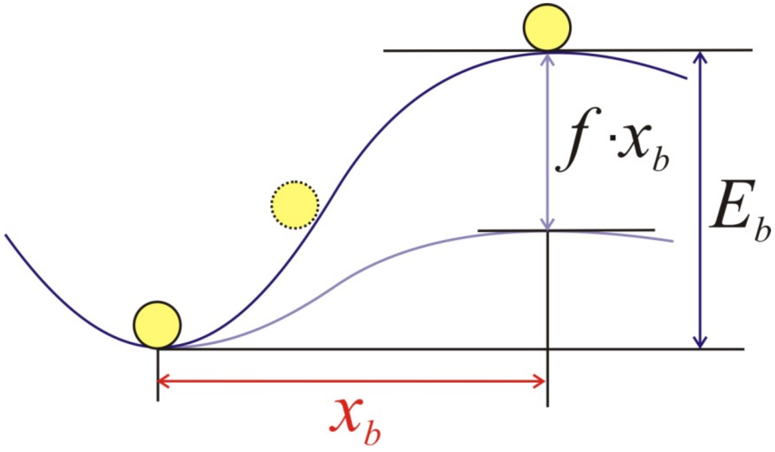
height of energy barrier

"bond"

Bell model

Probability for bond rupture (Arrhenius relation)

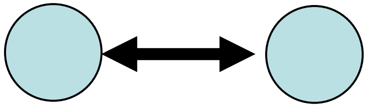
$$p = \exp\left(-\frac{E_b - f \cdot x_B}{k_B T}\right)$$



Off-rate = probability times vibrational frequency

$$\chi = \omega_0 \cdot p$$

$$\omega_0 = 1 \times 10^{13}\ 1/\sec$$

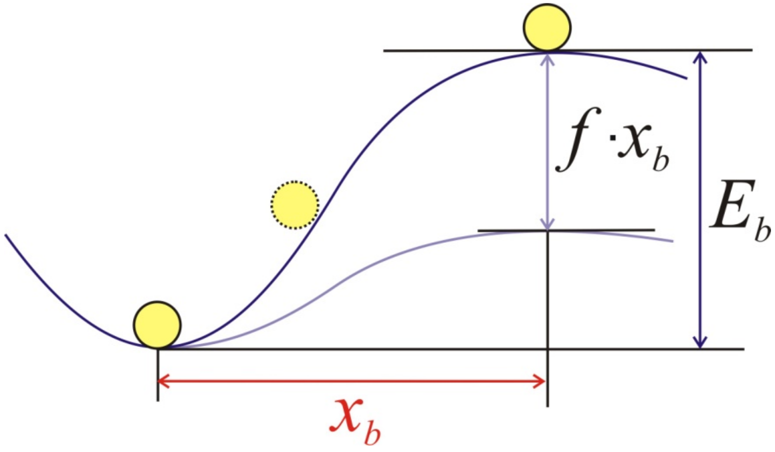


bond vibrations

Bell model

Probability for bond rupture (Arrhenius relation)

$$p = \exp\left(-\frac{E_b - f \cdot x_B}{k_B T}\right)$$

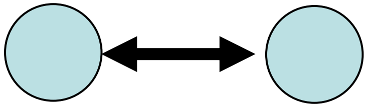


Off-rate = probability times vibrational frequency

$$\chi = \omega_0 \cdot p = \omega_0 \cdot \exp\left(-\frac{(E_b - f \cdot x_b)}{k_b \cdot T}\right)$$

“How often bond breaks per unit time”

$$\omega_0 = 1 \times 10^{13}\ 1/\sec$$

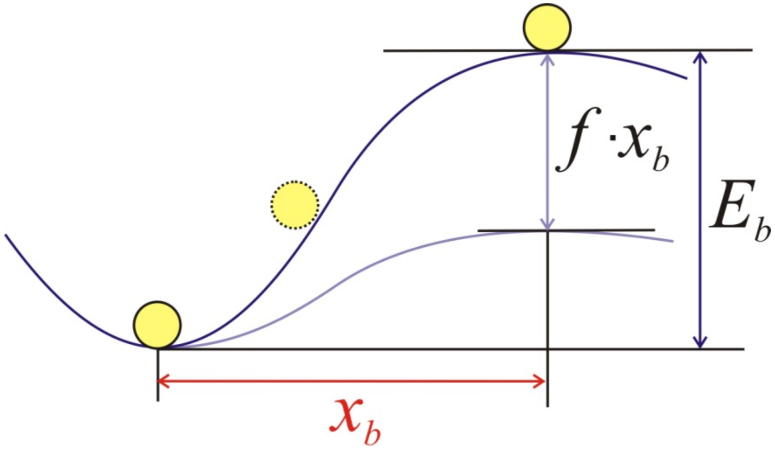


bond vibrations

Bell model

Probability for bond rupture (Arrhenius relation)

$$p = \exp\left(-\frac{E_b - f \cdot x_B}{k_B T}\right)$$

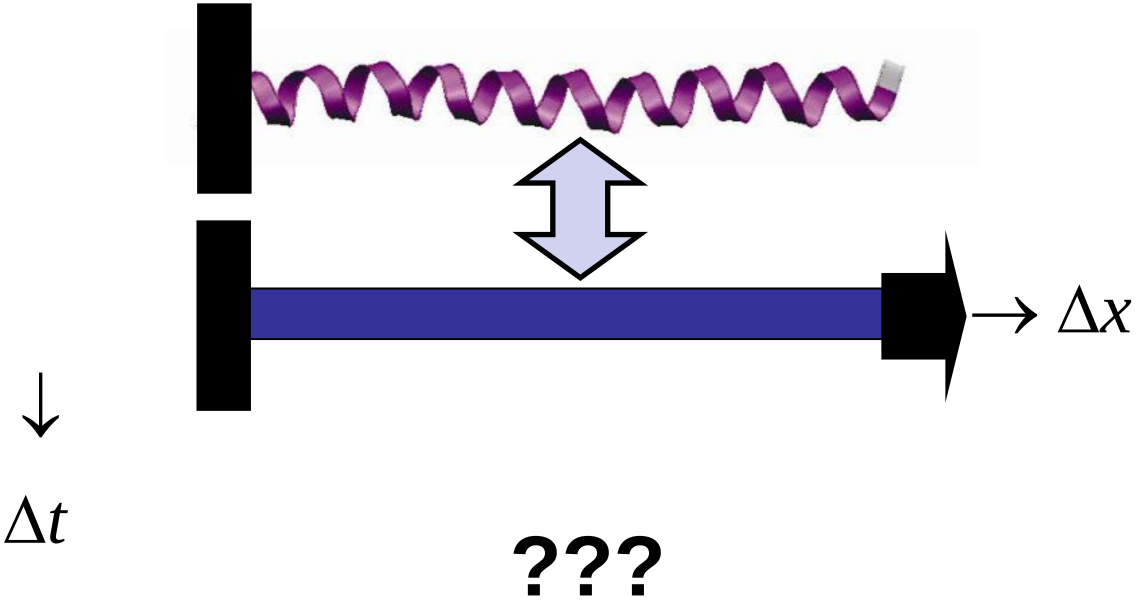


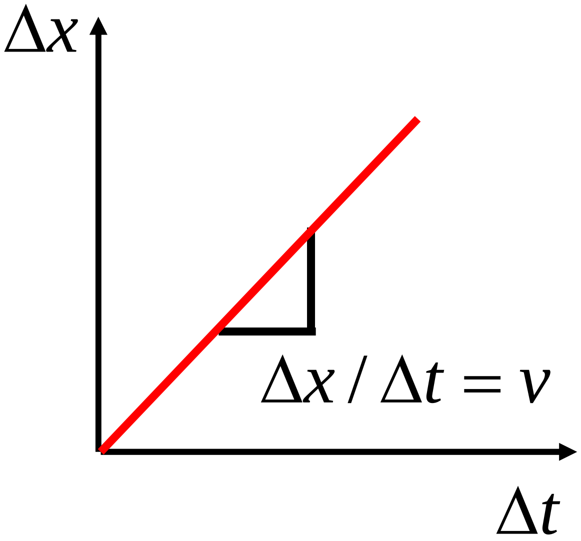
Off-rate = probability times vibrational frequency

$$\chi = \omega_0 \cdot p = \omega_0 \cdot \exp\left(-\frac{(E_b - f \cdot x_b)}{k_b \cdot T}\right) = \boxed{\frac{1}{\tau}} \qquad \omega_0 = 1 \times 10^{13}\ 1/\sec$$

τ = bond lifetime (inverse of off-rate)

