1.021, 3.021, 10.333, 22.00 Introduction to Modeling and Simulation
Spring 2011

Part I – Continuum and particle methods

Applications to biophysics and bionanomechanics

Lecture 10

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Content overview

I. Particle and continuum methods

Lectures 1-13

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 10: Applications to biophysics and bionanomechanics

Outline:

1. Protein force fields
2. Single molecule mechanics
3. Fracture of protein domains – Bell model

Goal of today's lecture:

- Force fields for organic materials, and specifically proteins
- Basic introduction into modeling of biological materials
- Fracture model for protein domains

1. Force fields for organic chemistry - how to model proteins

Significance of proteins

- Proteins are **basic building blocks of life**
- **Define tissues, organs, cells**
- Provide a **variety of functions and properties**, such as mechanical stability (strength), elasticity, catalytic activity (enzyme), electrochemical properties, optical properties, energy conversion
- Molecular simulation is an **important tool in the analysis of protein structures and protein materials**

Goal here: *To train you in the fundamentals of modeling techniques for proteins, to enable you to carry out protein simulations*

*Explain the significance of proteins (**application**)*

Human body: Composed of diverse array of protein materials

Eye's cornea (collagen material)

Skin (complex composite of collagen, elastin)

Cells (complex material/system based on proteins)

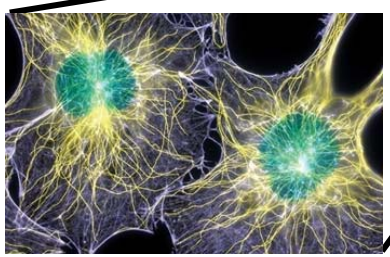

Image courtesy of NIH.

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Human Body 3D View™ image of whole bodies.

Muscle tissue (motor proteins)

Nerve cells

Blood vessels

Tendon (links bone, muscles)

Cartilage (reduce friction in joints)

Bone (structural stability)

http://www.humanbody3d.com/ and http://publications.nigms.nih.gov/insidethecell/images/ch1_cellscolor.jpg

Cellular structure: Protein networks

Cell nucleus

Actin network

Microtubulus
(e.g. cargo)

Vimentin
(extensible, flexible, provide strength)

= cytoskeleton

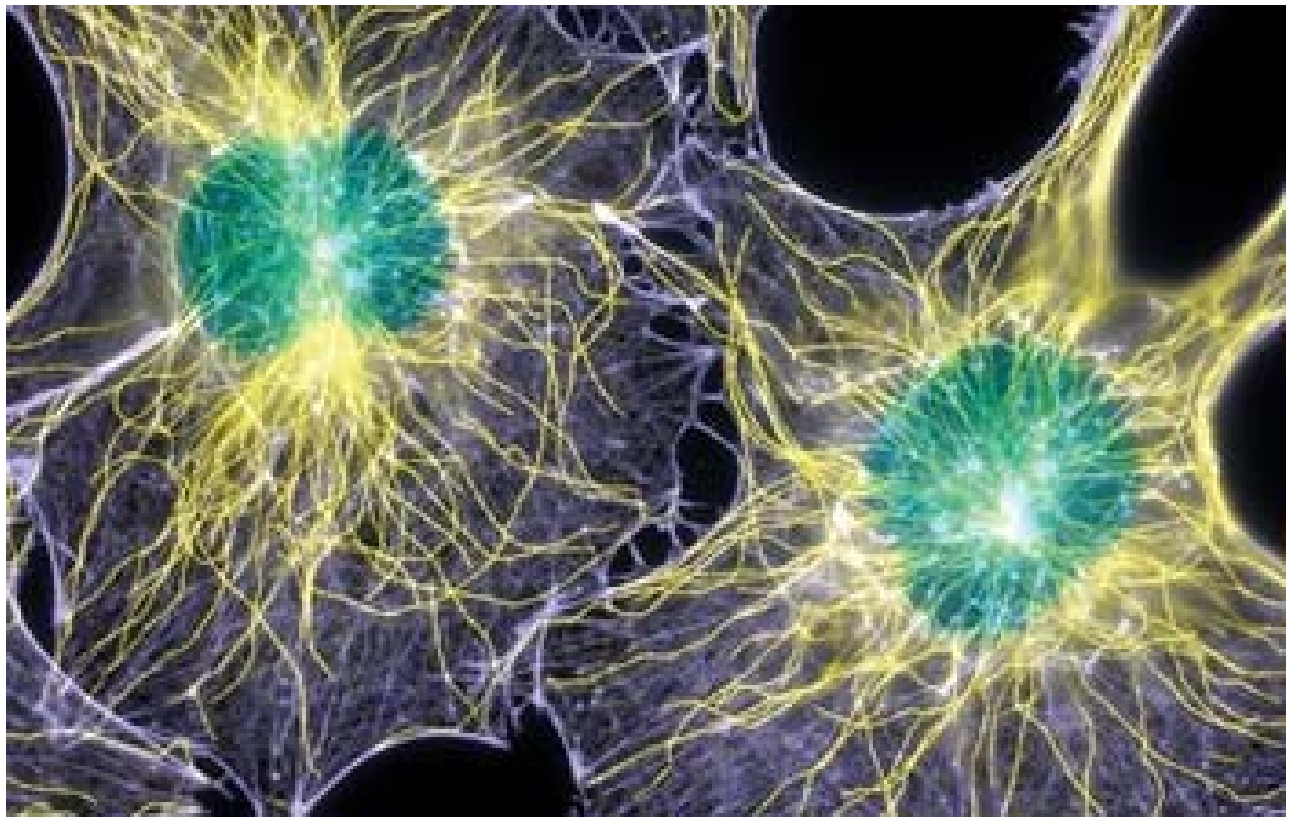


Image courtesy of NIH.

Protein structures define the cellular architecture

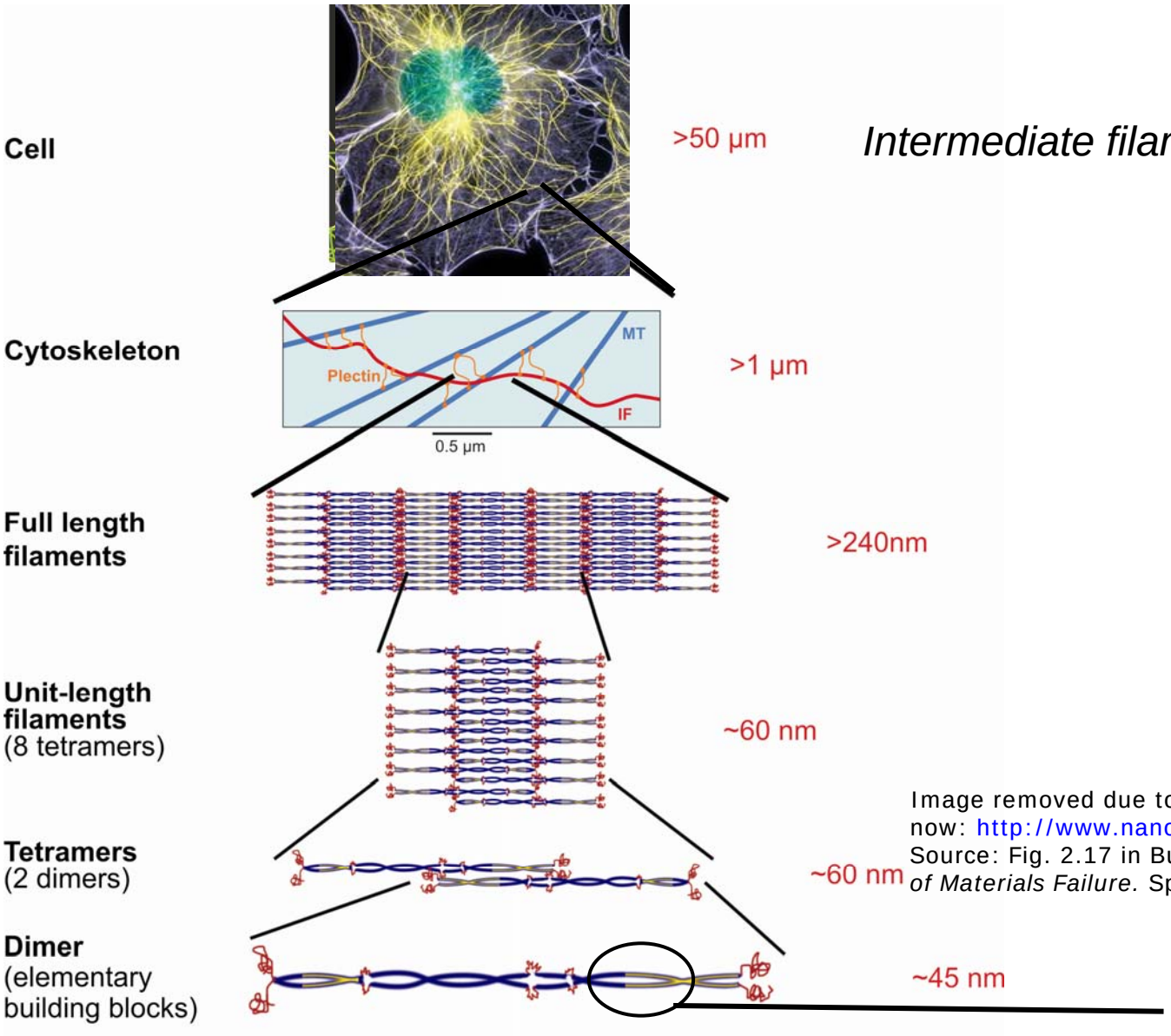


Image removed due to copyright restrictions; see image now: http://www.nanowerk.com/spotlight/id2878_1.jpg. Source: Fig. 2.17 in Buehler, Markus J. *Atomistic Modeling of Materials Failure.* Springer, 2008.

How protein materials are made – the genetic code

- Proteins: Encoded by DNA (three “letters”), utilize 20 basic building blocks (amino acids) to form polypeptides

- Polypeptides arrange in complex folded 3D structures with specific properties

1D structure transforms into complex 3D folded configuration

ACGT →

Four letter code “DNA”

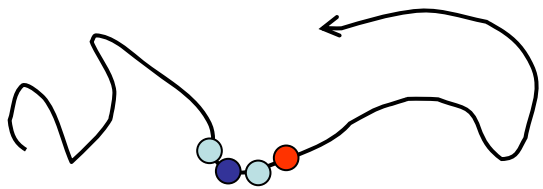
Combination of 3 DNA letters equals a amino acid

E.g.: Proline –

CCT, CCC, CCA, CCG

Transcription/ translation

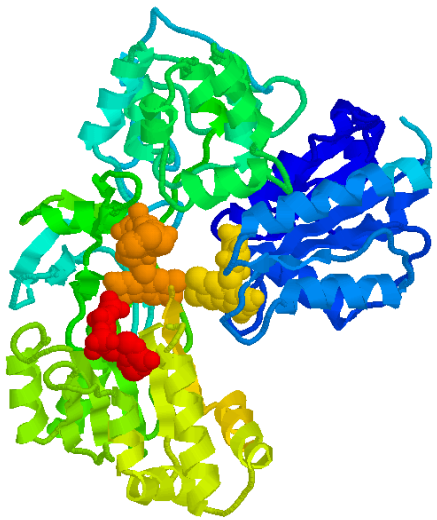
→



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

Sequence of amino acids “polypeptide” (1D structure)

→

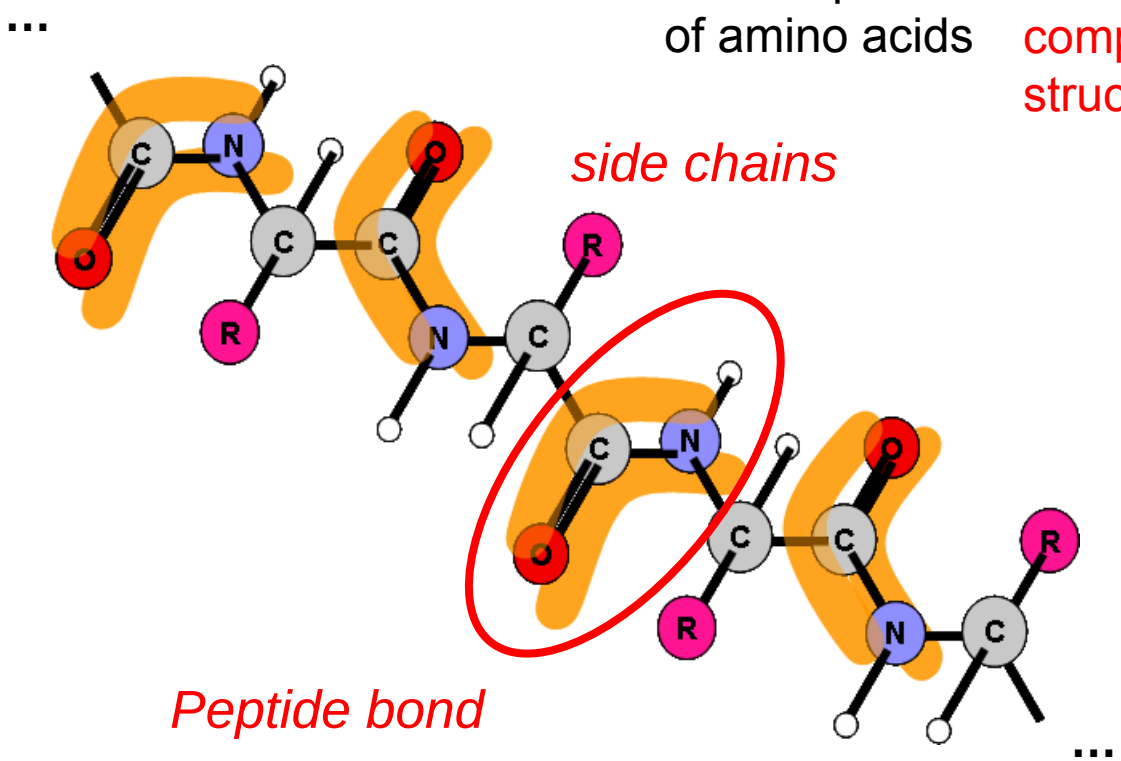


Folding (3D structure)

Chemical structure of peptides/proteins

Typically short sequence of amino acids

Longer sequence of amino acids, often complex 3D structure



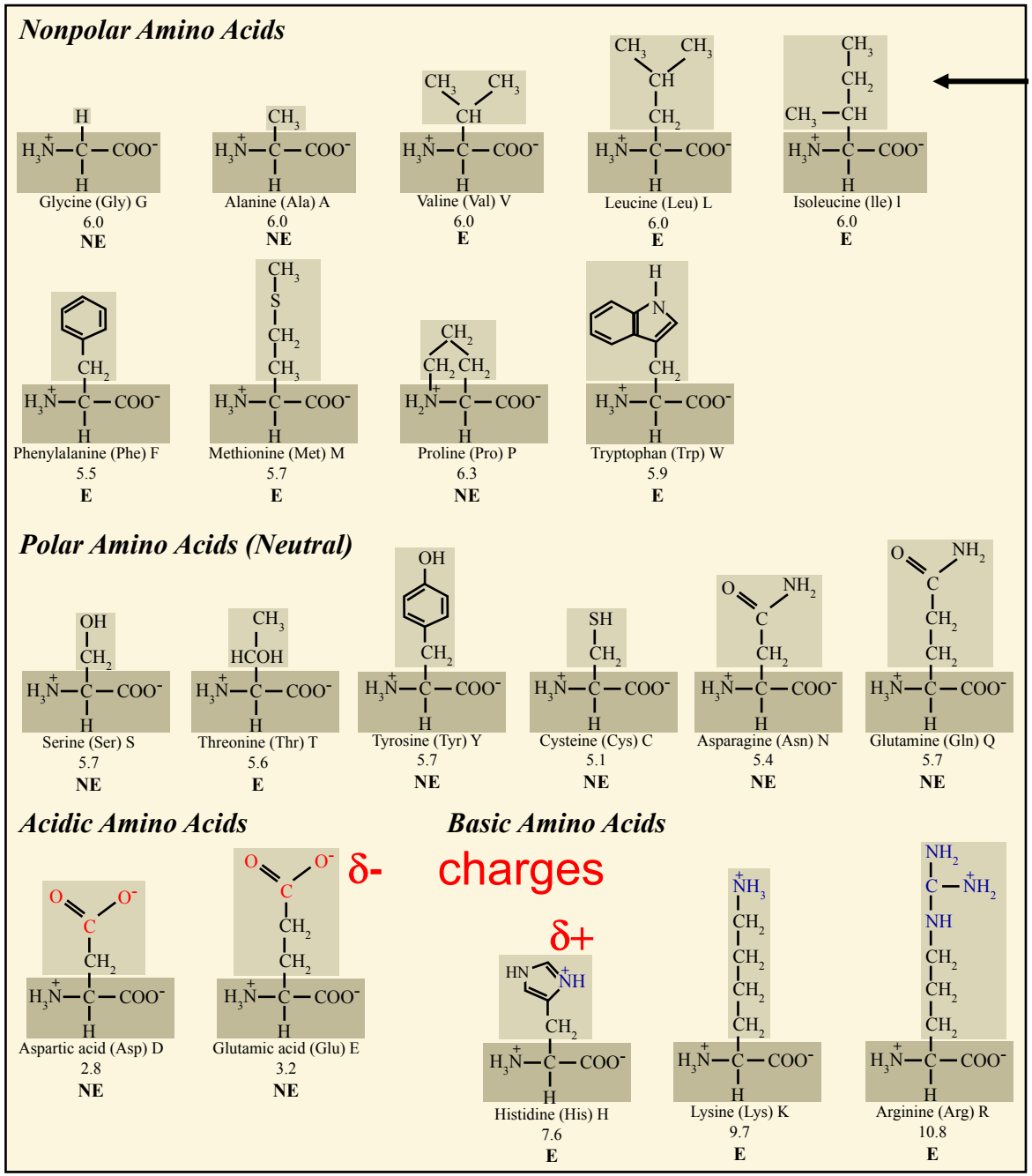
R = side chain, one of the 20 natural amino acids