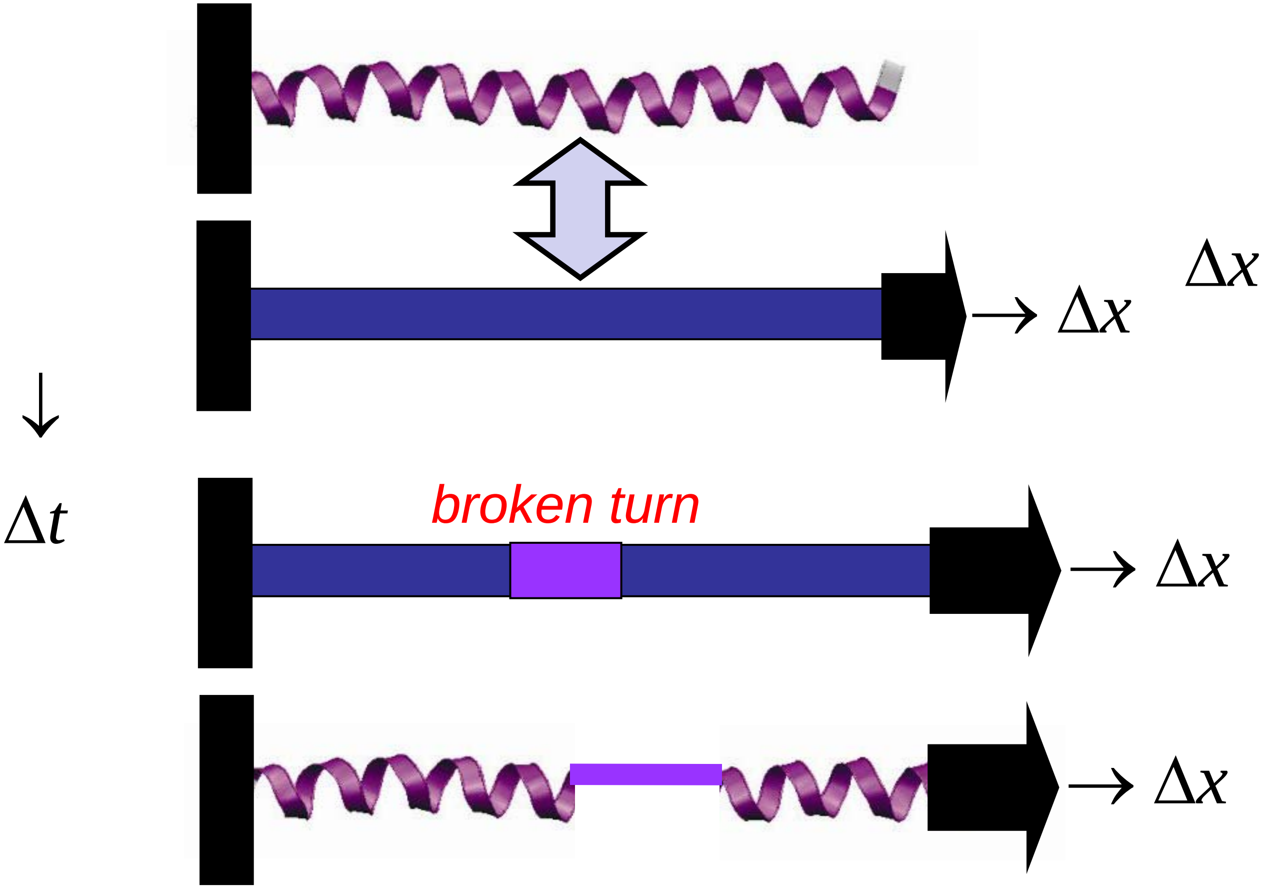
Bell model

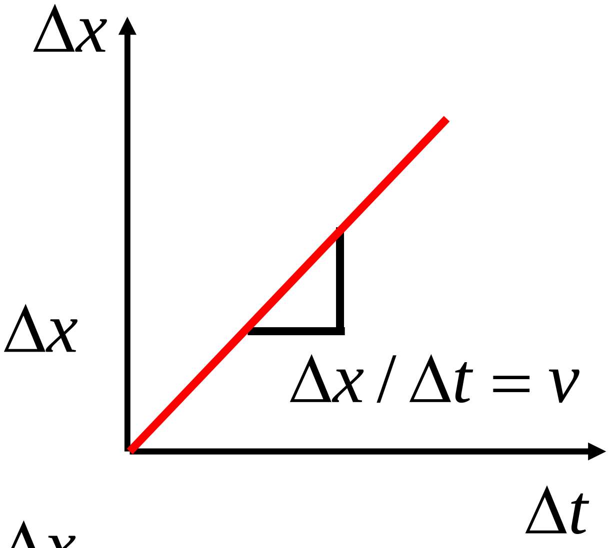




$\Delta x / \Delta t = v$ pulling speed (at end of molecule)

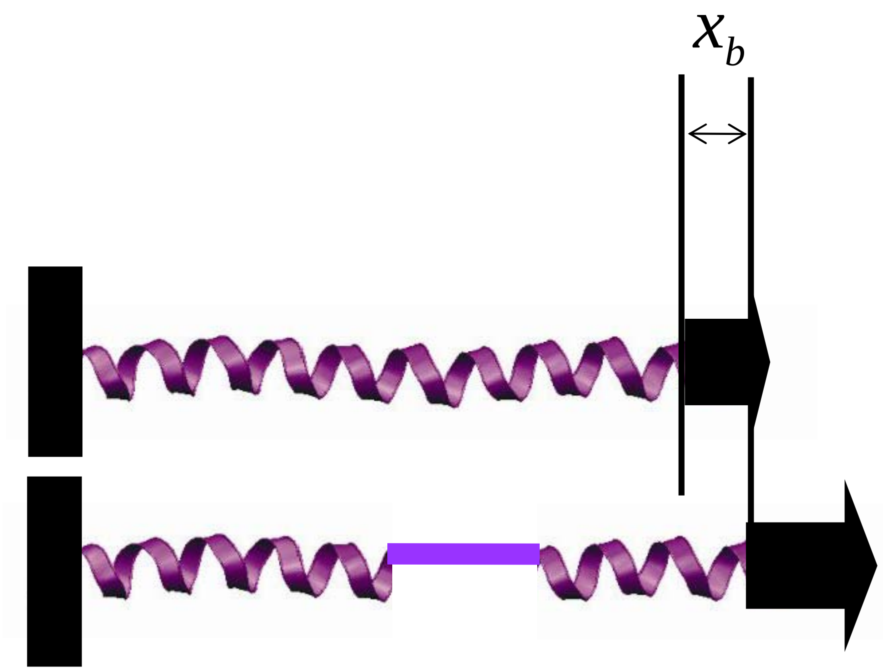
Bell model

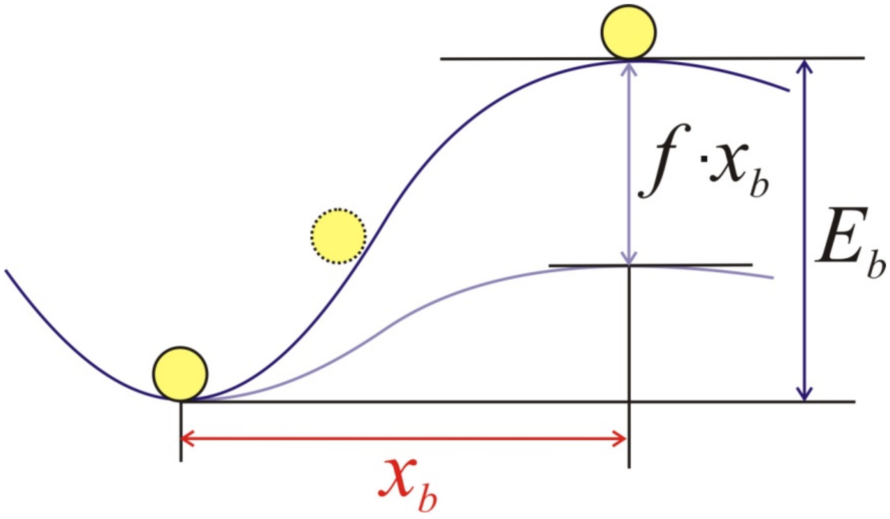




$\Delta x / \Delta t = v$ pulling speed (at end of molecule)

Structure-energy landscape link

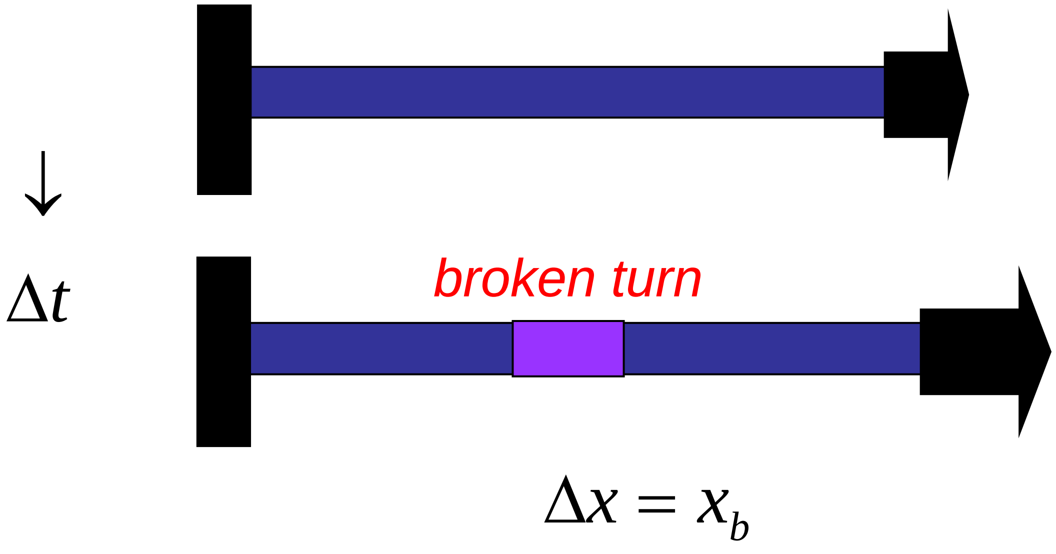


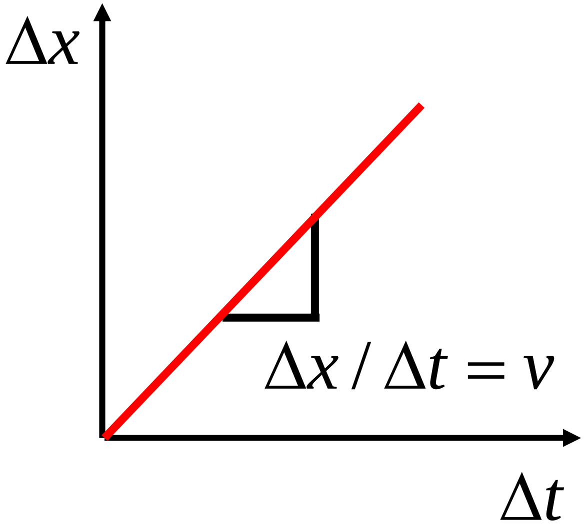


$$\Delta x = x_b$$

$$\Delta t = \tau \qquad \tau = \left[\omega_0 \cdot \exp\left(-\frac{(E_b - f \cdot x_b)}{k_b \cdot T}\right)\right]^{-1}$$

Bell model





Bond breaking at x_b (lateral applied displacement):

$$\underbrace{\chi}_{=1/\tau} \cdot x_b = \omega_0 \cdot \exp\left(-\frac{(E_b - f \cdot x_b)}{k_b \cdot T}\right) \cdot x_b = \Delta x / \Delta t = \underbrace{v}_{\text{pulling speed}}$$