20 natural amino acids differ in their side chain chemistry

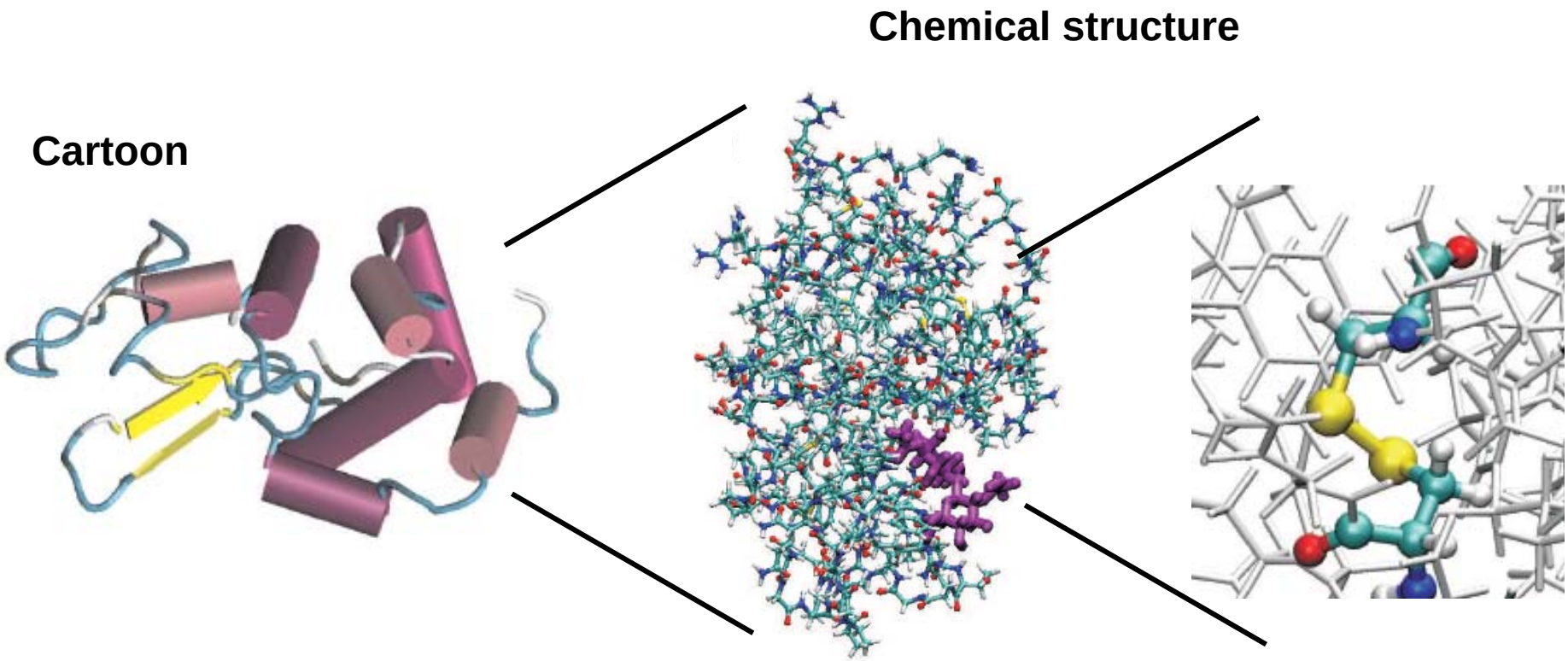
Forms peptide bond

There are 20 natural amino acids

Difference in side chain, **R**



Chemistry, structure and properties are linked



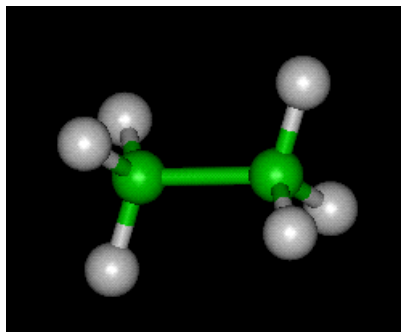
Presence of various chemical bonds:

- 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)

Concept: split energy contributions

=0 for proteins

$$U_{total} = U_{\text{Elec}} + U_{\text{Covalent}} + U_{\text{Metallic}} + U_{\text{vdW}} + U_{\text{H-bond}}$$



Ethane
C_2H_6

Covalent bond described as

1. Bond stretching part (energy penalty for bond stretching)
2. Bending part (energy penalty for bending three atoms)
3. Rotation part (energy penalty for bond rotation, $N \geq 4$)

Consider ethane molecule as "**elastic structure**"

$$U_{\text{Covalent}} = U_{\text{stretch}} + U_{\text{bend}} + U_{\text{rotate}}$$

Force fields for organics: Basic approach

=0 for proteins

$$U_{total} = U_{\text{Elec}} + U_{\text{Covalent}} + U_{\text{Metallic}} + U_{\text{vdW}} + U_{\text{H-bond}}$$

$$U_{\text{Covalent}} = U_{\text{stretch}} + U_{\text{bend}} + U_{\text{rot}}$$

$$\begin{cases} \phi_{\text{stretch}} = \frac{1}{2} k_{\text{stretch}} (r - r_0)^2 \\ U_{\text{stretch}} = \sum_{\text{pairs}} \phi_{\text{stretch}} \end{cases}$$

$$\begin{cases} \phi_{\text{bend}} = \frac{1}{2} k_{\text{bend}} (\theta - \theta_0)^2 \\ U_{\text{bend}} = \sum_{\text{triplets}} \phi_{\text{bend}} \end{cases}$$

$$\begin{cases} \phi_{\text{rot}} = \frac{1}{2} k_{\text{rot}} (1 - \cos(\vartheta)) \\ U_{\text{rot}} = \sum_{\text{quadruplets}} \phi_{\text{rot}} \end{cases}$$

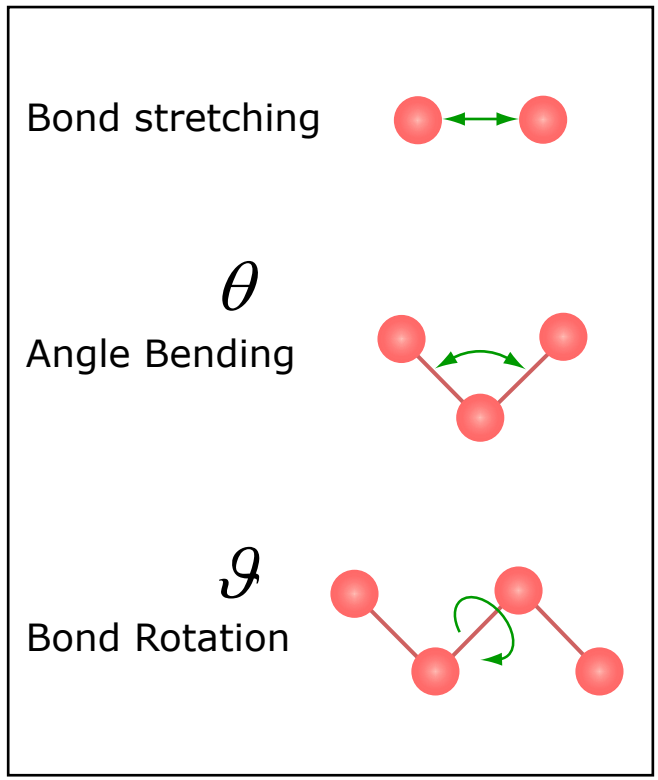
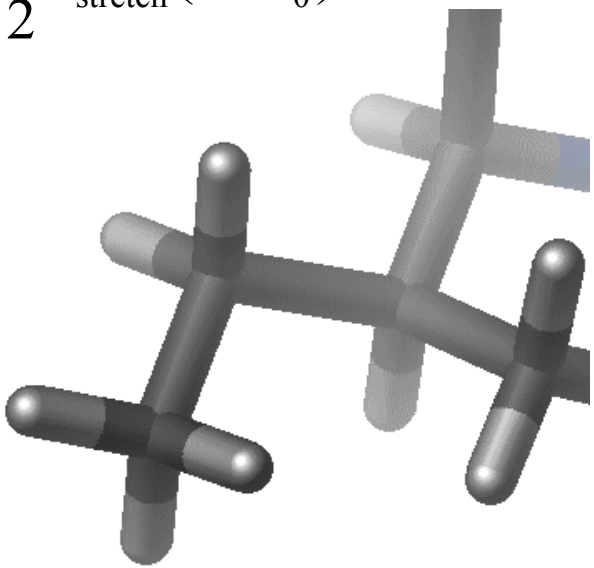


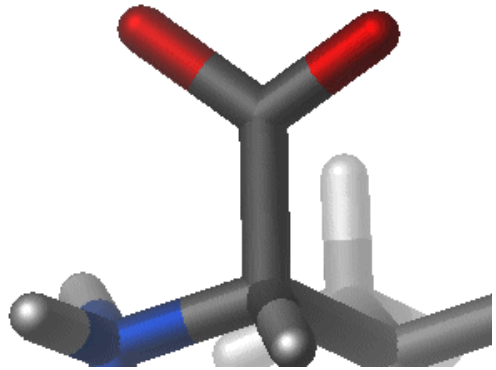
Image by MIT OpenCourseWare.

Model for covalent bonds

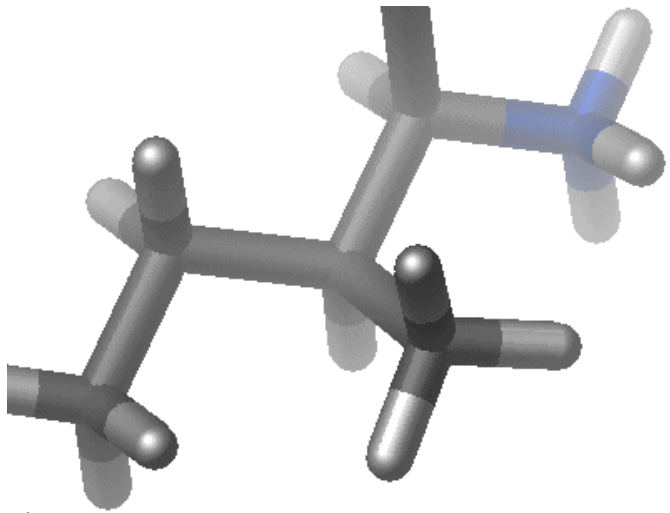
$$\phi_{\text{stretch}} = \frac{1}{2} k_{\text{stretch}} (r - r_0)^2$$



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



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



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

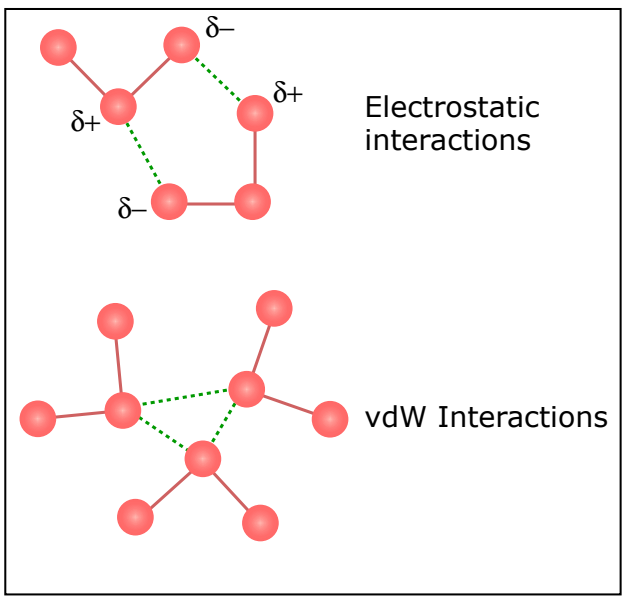
Force fields for organics: Basic approach

$$U_{total} = U_{\text{Elec}} + U_{\text{Covalent}} + U_{\text{Metallic}} + U_{\text{vdW}} + U_{\text{H-bond}}$$

=0 for proteins

U_{Elec}

q_i q_j



partial charges

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

electrostatic constant

distance

Coulomb forces $F(r_{ij}) = -\dfrac{q_i q_j}{\varepsilon_1 r_{ij}^2}$

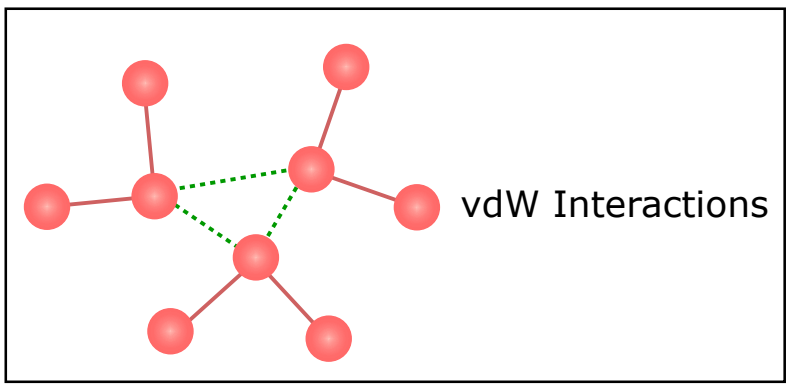
$\varepsilon_1 = 4\pi\varepsilon_0 \quad \varepsilon_0 = 1.602 \times 10^{-19}\ \text{C}$

Force fields for organics: Basic approach

$$U_{total} = U_{\text{Elec}} + U_{\text{Covalent}} + U_{\text{Metallic}} + U_{\text{vdW}} + U_{\text{H-bond}}$$

=0 for proteins

U_{vdW}



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

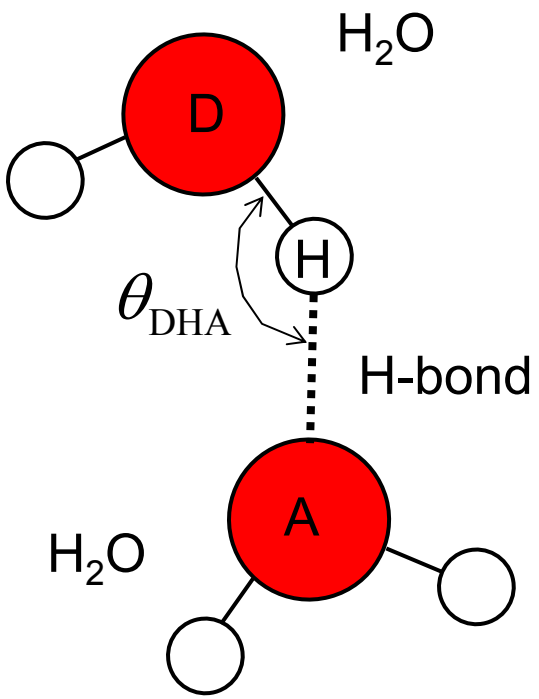
LJ potential is particularly good model for vdW interactions (Argon)

H-bond model

=0 for proteins

$$U_{total} = U_{\text{Elec}} + U_{\text{Covalent}} + U_{\text{Metallic}} + U_{\text{vdW}} + U_{\text{H-bond}}$$

$U_{\text{H-bond}}$



Evaluated between acceptor (A) /donor(D) pairs

Between electronegative atom and a H- atom that is bonded to another electronegative atom

Slightly modified LJ, different parameters

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

r_{ij} = distance between D-A

Summary

=0 for proteins

$$U_{total} = U_{\text{Elec}} + U_{\text{Covalent}} + U_{\text{Metallic}} + U_{\text{vdW}} + U_{\text{H-bond}}$$

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

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

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

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

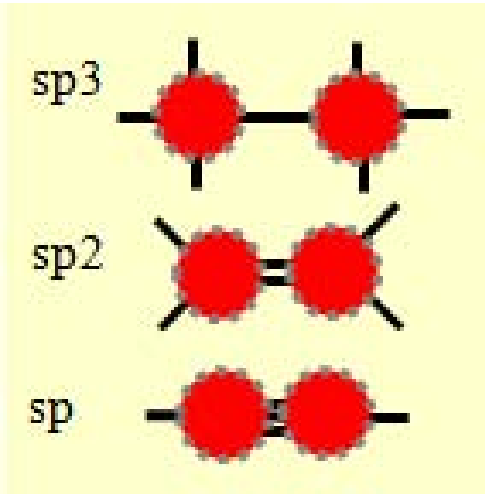
The need for atom typing

- **Limited transferability** of potential expressions: Must use different potential for different chemistry

- Different chemistry is captured in **different "tags"** for atoms: **Element type** is expanded by **additional information** on particular chemical state

- Tags specify if a C-atom is in **sp^3, sp^2, sp** or in aromatic state (that is, to capture resonance effects)

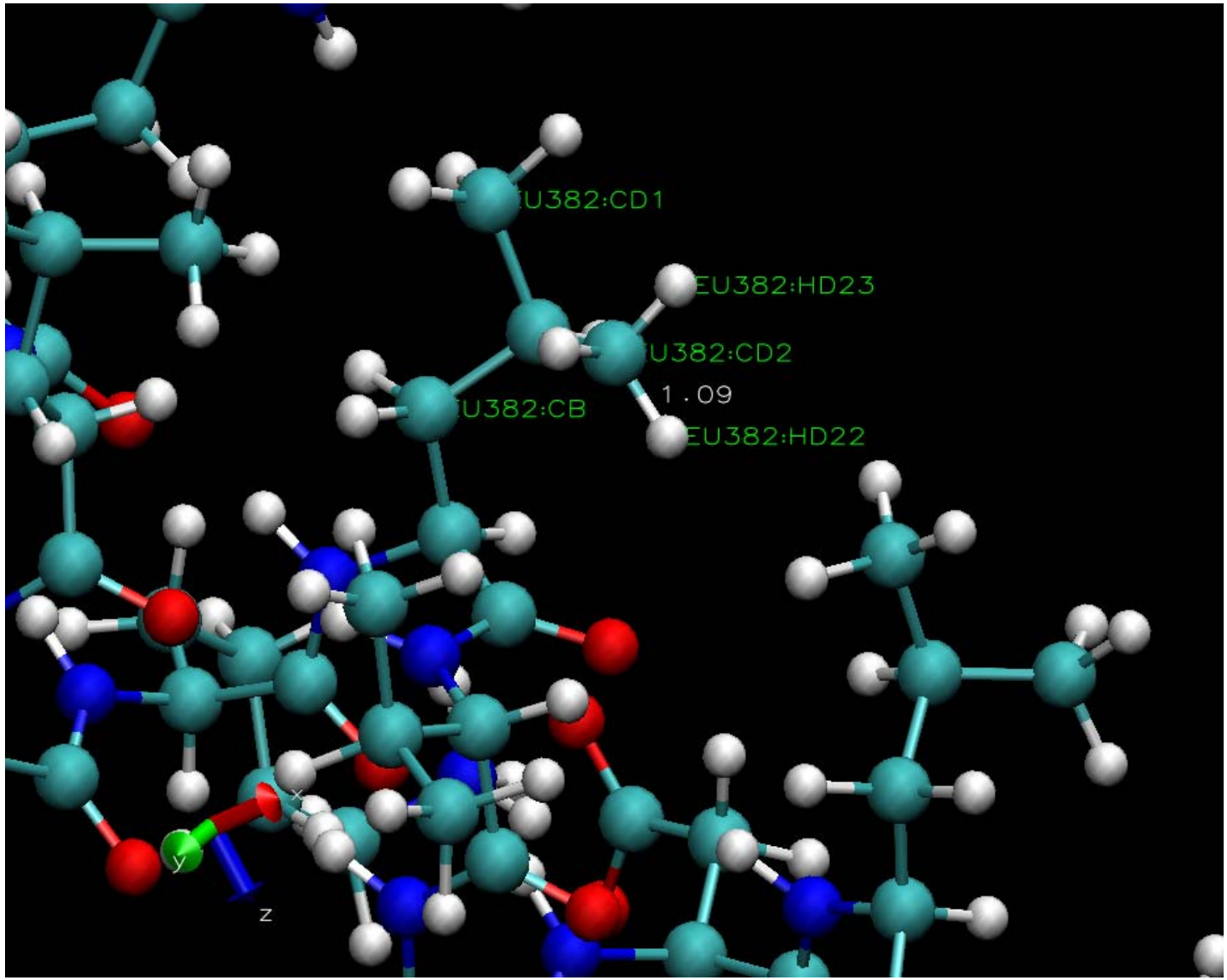
- **Example atom tags**: CA, C_1, C_2, C_3, C…, HN, HO, HC, …



Atom typing in CHARMM

```
Example of the RTF for the Alanine residue:
RESI ALA0.00
GROUP
ATOM NNH1-0.47  !     |
ATOM HNH 0.31   ! HN-N
ATOM CACT1 0.07 !     |    HB1
ATOM HAHB 0.09  !     |    /
GROUP           !HA-CA--CB-HB2
ATOM CBCT3-0.27 !     |    \
ATOM HB1HA 0.09 !     |    HB3
ATOM HB2HA 0.09 !   O=C
ATOM HB3HA 0.09 !     |
GROUP           !
ATOM CC 0.51
ATOM OO-0.51
BONDCB CA N HN N CA
BOND C CA C +N CA HA CB HB1 CB HB2 CB HB3
DOUBLE O C
IMPR N -C CA HN C CA +N O
DONOR HN N
ACCEPTOR O C
IC -C CA *N HN    1.3551 126.4900 180.0000 115.4200 0.9996
IC -C N CA C      1.3551 126.4900 180.0000 114.4400 1.5390
IC N CA C +N      1.4592 114.4400 180.0000 116.8400 1.3558
IC +N CA *C O     1.3558 116.8400 180.0000 122.5200 1.2297
IC CA C +N +CA    1.5390 116.8400 180.0000 126.7700 1.4613
IC N C *CA CB     1.4592 114.4400 123.2300 111.0900 1.5461
IC N C *CA HA     1.4592 114.4400 -120.4500 106.3900 1.0840
IC C CA CB HB1    1.5390 111.0900 177.2500 109.6000 1.1109
IC HB1 CA *CB HB2 1.1109 109.6000 119.1300 111.0500 1.1119
IC HB1 CA *CB HB3 1.1109 109.6000 -119.5800 111.6100 1.1114
```

VMD analysis of protein structure



Common empirical force fields for organics and proteins

Class I (experiment derived, simple form)

- CHARMM **pset #3**
- CHARMm (Accelrys)
- AMBER
- OPLS/AMBER/Schrödinger
- ECEPP (free energy force field)
- GROMOS

Harmonic terms; Derived from vibrational spectroscopy, gas-phase molecular structures Very system-specific

Class II (more complex, derived from QM)

- CFF95 (Biosym/Accelrys)
- MM3
- MMFF94 (CHARMM, Macromodel…)
- UFF, DREIDING

Include anharmonic terms Derived from QM, more general

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

CHARMM force field

- Widely used and accepted model for protein structures

- Programs such as NAMD have implemented the CHARMM force field

  Problem set #3, nanoHUB stretchmol module, study of a protein domain that is part of human vimentin intermediate filaments

Application – protein folding

ACGT →

Four letter code "DNA"

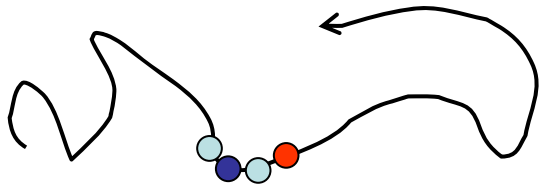
Combination of 3 DNA letters equals a amino acid

E.g.: Proline –

CCT, CCC, CCA, CCG

Transcription/ translation

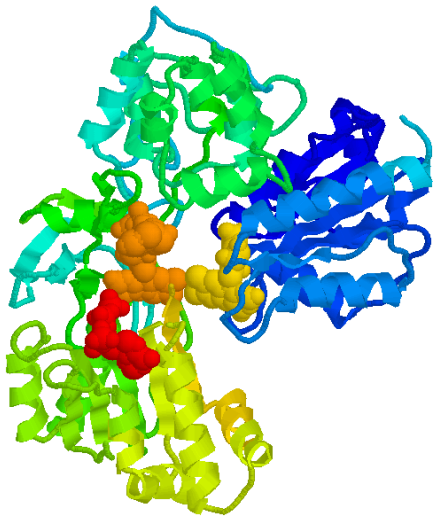
→



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

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

→



Folding (3D structure)

Goal of protein folding simulations:

Predict folded 3D structure based on polypeptide sequence

Movie: protein folding with CHARMM

- *de novo* Folding of a *Transmembrane fd Coat Protein*
  http://www.charmm-gui.org/?doc=gallery&id=23

Polypeptide chain

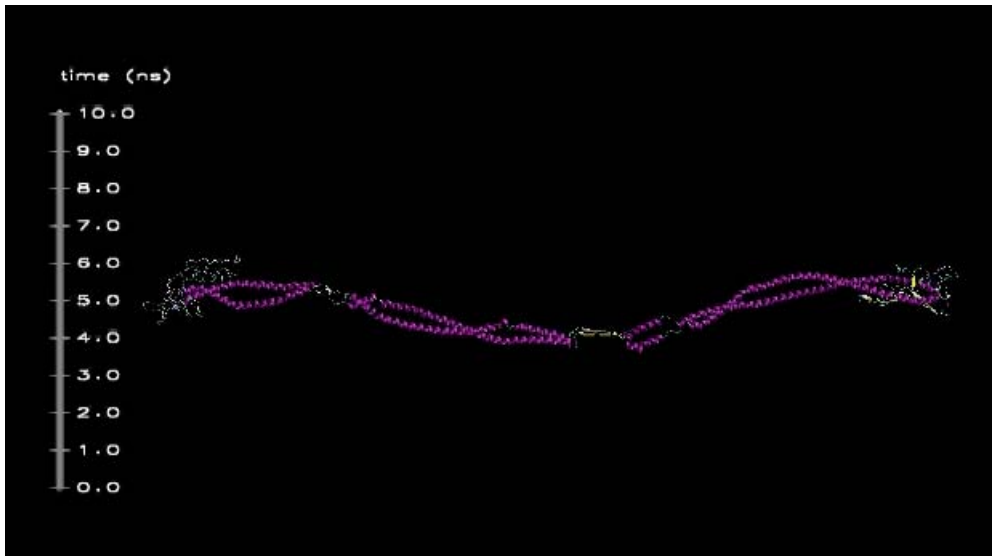
Images removed due to copyright restrictions.

Screenshots from protein folding video, which can be found here: http://www.charmm-gui.org/?doc=gallery&id=23.

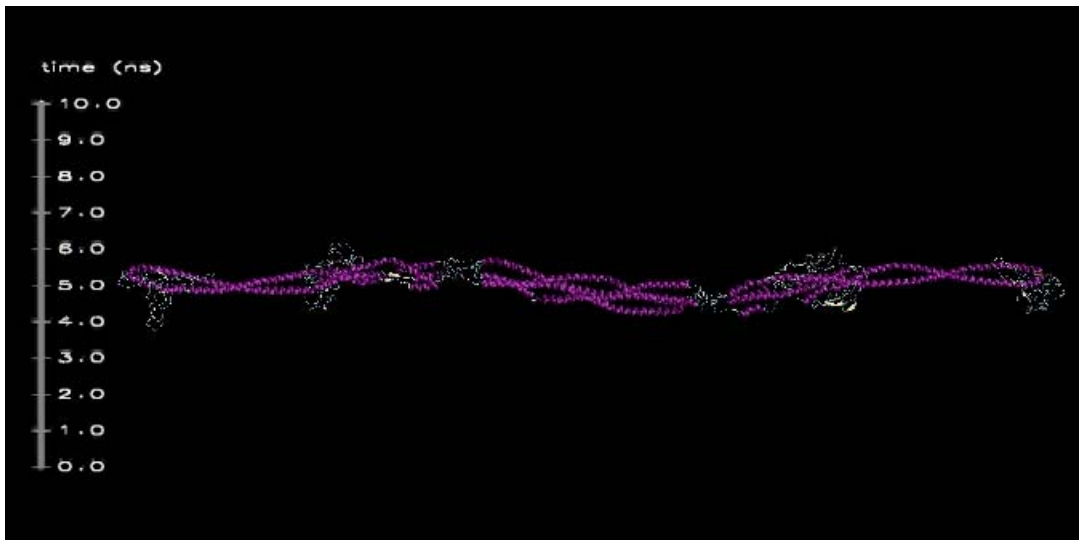
Quality of predicted structures quite good

Confirmed by comparison of the **MSD deviations** of a room temperature ensemble of conformations from the replica-exchange simulations and **experimental structures** from both **solid-state NMR** in lipid bilayers and solution-phase NMR on the protein in micelles)

Movies in equilibrium (temperature 300 K)



Dimer



Tetramer
(increased effective bending stiffness, interaction via overlap & head/tail domain)

Source: Qin, Z., L. Kreplak, and M. Buehler. "Hierarchical Structure Controls Nanomechanical Properties of Vimentin Intermediate Filaments." *PLoS ONE* (2009). License CC BY.

2. Single molecule mechanics

Structure and mechanics of protein, DNA, etc. molecules

Cooking spaghetti

Photo courtesy of HatM on Flickr.

stiff rods

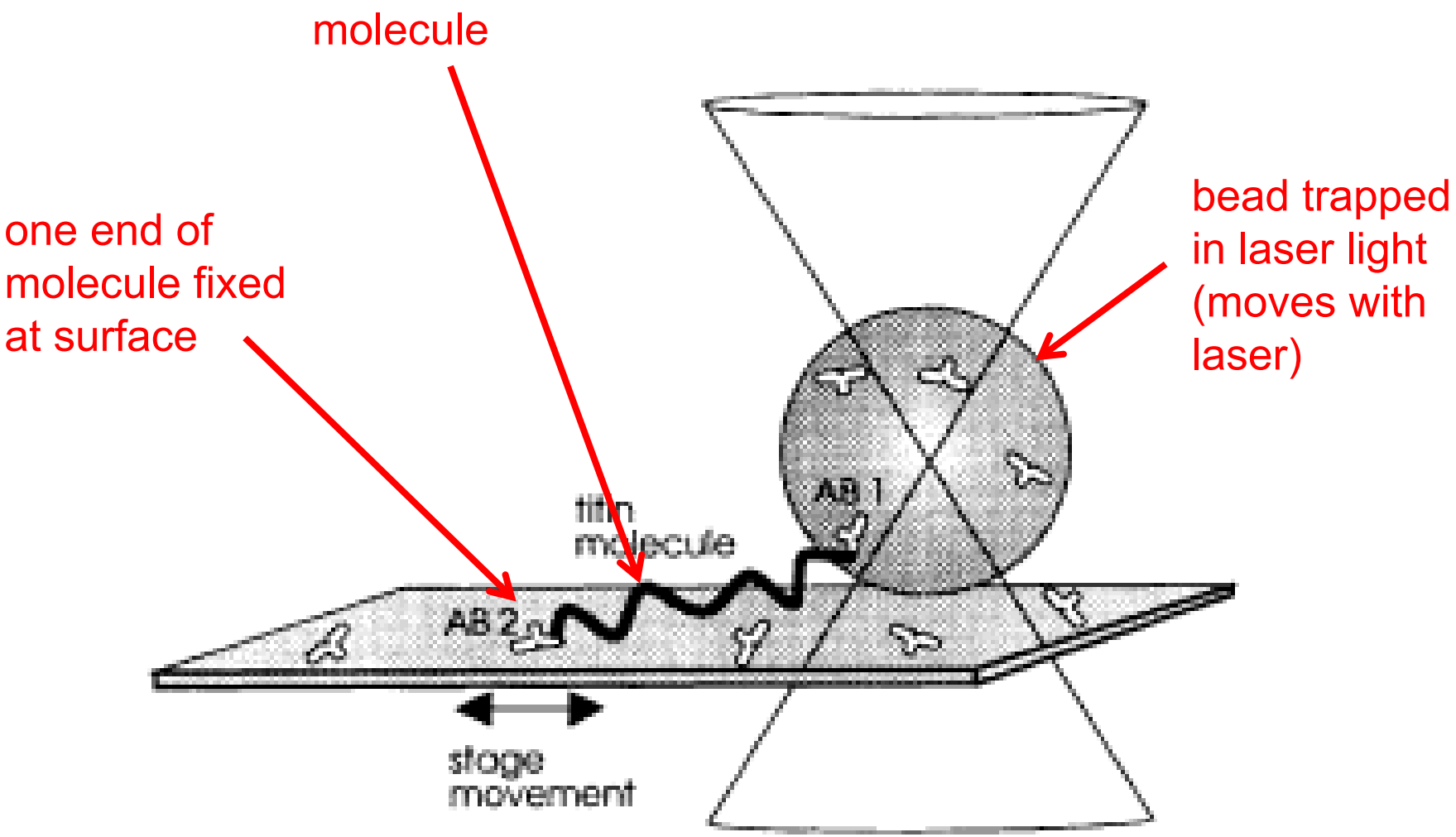
Public domain image.

cooking

Photo courtesy of HatM on Flickr.

soft, flexible rods (like many protein molecules)

Single molecule tensile test – “optical tweezer”