Bell model

$$\omega_0 \cdot \exp\left(-\frac{(E_b - f \cdot x_b)}{k_b \cdot T} \right) \cdot x_b = v$$

Solve this expression for f:

Bell model

$$\omega_0 \cdot \exp\left(-\frac{(E_b - f \cdot x_b)}{k_b \cdot T}\right) \cdot x_b = v$$

Solve this expression for f:

$$-\frac{(E_b - f \cdot x_b)}{k_b \cdot T} + \ln(\omega_0 \cdot x_b) = \ln v \quad \longleftarrow \quad \ln(..)$$

$$-E_b + f \cdot x_b = k_b \cdot T\left(\ln v - \ln(\omega_0 \cdot x_b)\right)$$

$$f = \frac{E_b + k_b \cdot T\left(\ln v - \ln(\omega_0 \cdot x_b)\right)}{x_b} = \frac{k_b \cdot T}{x_b}\ln v + \frac{k_b \cdot T}{x_b}\left(\frac{E_b}{k_b \cdot T} - \ln(\omega_0 \cdot x_b)\right)$$

$$f = \frac{k_b \cdot T}{x_b}\ln v - \frac{k_b \cdot T}{x_b}\left(\ln(\omega_0 \cdot x_b) - \frac{E_b}{k_b \cdot T}\right)$$

$$f = \frac{k_b \cdot T}{x_b}\ln v - \frac{k_b \cdot T}{x_b}\ln\left(\omega_0 \cdot x_b \cdot \exp\left(-\frac{E_b}{k_b \cdot T}\right)\right)$$

Simplification and grouping of variables

Only system parameters, [distance/length]

$$f(v; x_b, E_b) = \frac{k_b \cdot T}{x_b} \cdot \ln v - \frac{k_b \cdot T}{x_b} \cdot \ln\left(\underbrace{\omega_0 \cdot x_b \cdot \exp\left(-\frac{E_b}{k_b \cdot T} \right)}_{=: v_0 = \omega_0 \cdot x_b \cdot \exp\left(-\frac{E_b}{k_b \cdot T} \right)} \right)$$

Bell model

$$\omega_0 \cdot \exp\left(-\frac{(E_b - f \cdot x_b)}{k_b \cdot T} \right) \cdot x_b = v$$

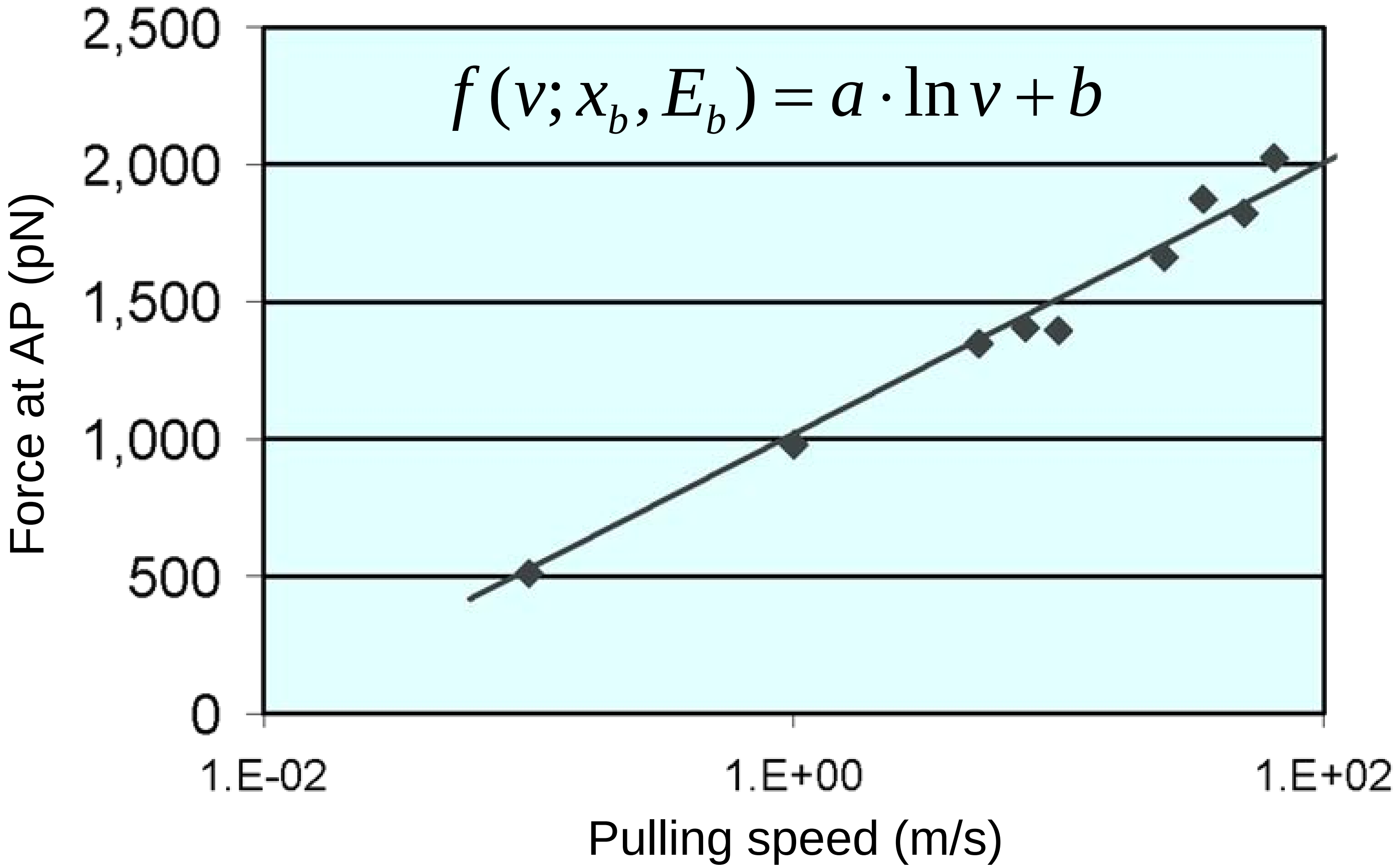
Results in:

$$f(v; x_b, E_b) = \frac{k_b \cdot T}{x_b} \cdot \ln v - \frac{k_b \cdot T}{x_b} \cdot \ln v_0 = \boxed{a \cdot \ln v + b}$$

$$a = \frac{k_B \cdot T}{x_b}$$

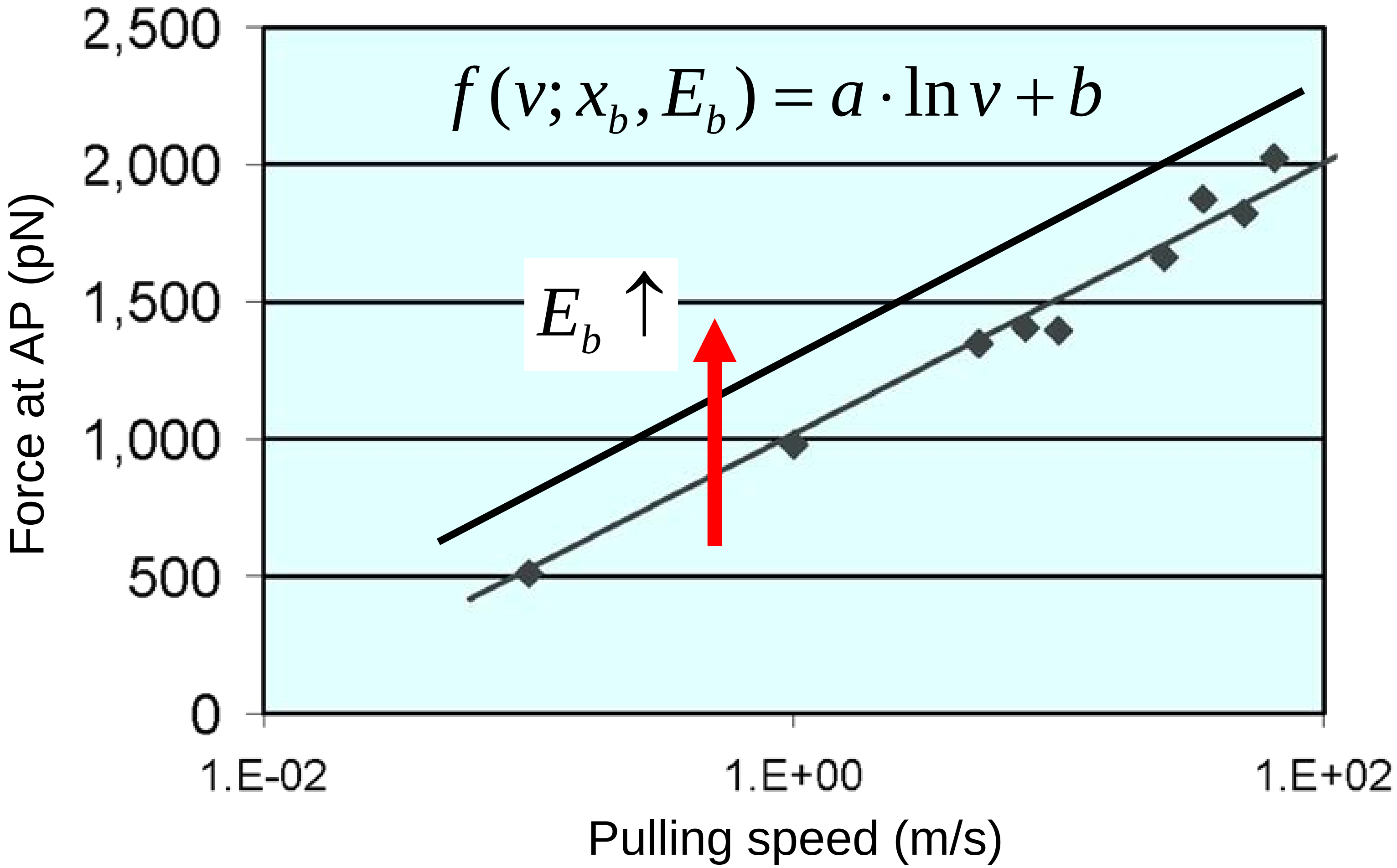
$$b = -\frac{k_B \cdot T}{x_b} \cdot \ln v_0$$