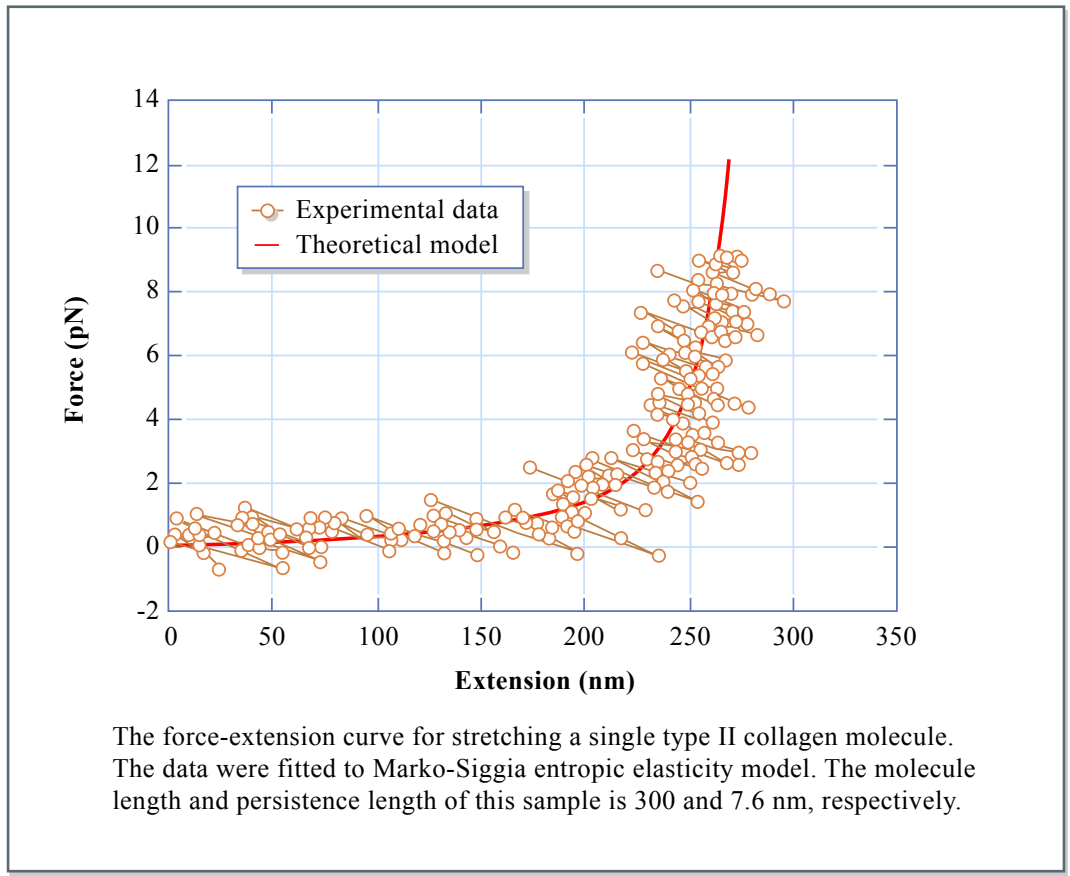


Example 1: Elasticity of tropocollagen molecules

300 nm length

Entropic elasticity leads to strongly nonlinear elasticity

Photo courtesy of HatM on Flickr.



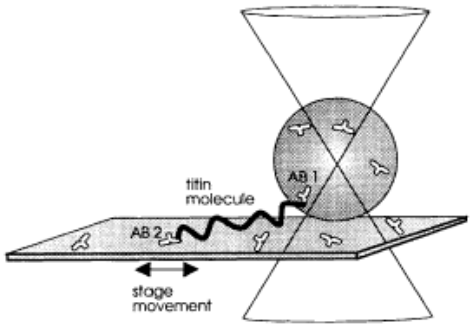
The force-extension curve for stretching a single type II collagen molecule. The data were fitted to Marko-Siggia entropic elasticity model. The molecule length and persistence length of this sample is 300 and 7.6 nm, respectively.

Image by MIT OpenCourseWare.

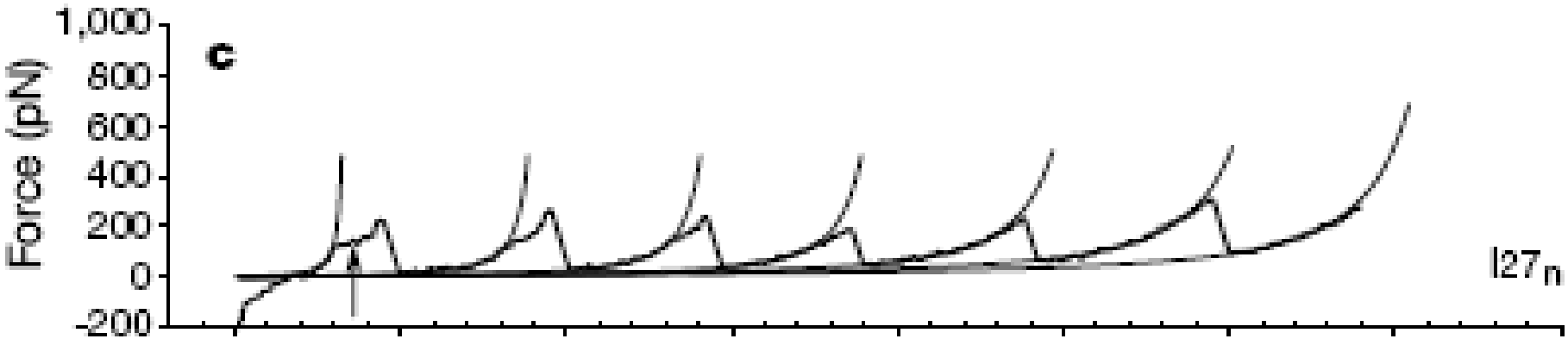
Courtesy of Elsevier, Inc., http://www.sciencedirect.com. Used with permission.

Example 2: Single protein molecule mechanics

Optical tweezers experiment

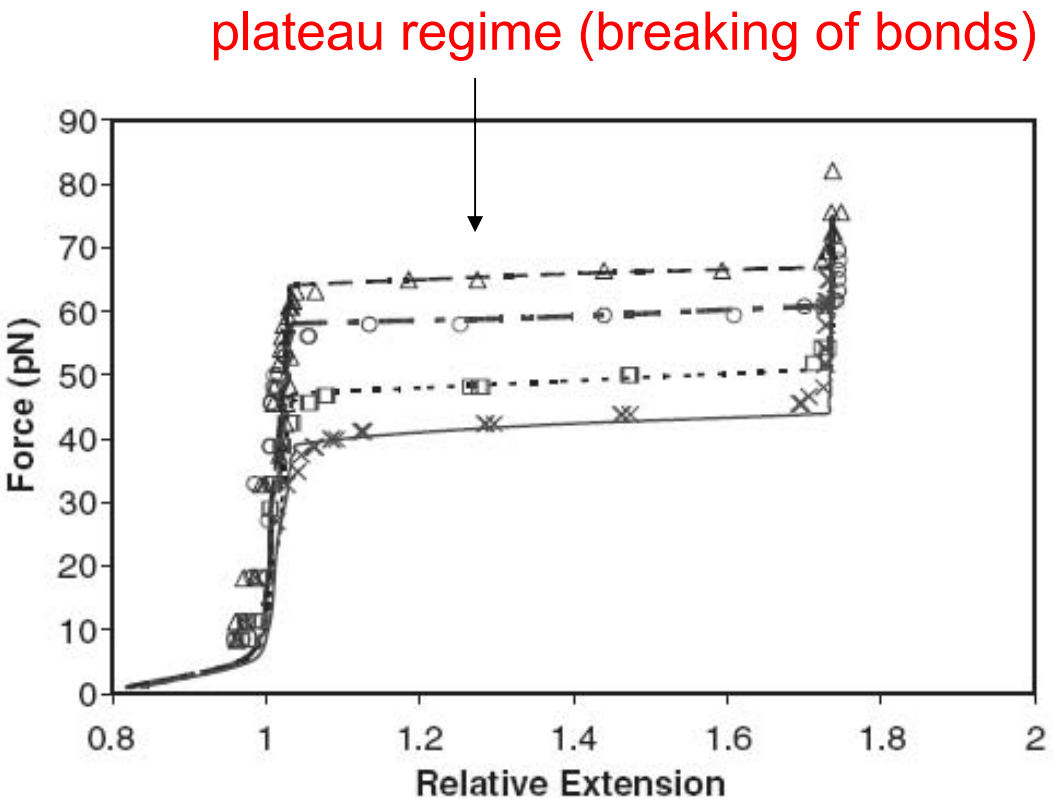


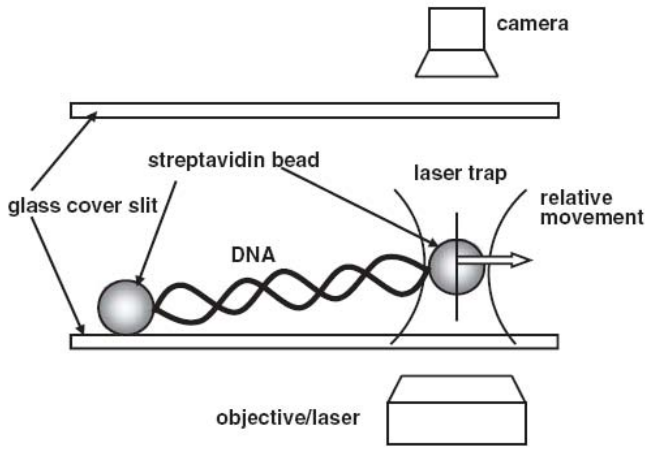
Protein structure (I27 multidomain titin in muscle)



http://www.nature.com/nature/journal/v387/n6630/pdf/387308a0.pdf
http://www.nature.com/nature/journal/v402/n6757/pdf/402100a0.pdf

Example 3: Single DNA molecule mechanics





Plots of stretching force against relative extension of the single DNA molecule (experimental results)

Structural makeup of protein materials

*Although very **diverse**, all protein materials have **universal** "protocols" of how they are made*

How protein materials are made–the genetic code

- Proteins: Encoded by DNA (three “letters”), utilize 20 basic building blocks (amino acids) to form polypeptides

- Polypeptides arrange in complex folded 3D structures with specific properties

1D structure transforms into complex 3D folded configuration

ACGT ⟶

Four letter code “DNA”

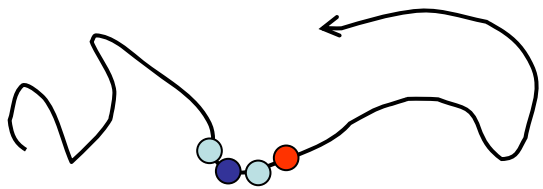
Combination of 3 DNA letters (=codon) defines one amino acid

E.g.: Proline –

CCT, CCC, CCA, or CCG

Transcription/ translation

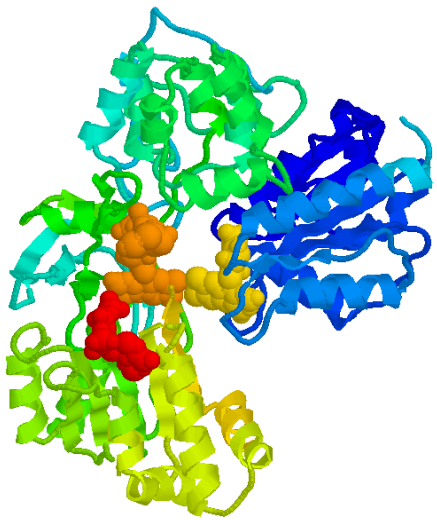
⟶



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

Sequence of amino acids “polypeptide” (1D structure)

⟶

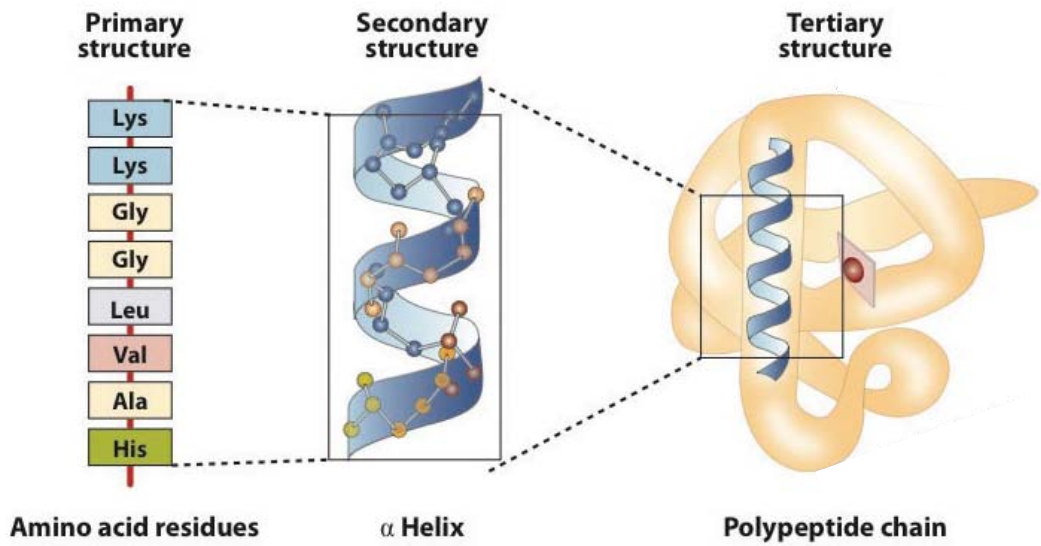


Folding (3D structure)

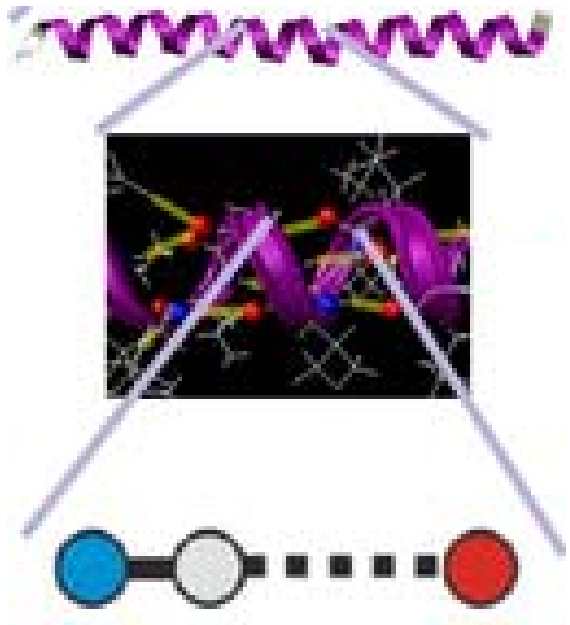
Alpha-helix (abbreviated as AH)

Concept: hydrogen bonding (H-bonding)
e.g. between O and H in H_2O
Between N and O in proteins
Drives formation of helical structures

AHs found in: hair, cells, wool, skin, etc.

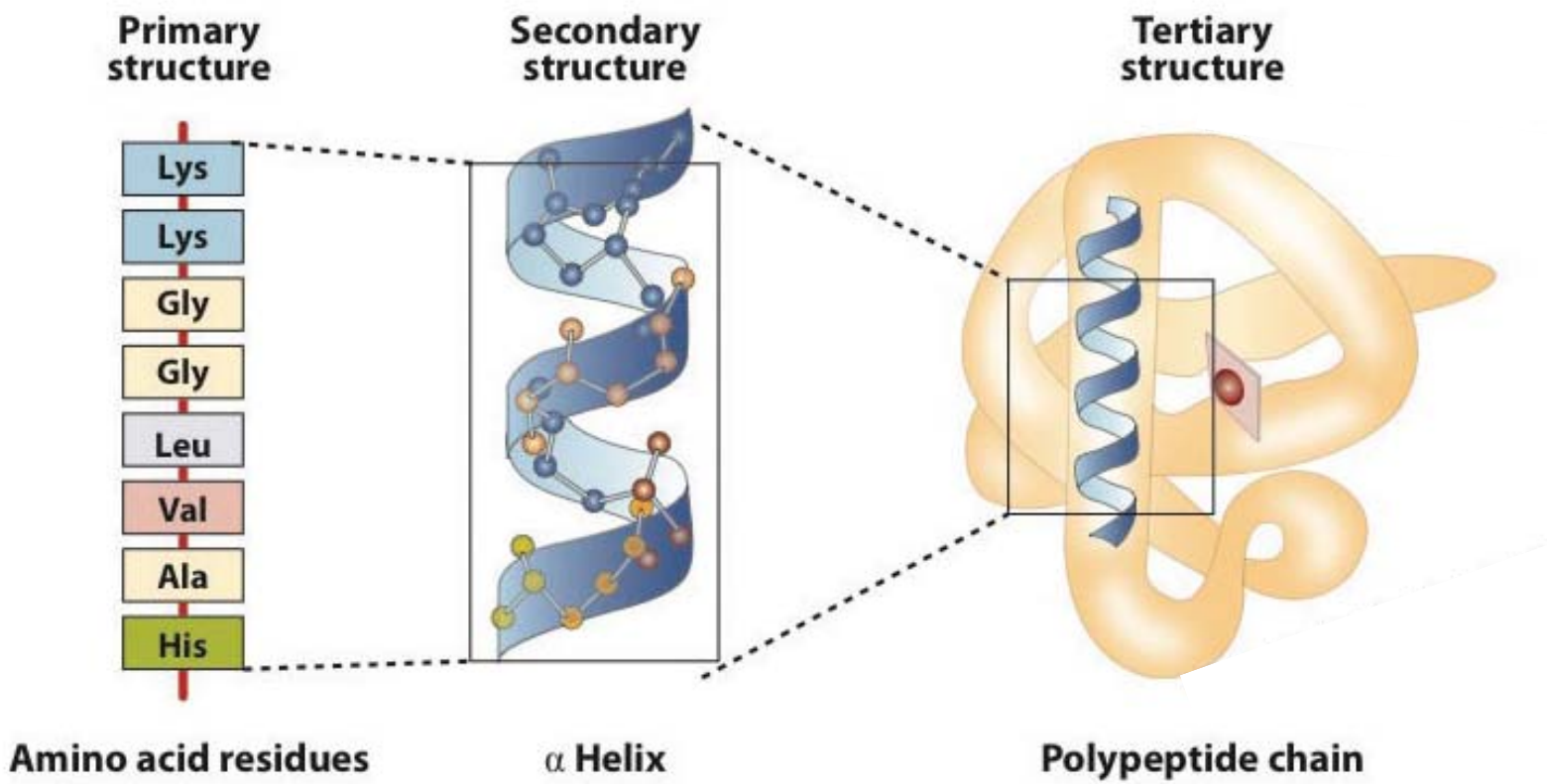


Adapted from Ball, D., Hill, J., et al. *The Basics of General, Organic, and Biological Chemistry.* Flatworld Knowledge, 2011. Courtesy of Flatworld Knowledge.



Source: Qin, Z., L. Kreplak, and M. Buehler. "Hierarchical structure controls nanomechanical properties of vimentin intermediate filaments." *PLoS ONE* (2009). License CC BY.

Primary, secondary, tertiary structure



Adapted from Ball, D., Hill, J., and R. Scott. *The Basics of General, Organic, and Biological Chemistry*. Flatworld Knowledge, 2011. Courtesy of Flatworld Knowledge.

Beta-sheets (abbreviated as BS)

Beta-sheet

Images removed due to copyright restrictions.

Found in many mechanically relevant proteins

Spider silk

Fibronectin

Titin (muscle tissue)

Amyloids (Alzheimer's disease)

Amyloid proteins (Alzheimer's disease)

Please see Fig. 8 from http://web.mit.edu/mbuehler/www/papers/final_JCTN_preprint.pdf.

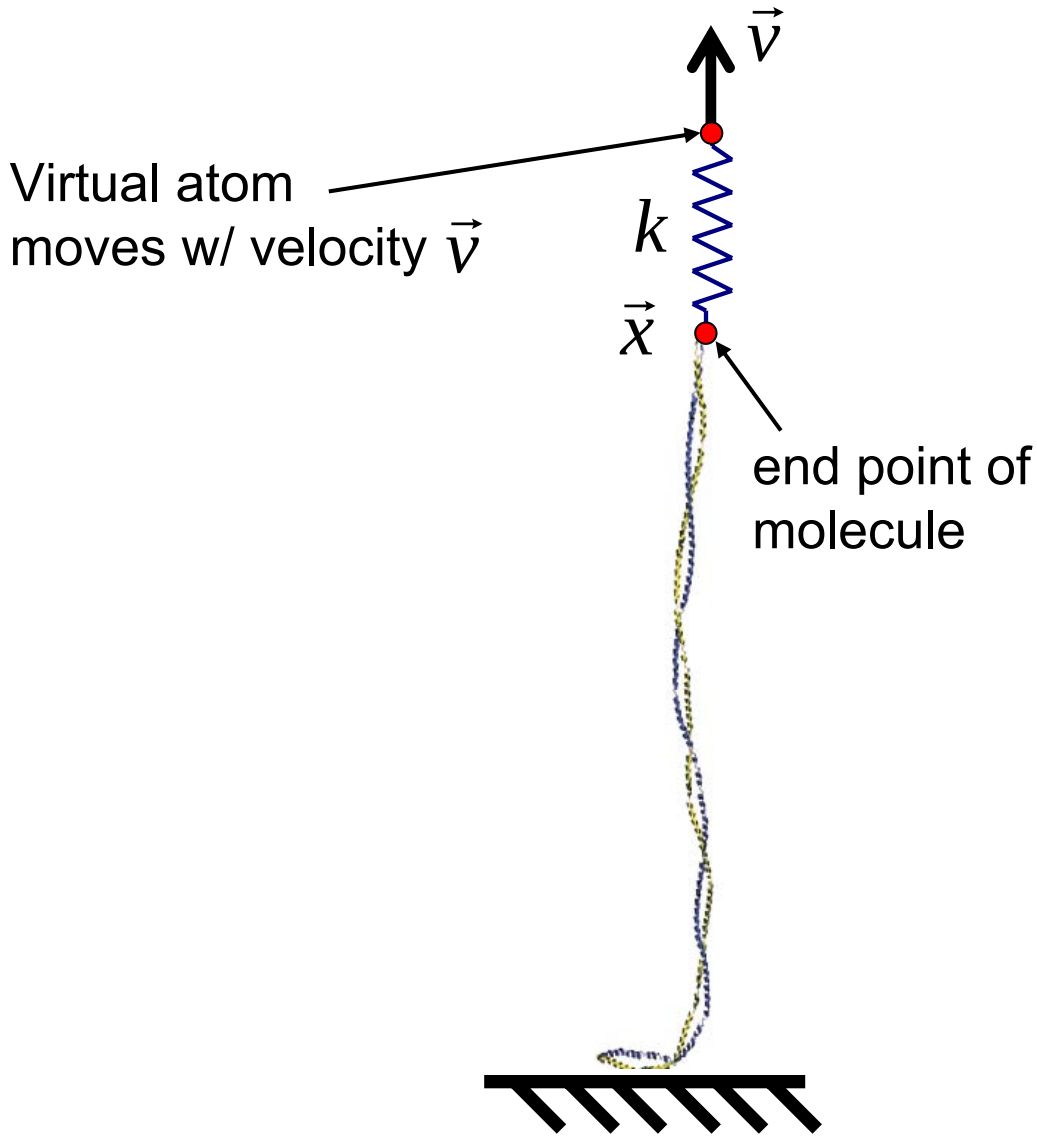
3. Fracture of protein domains – Bell model

How to apply load to a molecule

(in molecular dynamics simulations)

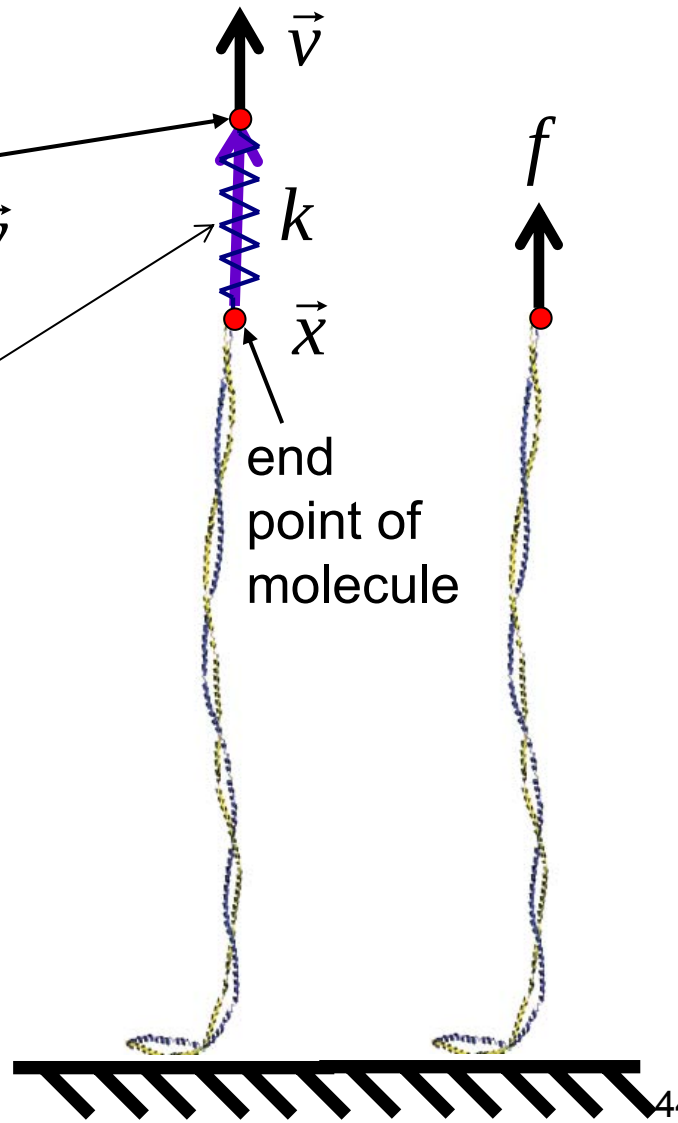
Steered molecular dynamics (SMD)

Steered molecular dynamics used to apply forces to protein structures



Steered molecular dynamics (SMD)

Steered molecular dynamics used to apply forces to protein structures



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

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

SMD spring constant

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

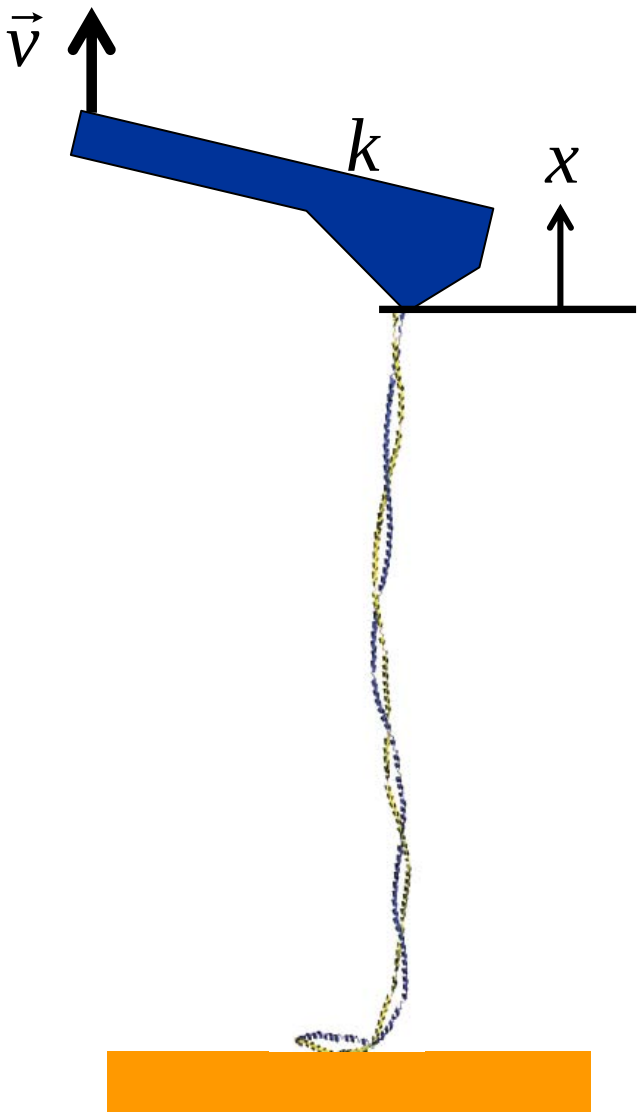
SMD deformation speed vector

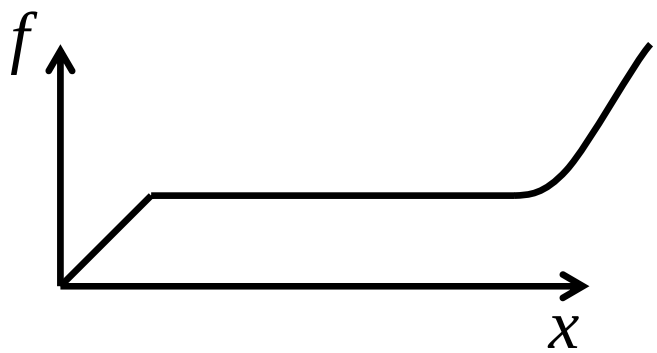
time

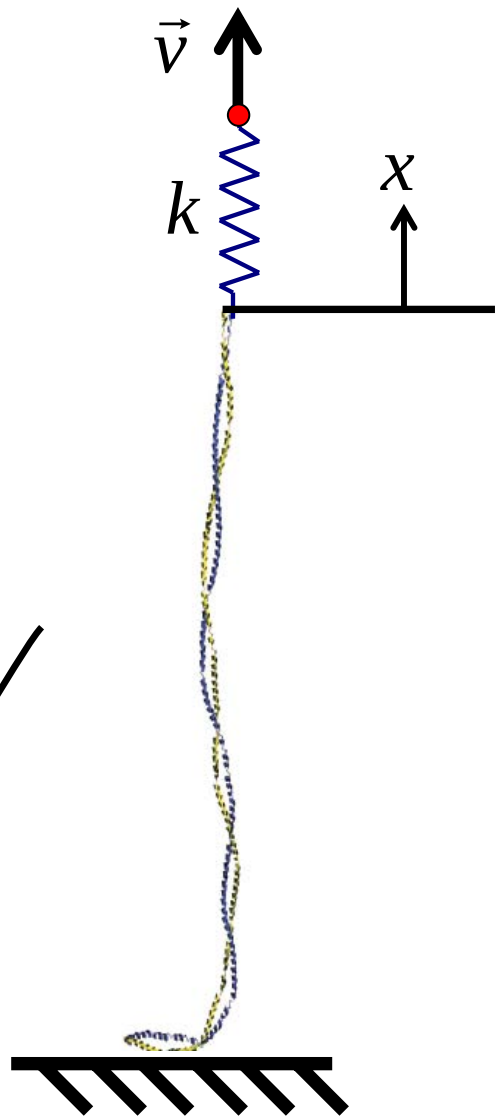
Distance between end point of molecule and virtual atom

SMD mimics AFM single molecule experiments

Atomic force microscope



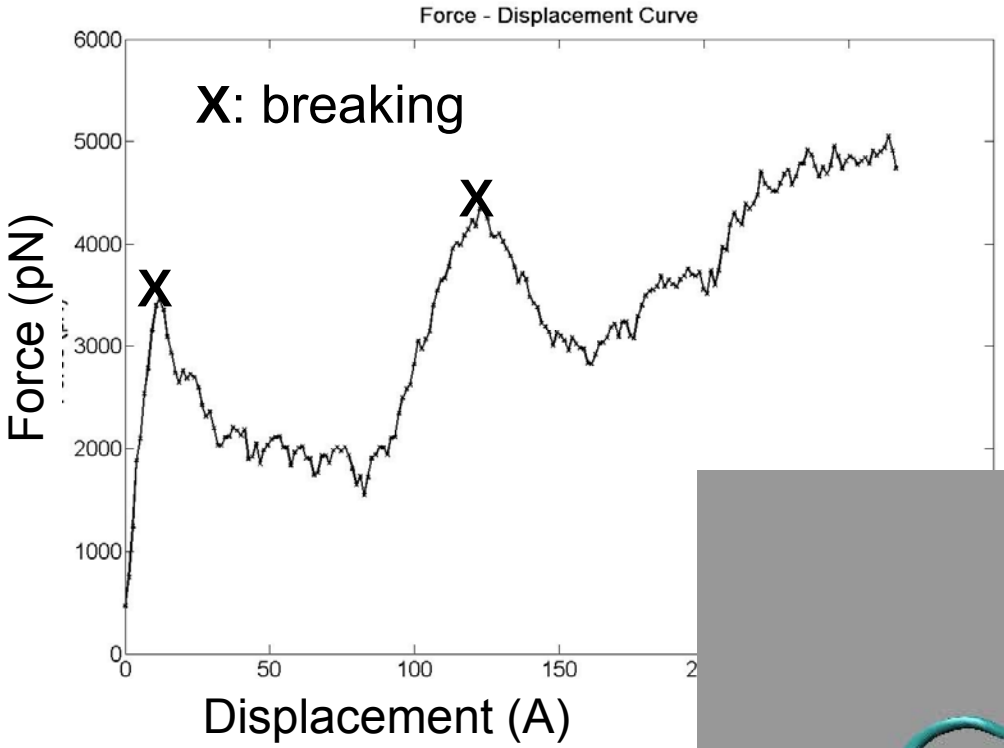




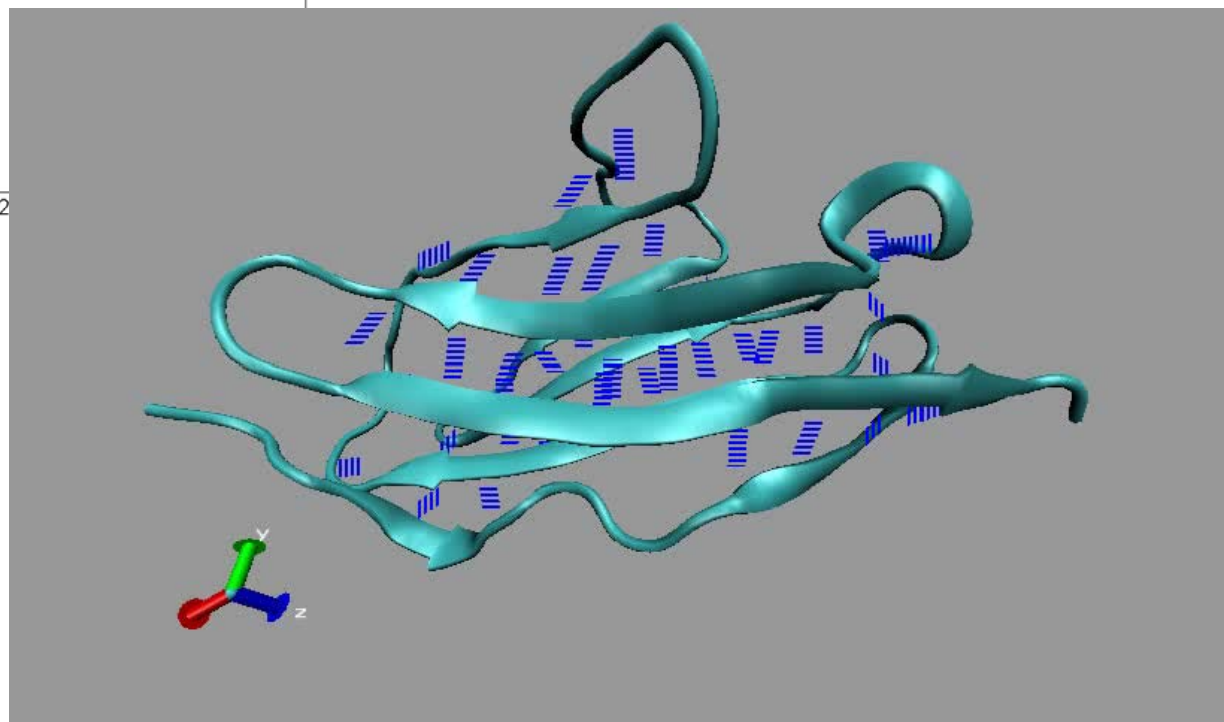
SMD is a useful approach to probe the nanomechanics of proteins (elastic deformation, "plastic" – permanent deformation, etc.)