$f \sim \ln v$ behavior of strength



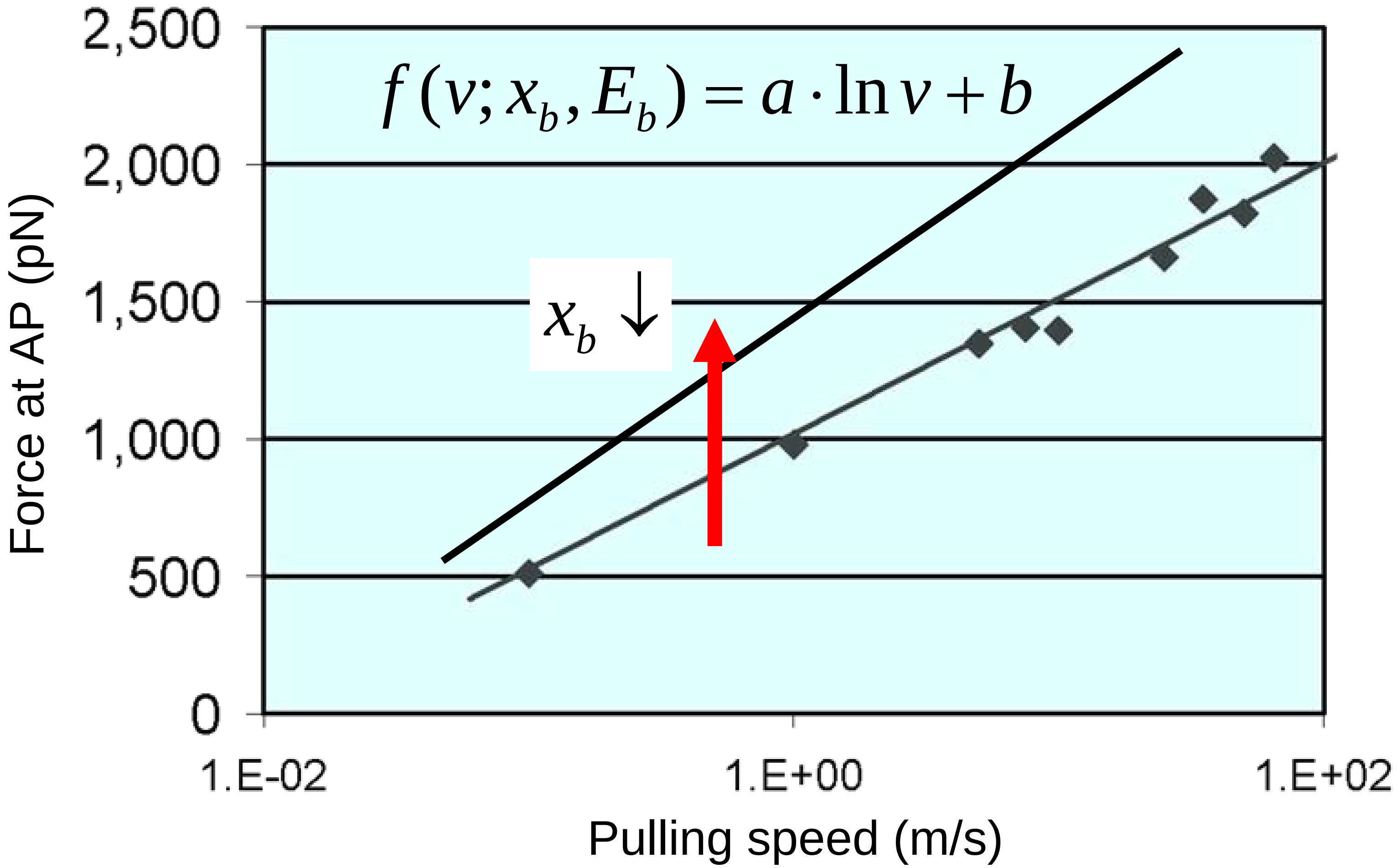
E_b= 5.6 kcal/mol and x_b= 0.17 Å (results obtained from fitting to the simulation data)

Scaling with E_b: shifts curve



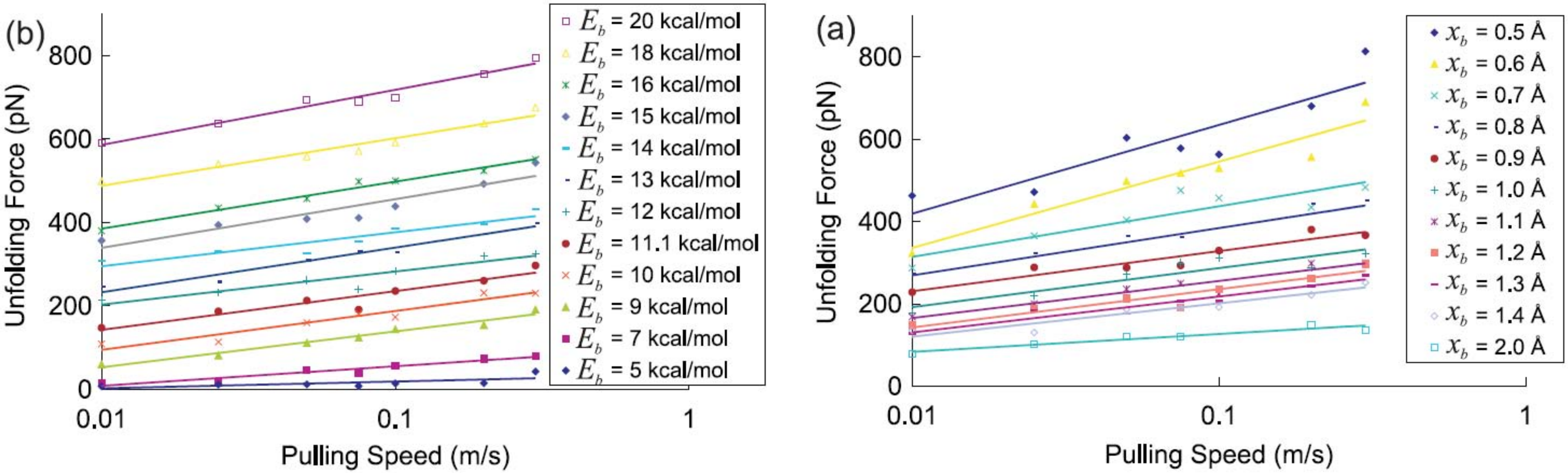
$$a = \frac{k_B \cdot T}{x_b} \qquad b = -\frac{k_B \cdot T}{x_b} \cdot \ln v_0 \qquad v_0 = \omega_0 \cdot x_b \cdot \exp\left(-\frac{E_b}{k_b \cdot T}\right)$$

Scaling with x_b: changes slope

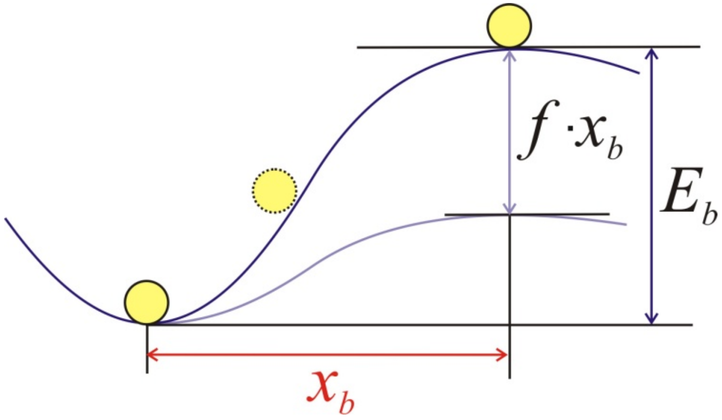


$$a = \frac{k_B \cdot T}{x_b} \qquad b = -\frac{k_B \cdot T}{x_b} \cdot \ln v_0 \qquad v_0 = \omega_0 \cdot x_b \cdot \exp\left(-\frac{E_b}{k_b \cdot T}\right)$$

Simulation results



Courtesy of IOP Publishing, Inc. Used with permission. Source: Fig. 3 from Bertaud, J., Hester, J. et al. "Energy Landscape, Structure and Rate Effects on Strength Properties of Alpha-helical Proteins." *J Phys.: Condens. Matter* 22 (2010): 035102. doi:10.1088/0953-8984/22/3/035102.

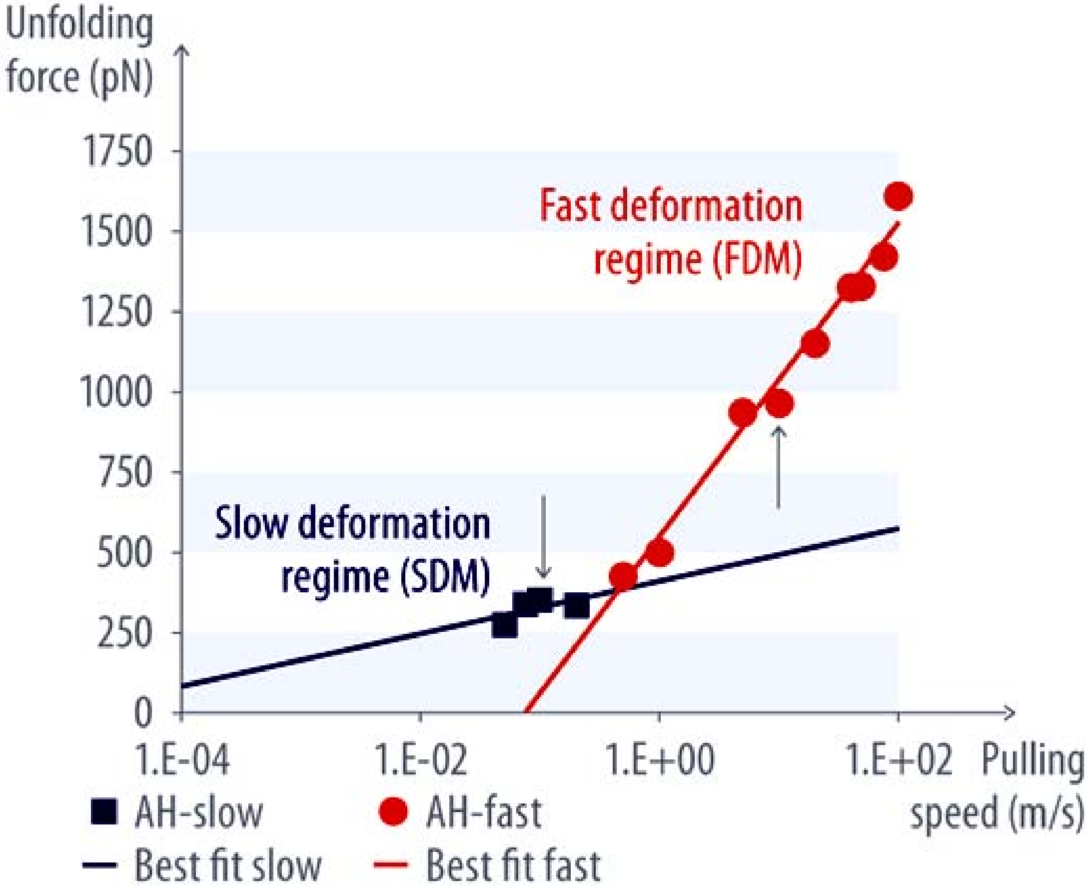


Bertaud, Hester, Jimenez, and Buehler, *J. Phys. Cond. Matt.,* 2010

Mechanisms associated with protein fracture

Change in fracture mechanism

Single AH structure



FDM: Sequential HB breaking

SDM: Concurrent HB breaking (3..5 HBs)

Simulation span: 250 ns
Reaches deformation speed O(cm/sec)

Courtesy of National Academy of Sciences, U. S. A. Used with permission. Source: Ackbarow, Theodor, et al. "Hierarchies, Multiple Energy Barriers, and Robustness Govern the Fracture Mechanics of Alpha-helical and Beta-sheet Protein Domains." *PNAS* 104 (October 16, 2007): 16410-5. Copyright 2007 National Academy of Sciences, U.S.A.

Analysis of energy landscape parameters

Table 1. Summary of the differences between the SDM and FDM, for AH1, AH2, and BS

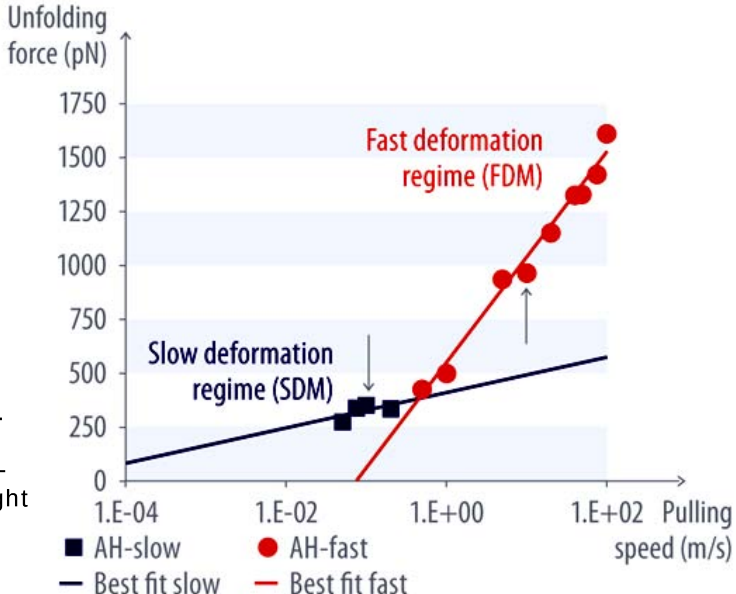
	AH1 (AH2) domain		BS domain	
Parameter	SDM	FDM	SDM	FDM
Pulling speed, m/s	$v < 0.4$ (4)	$v > 0.4$ (4)	$v < 10$	$v > 10$
Unfolding force, pN	$F < 350$ (400)	$F > 350$ (400)	$F < 4{,}800$	$F > 4{,}800$
E_b, kcal/mol	11.1 (9.11)	4.87 (3.08)	11.08	1.82
x_b, Å	1.2 (1.19)	0.2 (0.11)	0.138	0.019
HB-breaking mechanism	Simultaneous	Sequential	Simultaneous	Sequential

The values in parentheses in the AH columns represent the results for AH2.

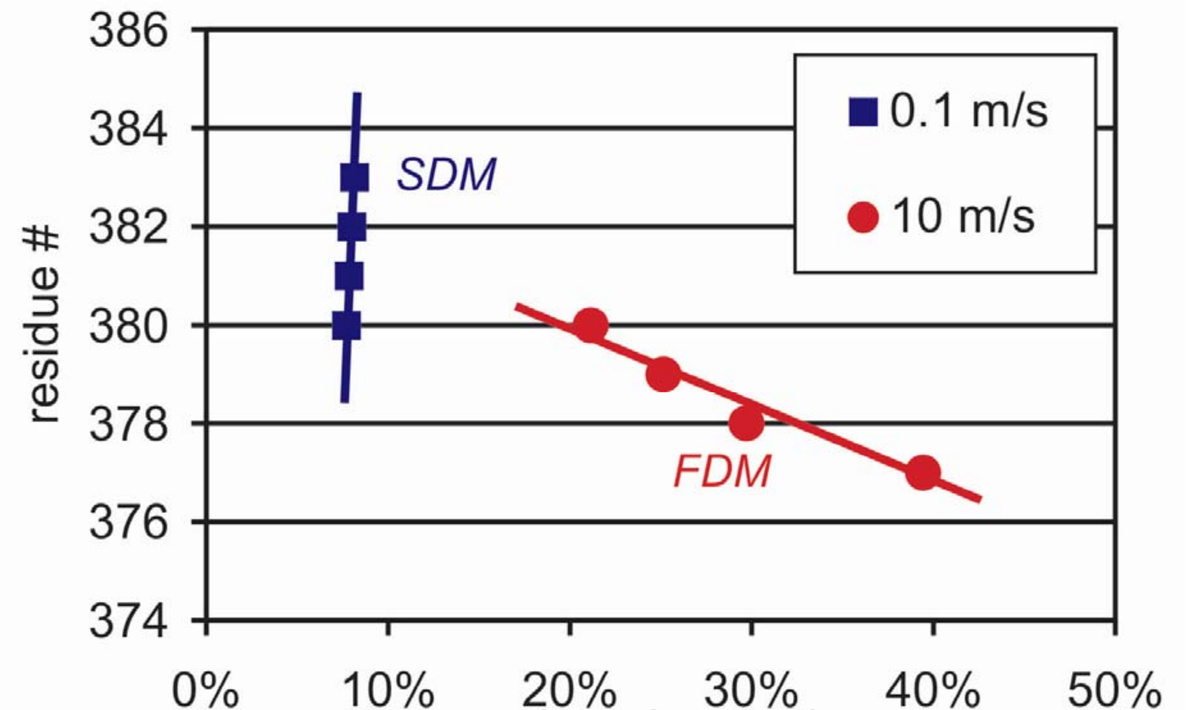
Energy single H-bond: ≈3-4 kcal/mol

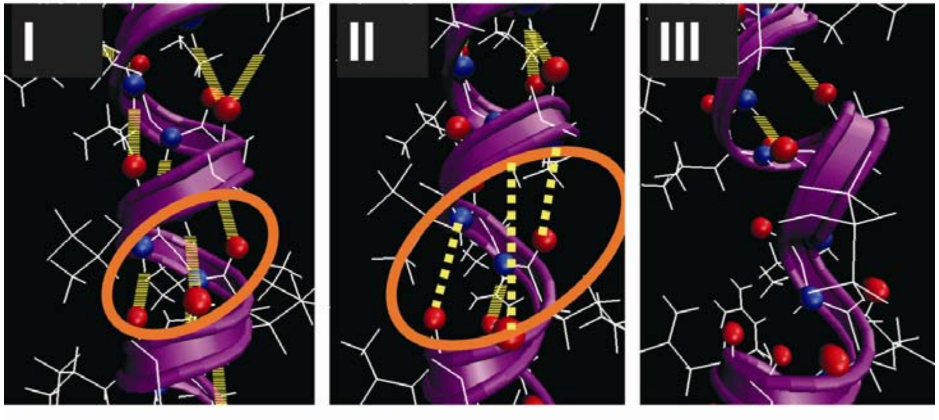
What does this mean???

Courtesy of National Academy of Sciences, U. S. A. Used with permission. Source: Ackbarow, Theodor, et al. "Hierarchies, Multiple Energy Barriers, and Robustness Govern the Fracture Mechanics of Alpha-helical and Beta-sheet Protein Domains." *PNAS* 104 (October 16, 2007): 16410-5. Copyright 2007 National Academy of Sciences, U.S.A.