Example: titin unfolding (CHARMM force field)

Unfolding of titin molecule

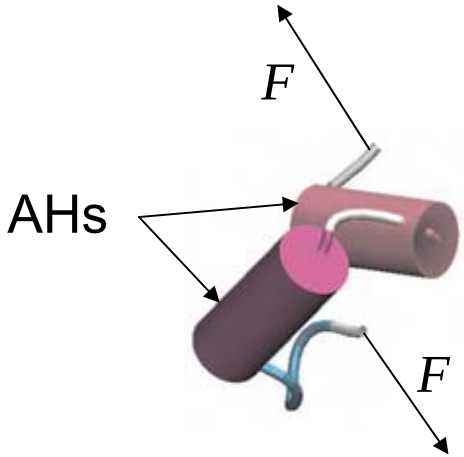


Titin I27 domain: Very resistant to unfolding due to parallel H-bonded strands

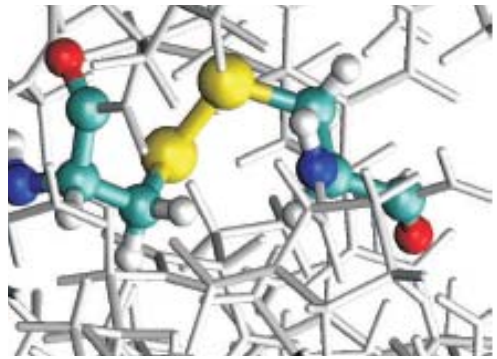


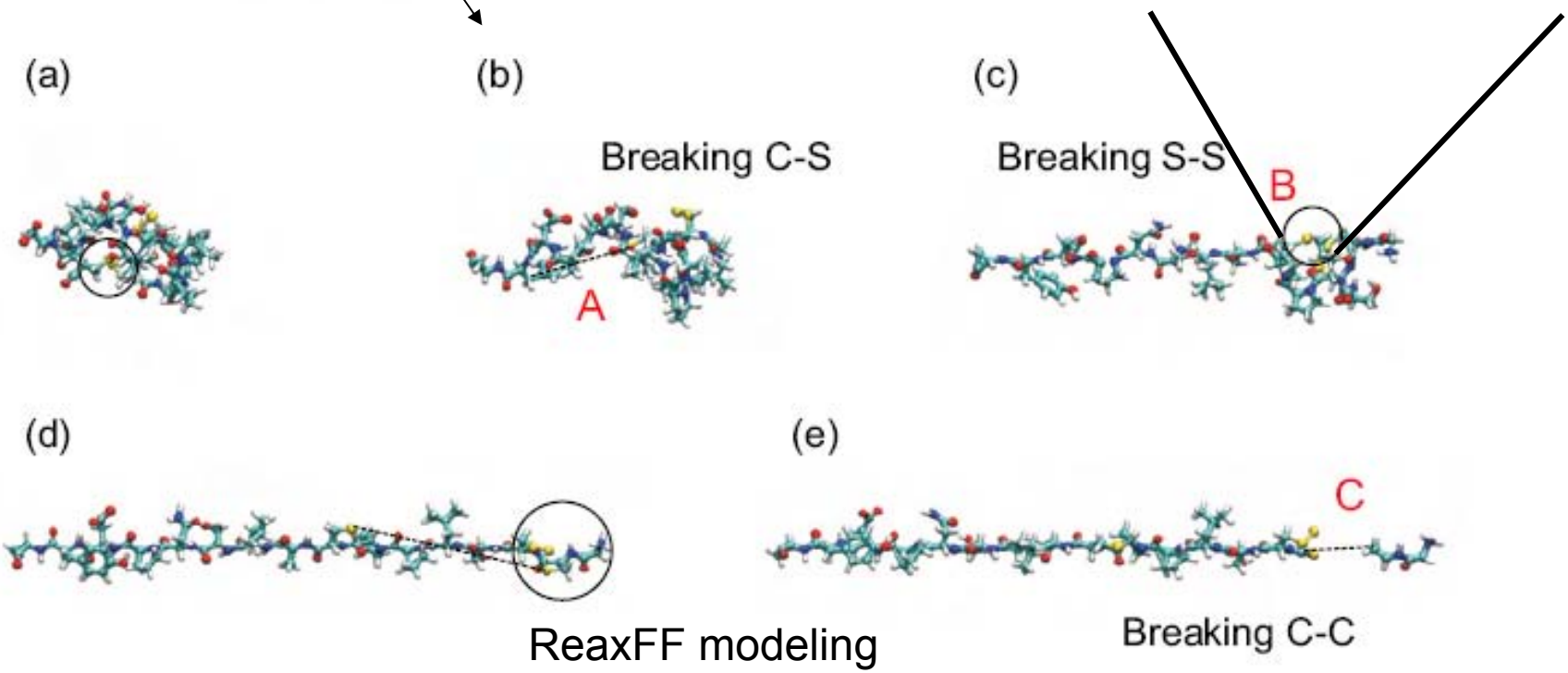
Keten and Buehler, 2007

Protein unfolding - ReaxFF



PnIB 1AKG

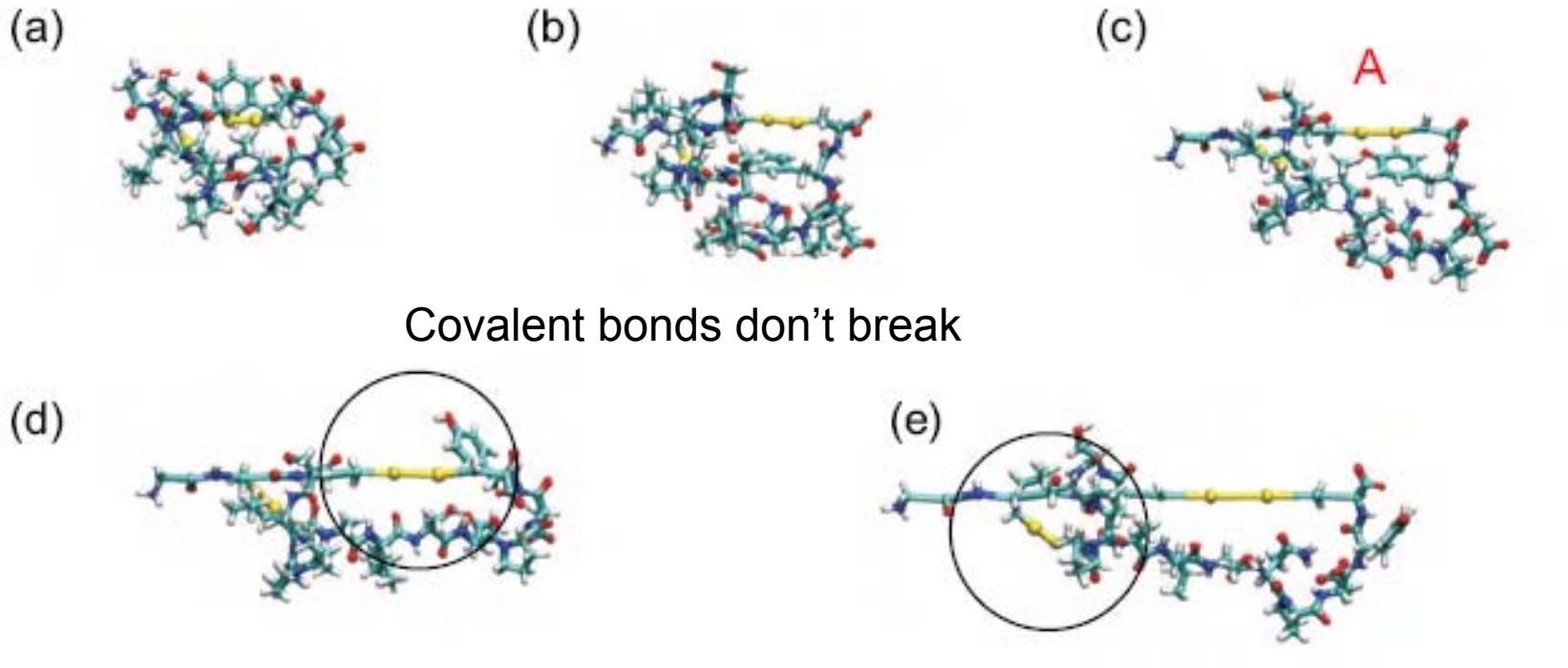




ReaxFF modeling

Buehler, M. "Hierarchical Chemo-nanomechanics of Proteins: Entropic Elasticity, Protein Unfolding and Molecular Fracture." Journal of Mechanics and Materials and Structures 2, no. 6 (2007).

Protein unfolding - CHARMM

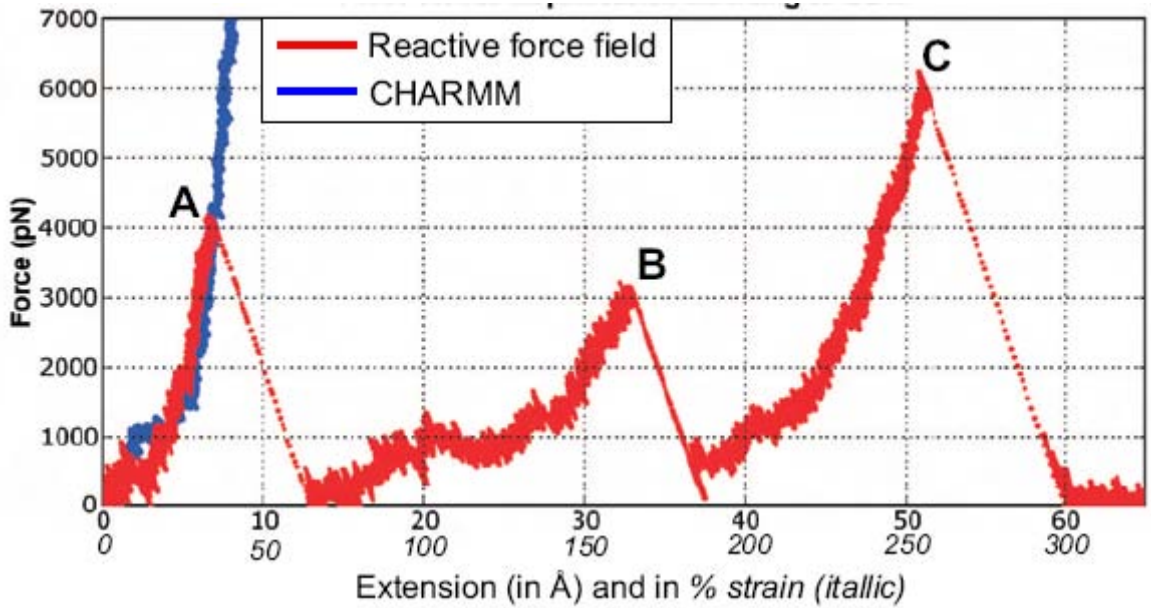


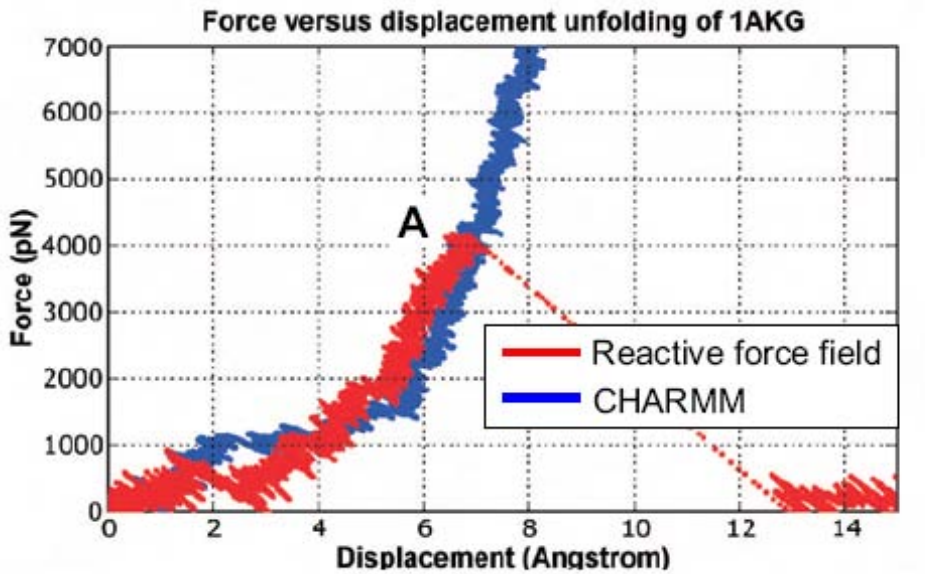
Covalent bonds don’t break

CHARMM modeling

Buehler, M. "Hierarchical Chemo-nanomechanics of Proteins: Entropic Elasticity, Protein Unfolding and Molecular Fracture." Journal of Mechanics and Materials and Structures 2, no. 6 (2007).

Comparison – CHARMM vs. ReaxFF

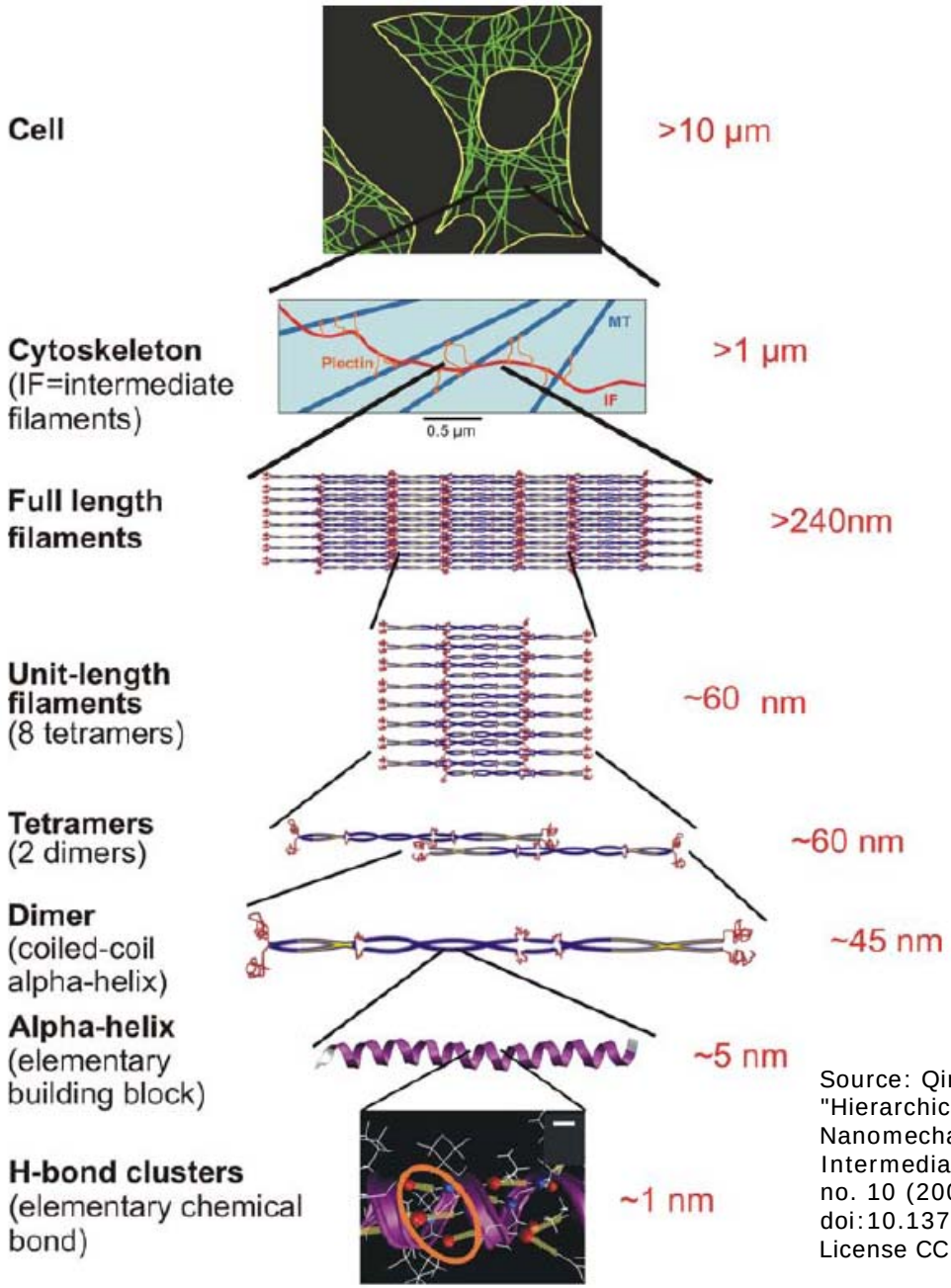




Buehler, M. "Hierarchical Chemo-nanomechanics of Proteins: Entropic Elasticity, Protein Unfolding and Molecular Fracture." Journal of Mechanics and Materials and Structures 2, no. 6 (2007).