H-bond rupture dynamics: mechanism





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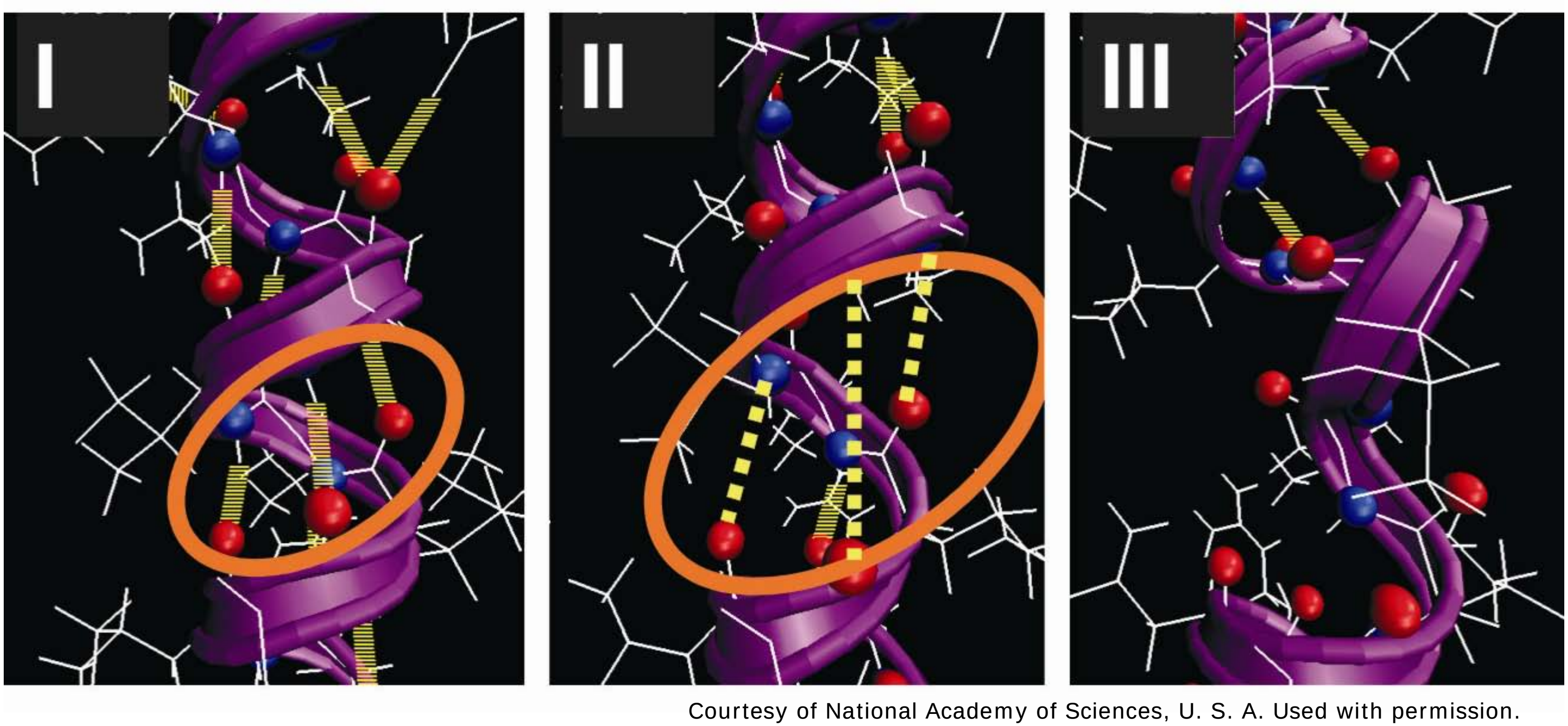
H-bond rupture dynamics: mechanism



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I: All HBs are intact

II: Rupture of 3 HBs – simultaneously; **within $\tau \approx$ 20 ps**

III: Rest of the AH relaxes – slower deformation…

3. Examples – materials and applications

E.g. disease diagnosis,
mechanisms, etc.

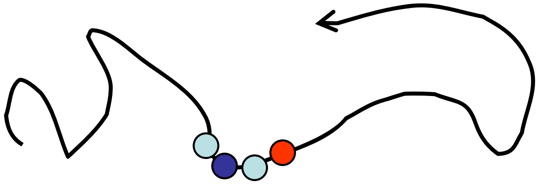
Genetic diseases – defects in protein materials

- **Defect at DNA level causes structure modification**
- Question: how does such a structure modification influence material behavior / material properties?

ACGT

Four letter code "DNA"

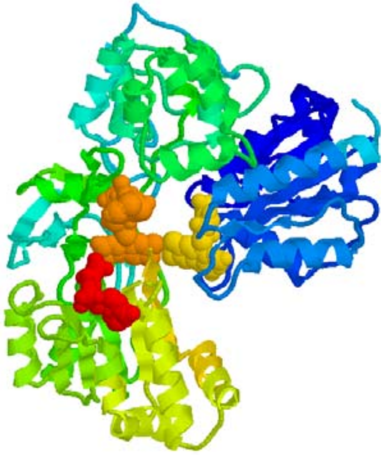
DEFECT IN SEQUENCE



.. - Proline - Serine – Proline - Alanine - ..

Sequence of amino acids "polypeptide" (1D structure)

CHANGED



Folding (3D structure)

STRUCTURAL DEFECT

Structural change in protein molecules can lead to fatal diseases

- Single point mutations in IF structure causes severe diseases such as **rapid aging disease progeria – HGPS** (*Nature*, 2003; *Nature*, 2006, *PNAS*, 2006)
- Cell nucleus loses stability under mechanical (e.g. cyclic) loading, failure occurs at heart (fatigue)

Image of patient removed due to copyright restrictions.

Genetic defect:

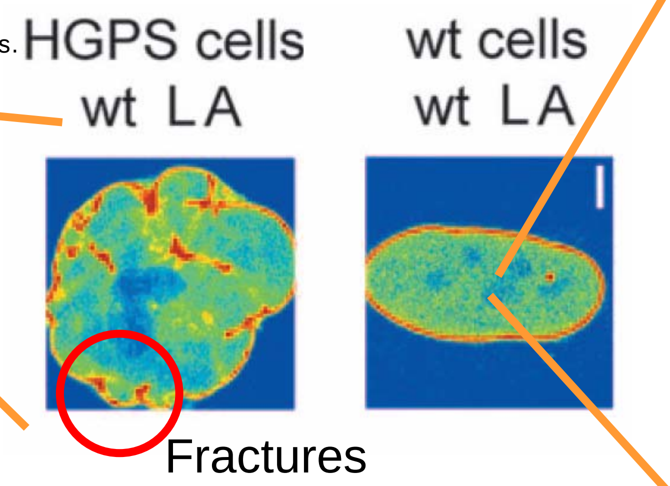
substitution of a single DNA base: Amino acid guanine is switched to adenine

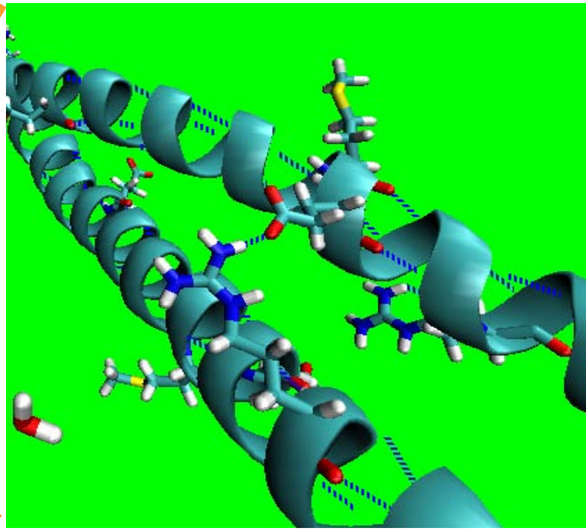
Structural change in protein molecules can lead to fatal diseases

- Single point mutations in IF structure causes severe diseases such as **rapid aging disease progeria – HGPS** (*Nature*, 2003; *Nature*, 2006, *PNAS*, 2006)
- Cell nucleus loses stability under cyclic loading
- Failure occurs at heart (fatigue)

Experiment suggests that mechanical properties of nucleus change

Image of patient removed due to copyright restrictions.





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Source: Dahl, et al. "Distinct Structural and Mechanical Properties of the Nuclear Lamina in Hutchinson–Gilford Progeria Syndrome." *PNAS* 103 (2006): 10271-6.
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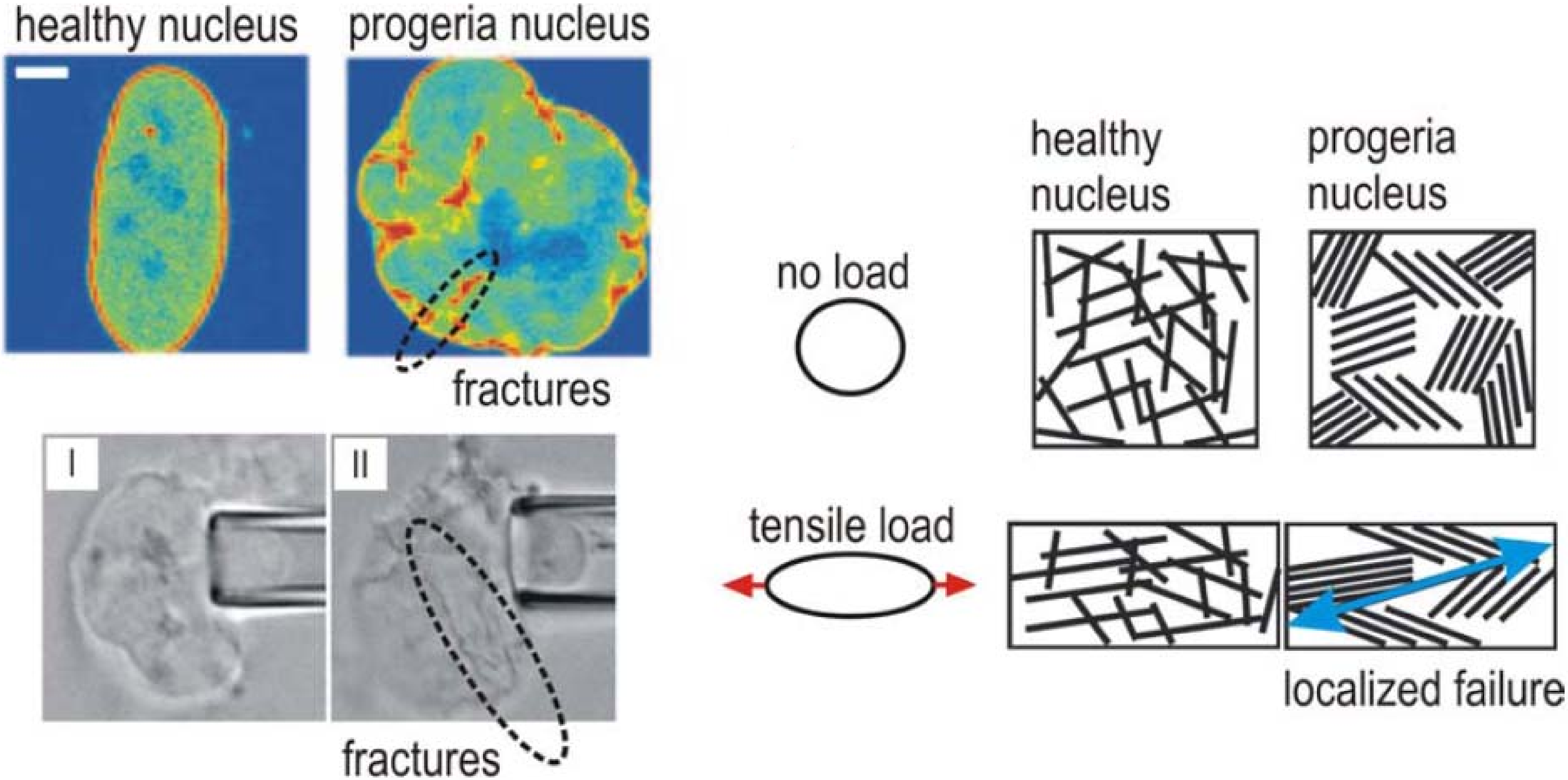
Mechanisms of *progeria*



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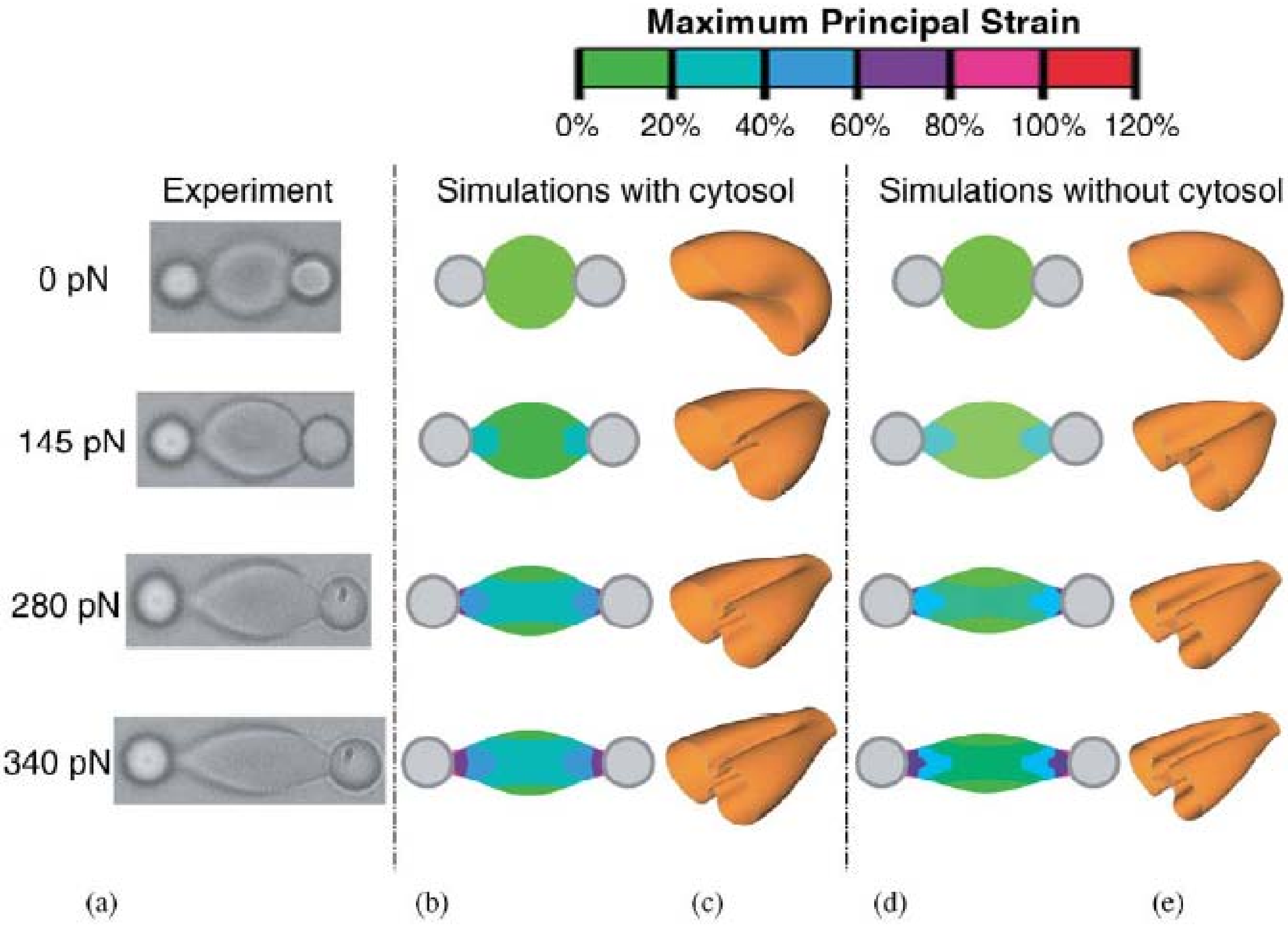
Source: Dahl, et al. "Distinct Structural and Mechanical Properties of the Nuclear Lamina in Hutchinson–Gilford Progeria Syndrome." *PNAS* 103 (2006): 10271-6. Copyright 2006 National Academy of Sciences, U.S.A.

Deformation of red blood cells



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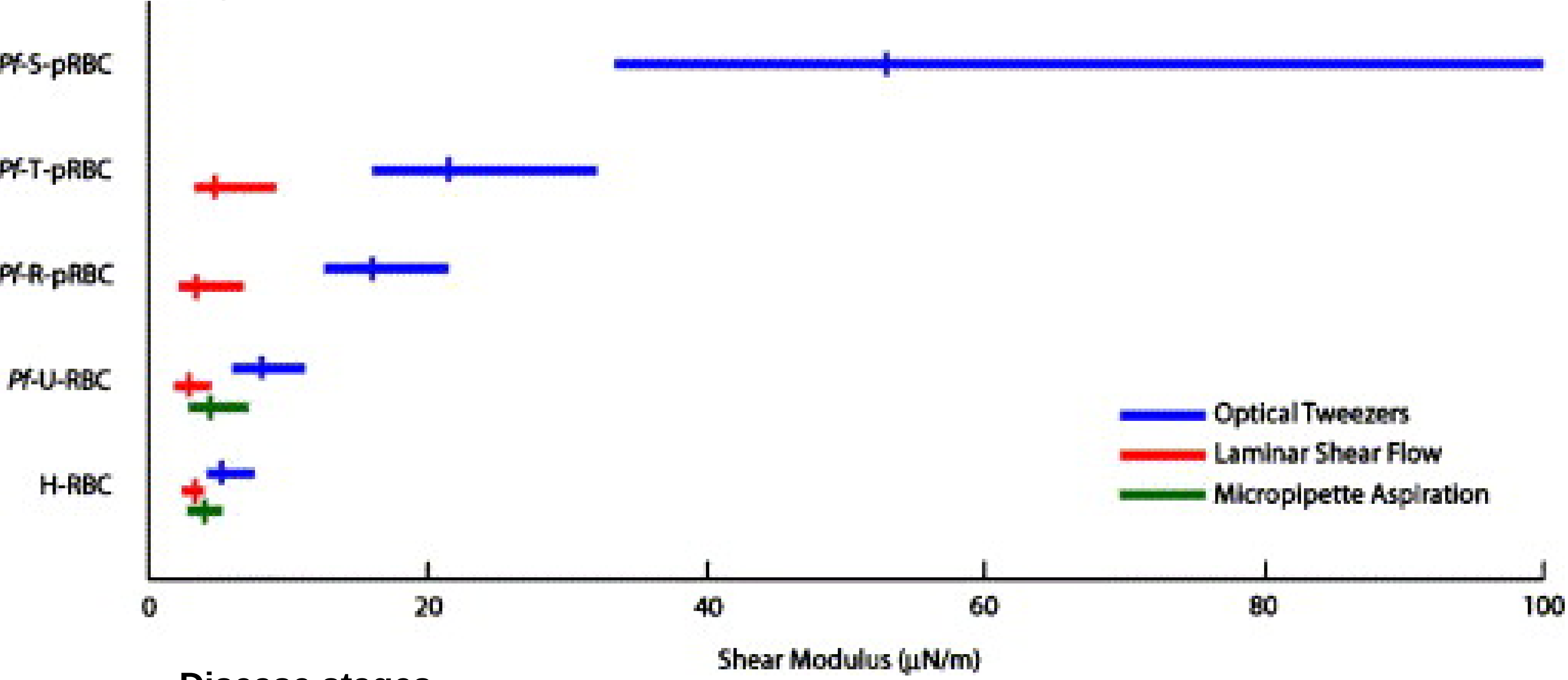
Stages of malaria and effect on cell stiffness



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Disease stages

H-RBC (healthy)

Pf-U-RBC (exposed but not infected)