Application to alpha-helical proteins

Vimentin intermediate filaments



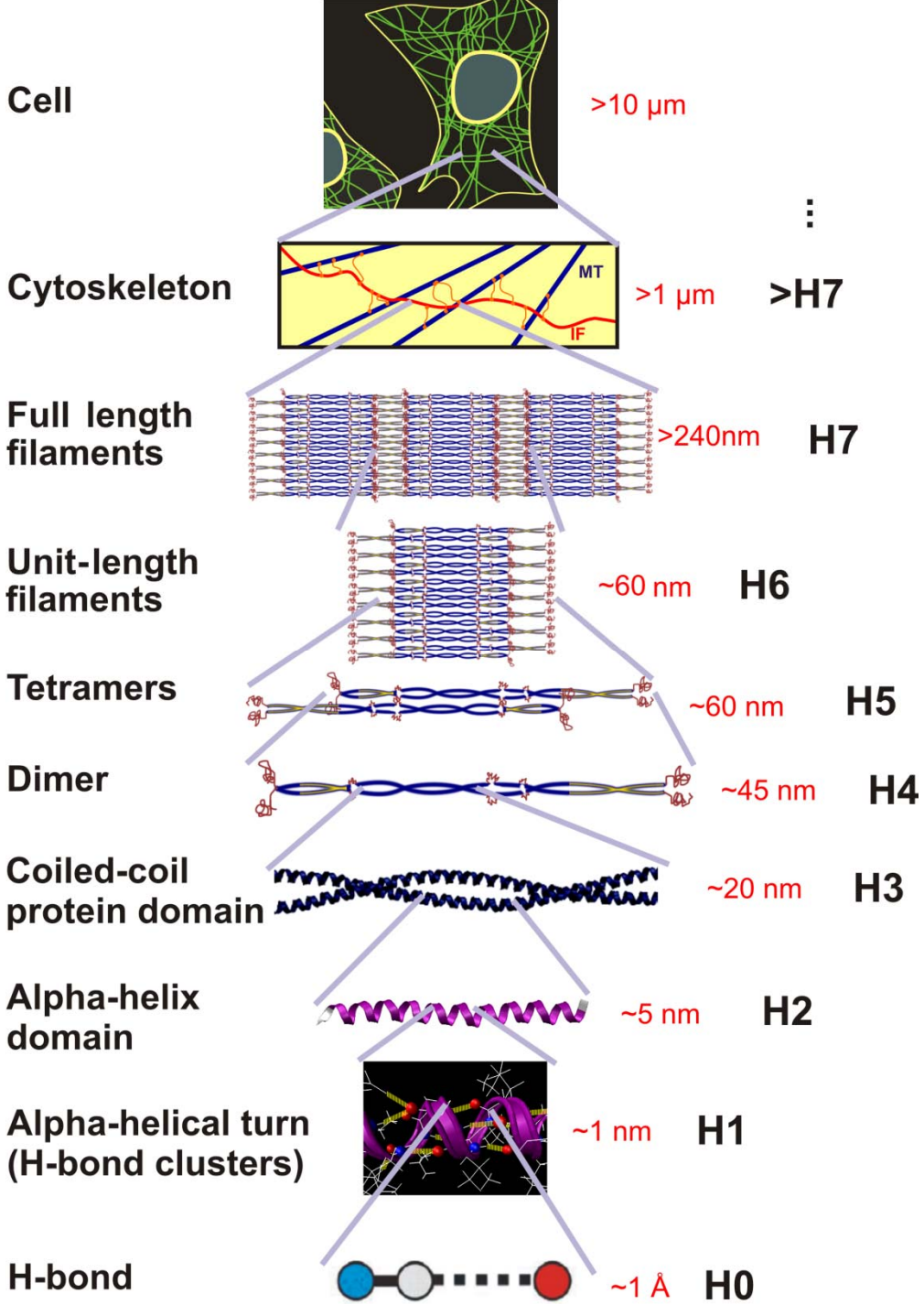
Source: Qin, Z., L. Kreplak, et al. "Hierarchical Structure Controls Nanomechanical Properties of Vimentin Intermediate Filaments." *PLoSONE* 4, no. 10 (2009). doi:10.1371/journal.pone.0007294. License CC BY.

Cells

Filaments

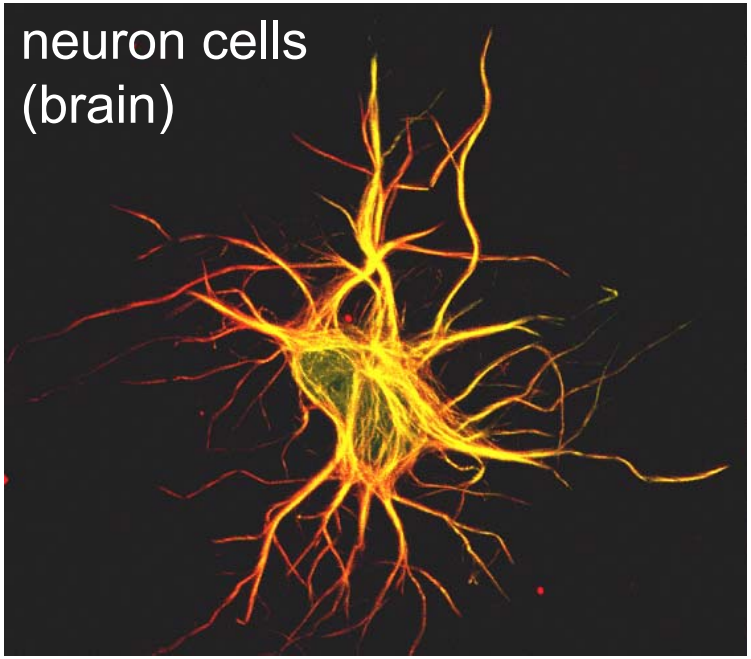
Protein molecule

Chemical bonding

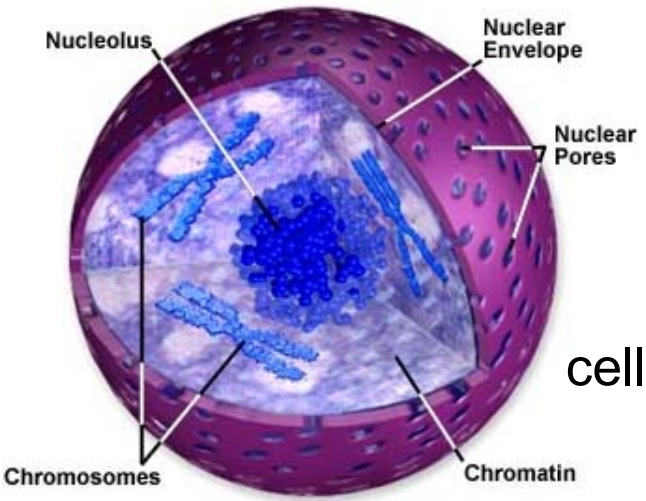


Vimentin intermediate filament

Intermediate filaments – occurrence

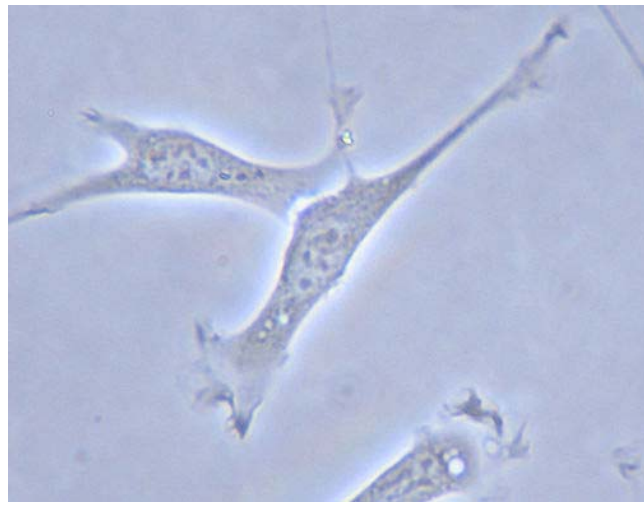


hair, hoof

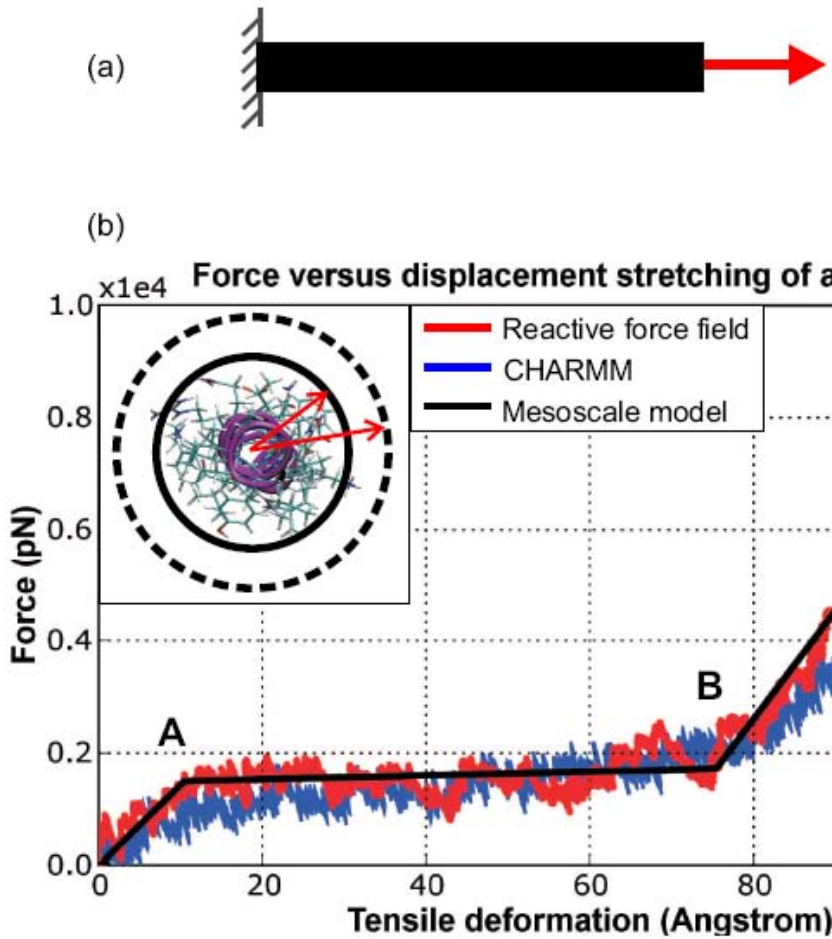


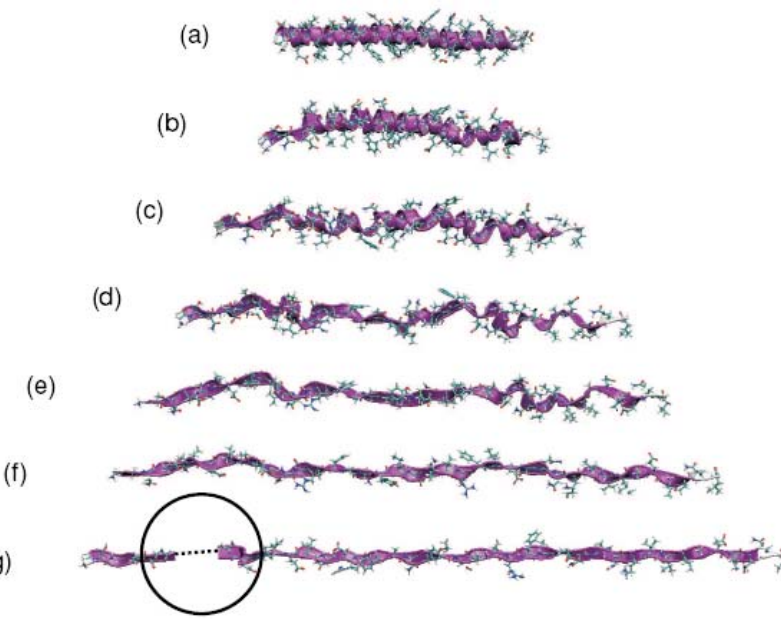
cell nucleus

fibroblast cells
(make collagen)



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

What about varying pulling speeds?

Variation of pulling speed

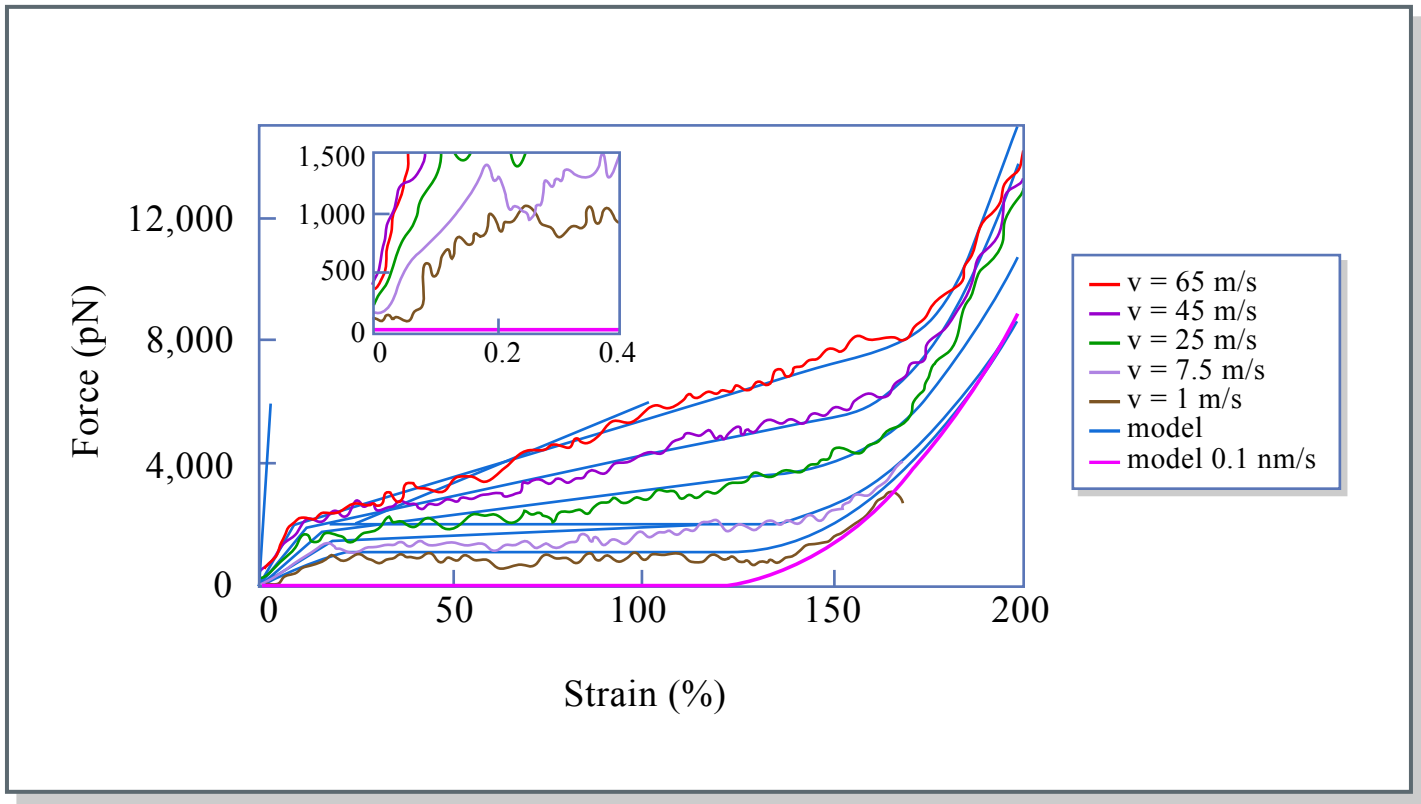
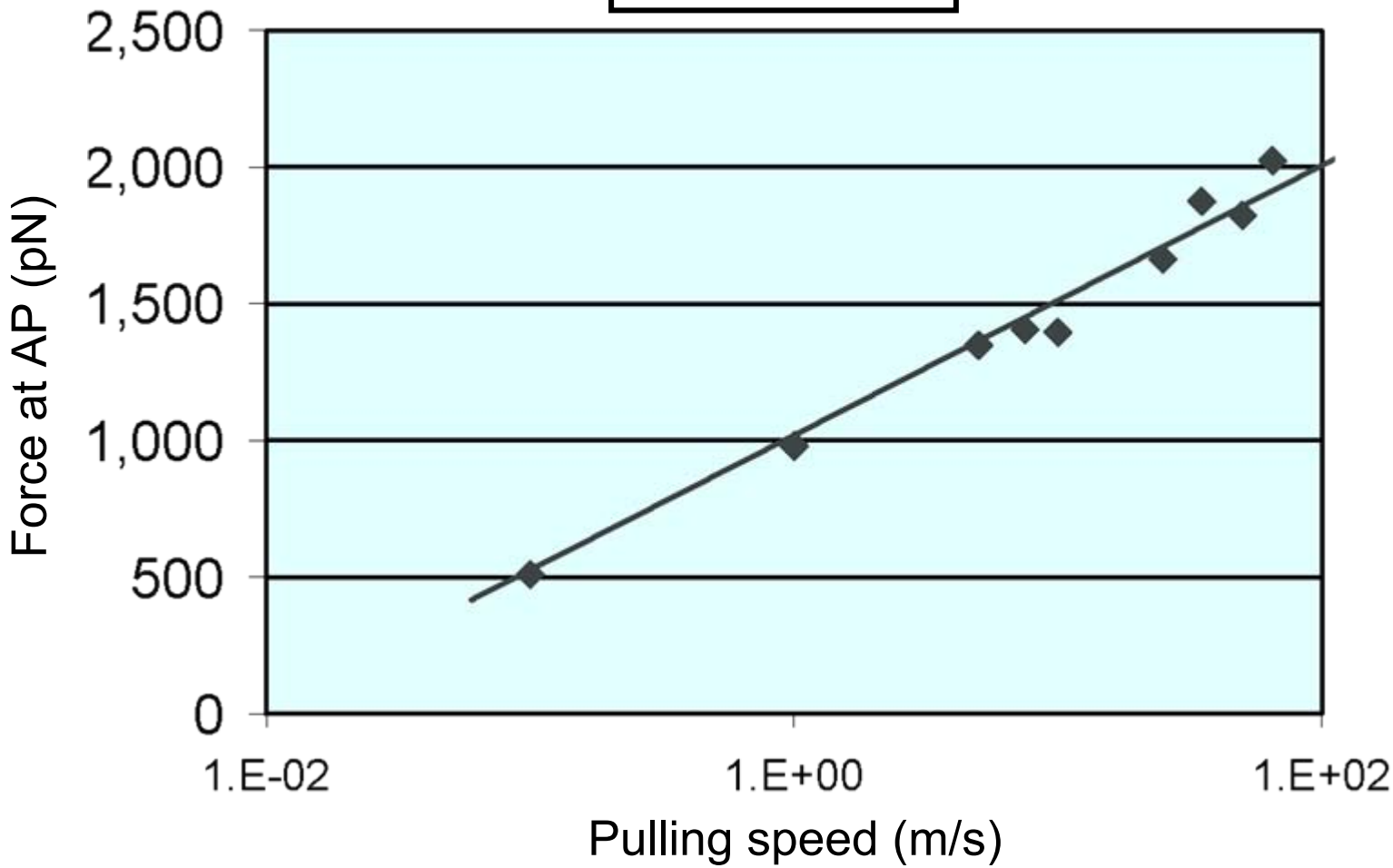