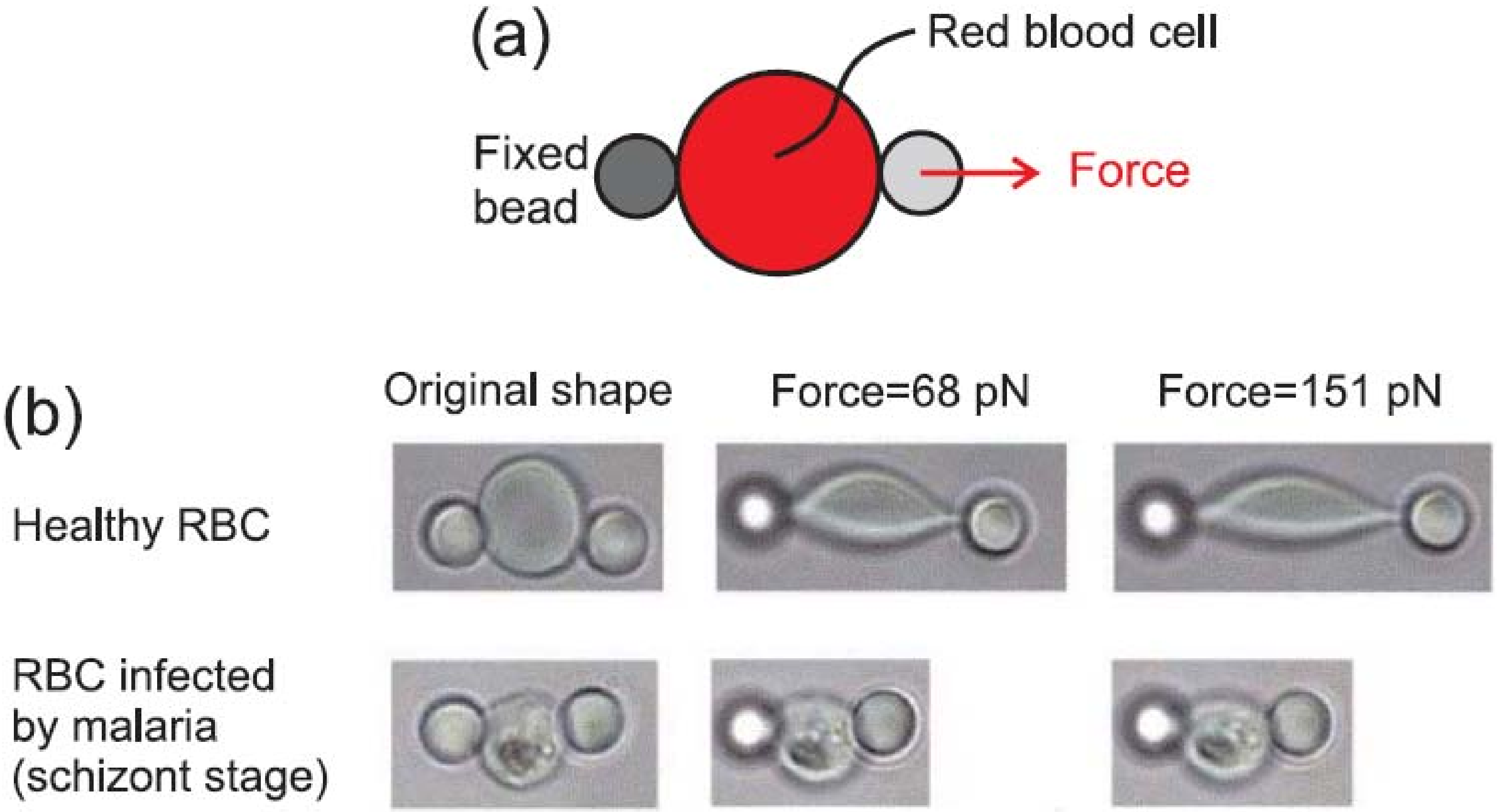
Pf-R-pRBC (ring stage)

Pf-T-pRBC
(trophozoite stage)

Pf-S-pRBC
(schizont stage)

Consequence: Due to rigidity, RBCs can not move easily through capillaries in the lung

Cell deformation



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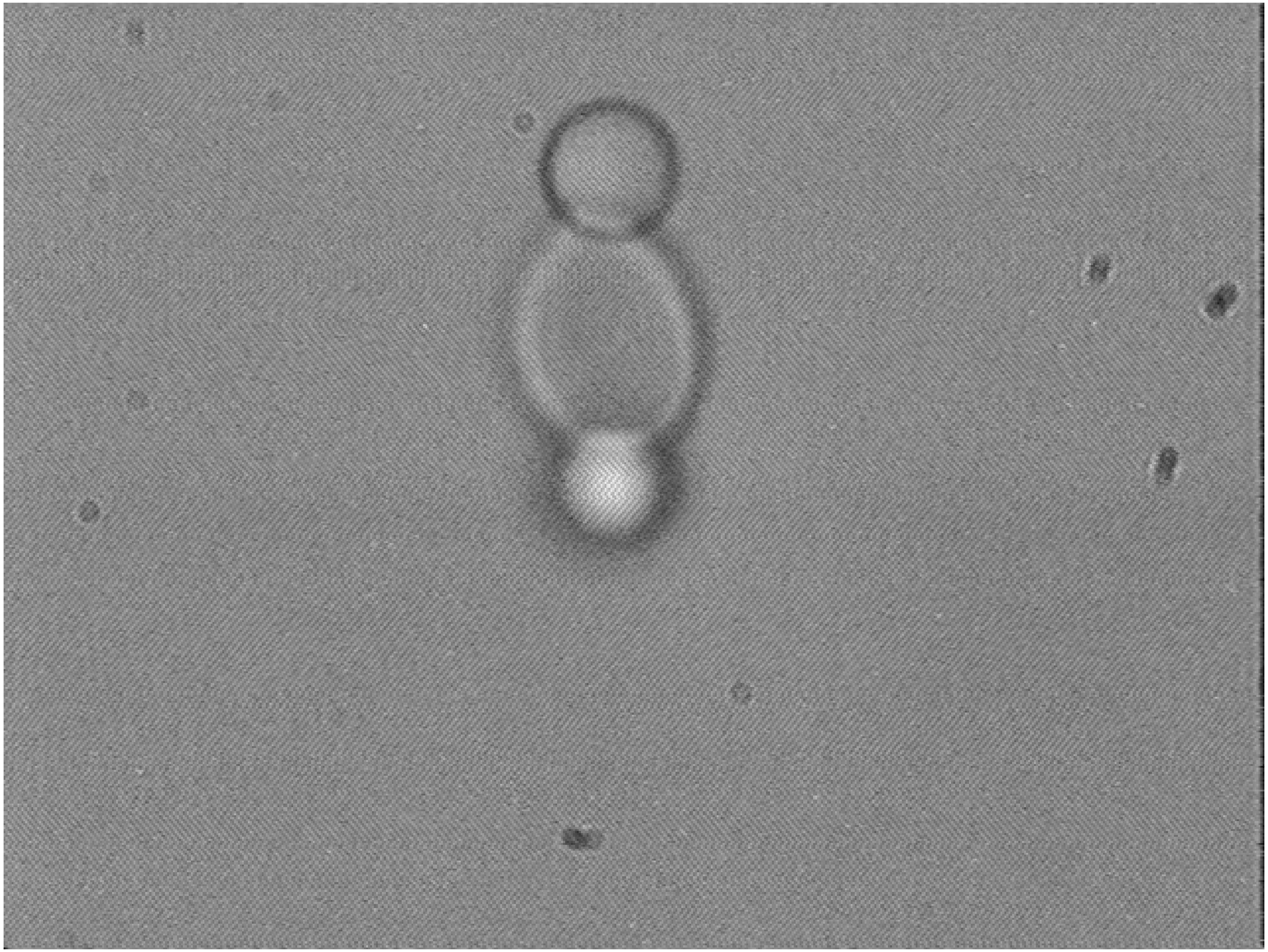
Deformation of red blood cells



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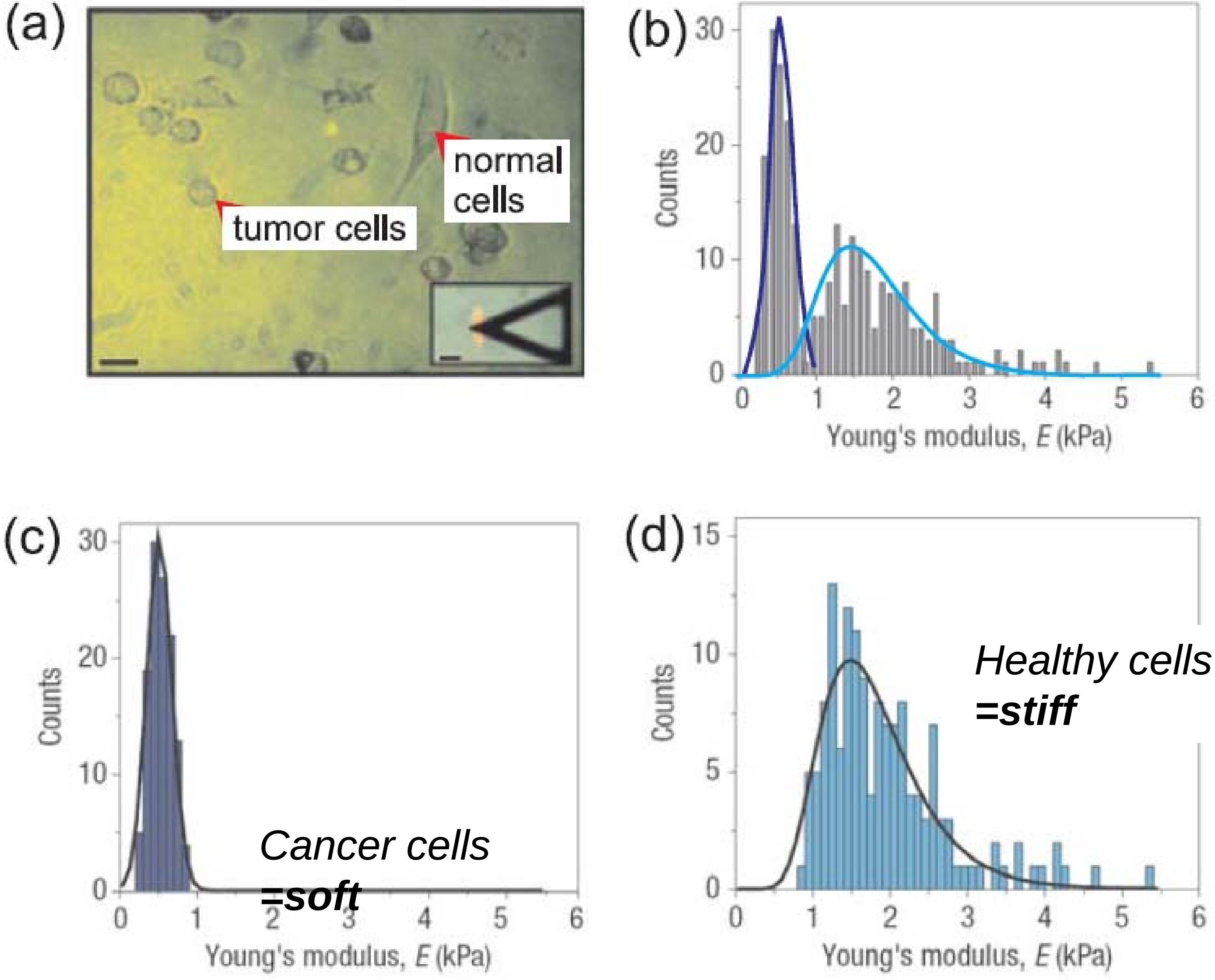
Mechanical signature of cancer cells (AFM)



Healthy cells
=stiff

Cancer cells
=soft

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Spring 2012