Image by MIT OpenCourseWare. After Ackbarow and Buehler, 2007.

Force at angular point f_{AP}=fracture force

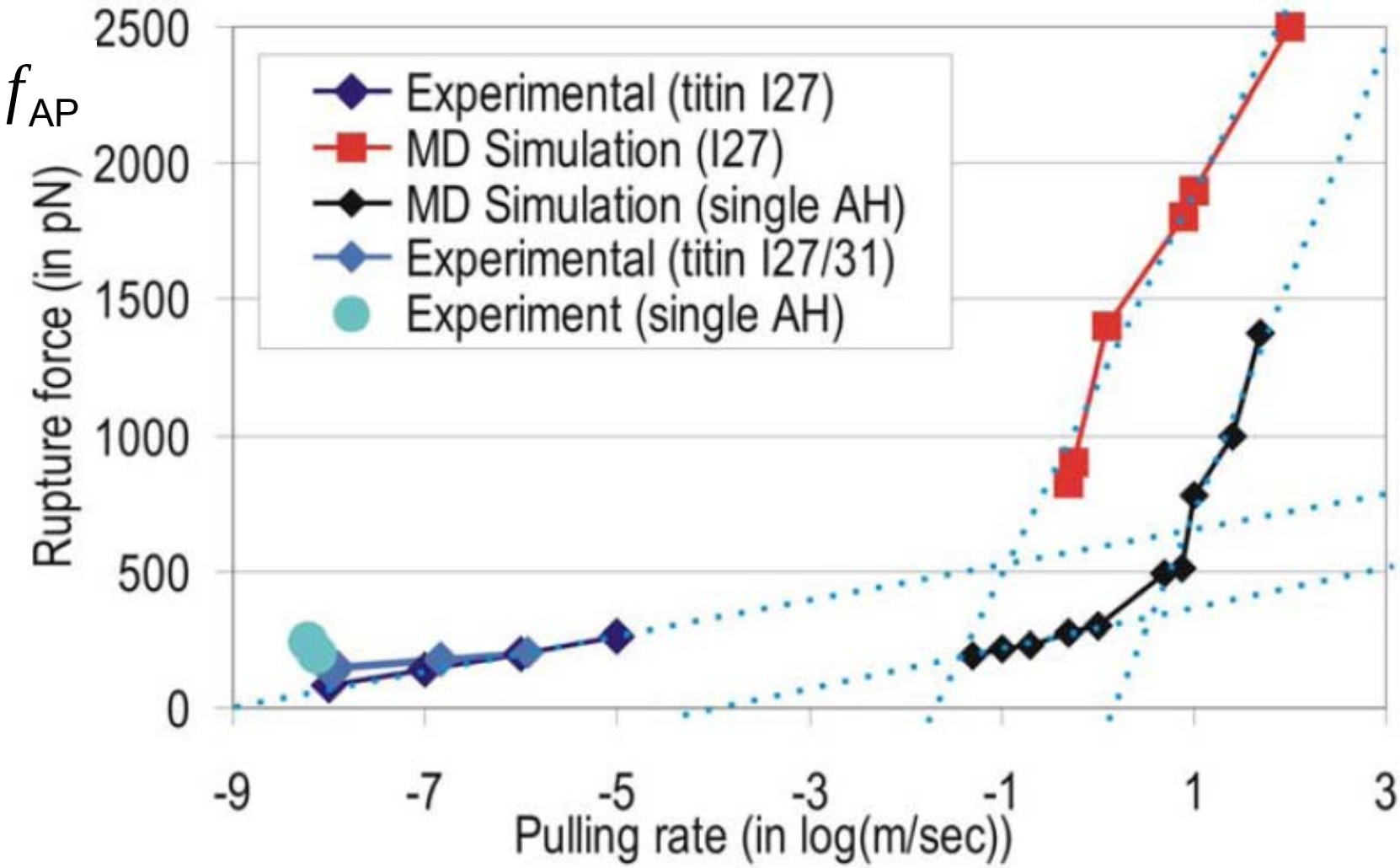
$$f_{AP} \sim \ln v$$



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

General results…

Rupture force vs. pulling speed



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

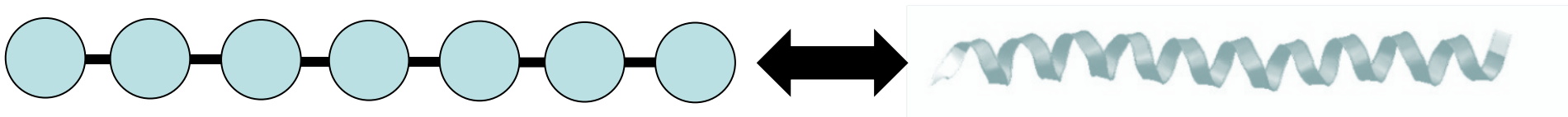
How to make sense of these results?

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

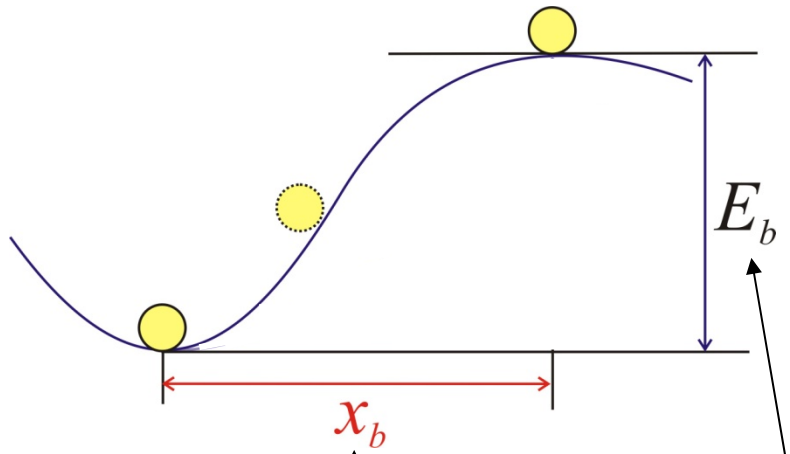
Probability for bond rupture (Arrhenius relation)

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

Boltzmann constant

temperature

"bond"



distance to energy barrier

height of energy barrier

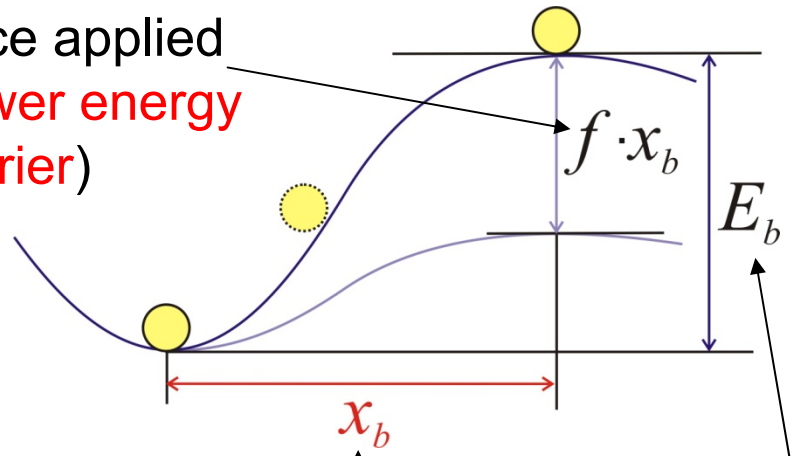
Bell model

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

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

Boltzmann constant

temperature



distance to energy barrier

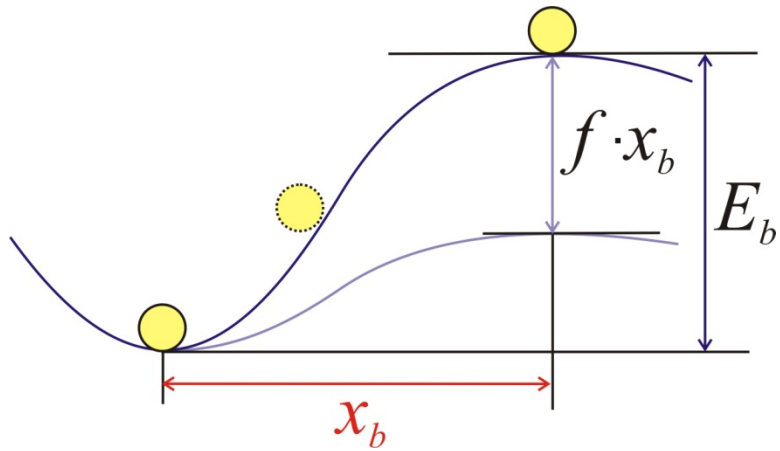
height of energy barrier

"bond"

Bell model

Probability for bond rupture (Arrhenius relation)

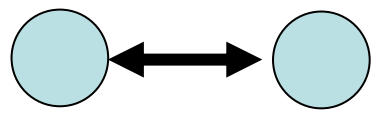
$$p = \exp\left(-\frac{E_b - f \cdot x_B}{k_B T}\right)$$



Off-rate = probability times vibrational frequency

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

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

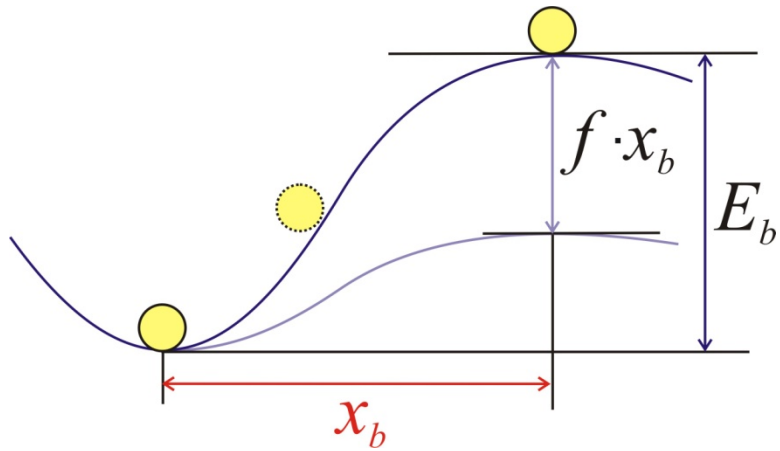


bond vibrations

Bell model

Probability for bond rupture (Arrhenius relation)

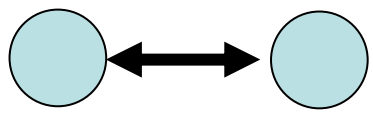
$$p = \exp\left(-\frac{E_b - f \cdot x_B}{k_B T}\right)$$



Off-rate = probability times vibrational frequency

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

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



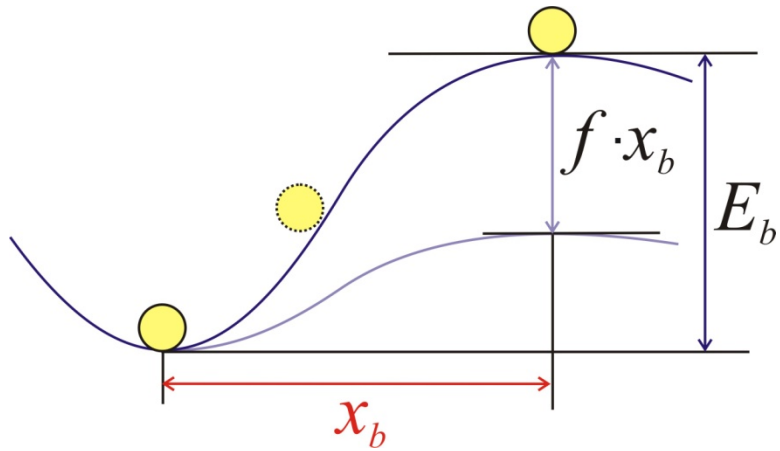
bond vibrations

"How often bond breaks per unit time"

Bell model

Probability for bond rupture (Arrhenius relation)

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

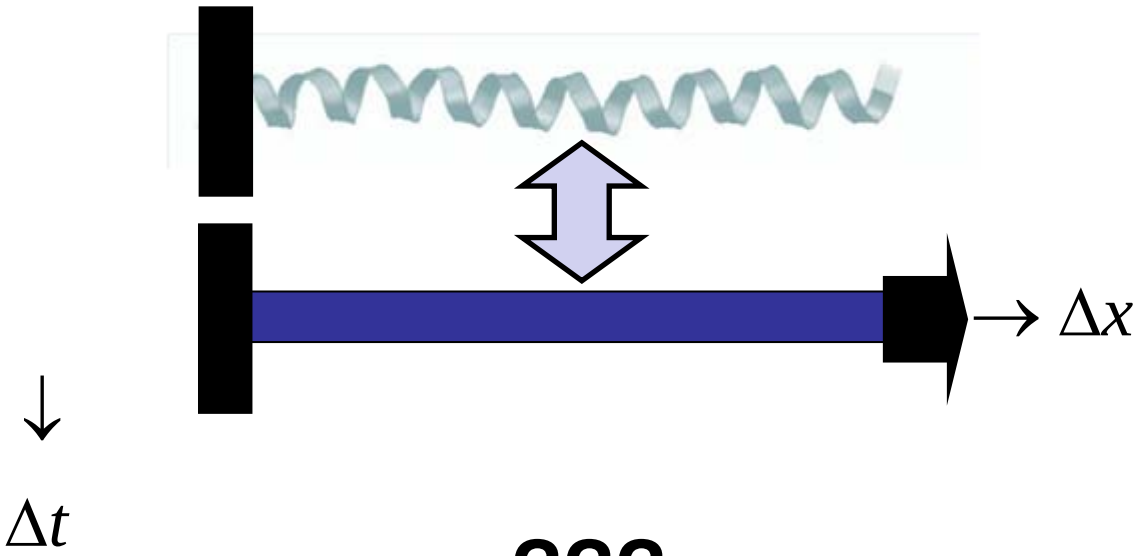


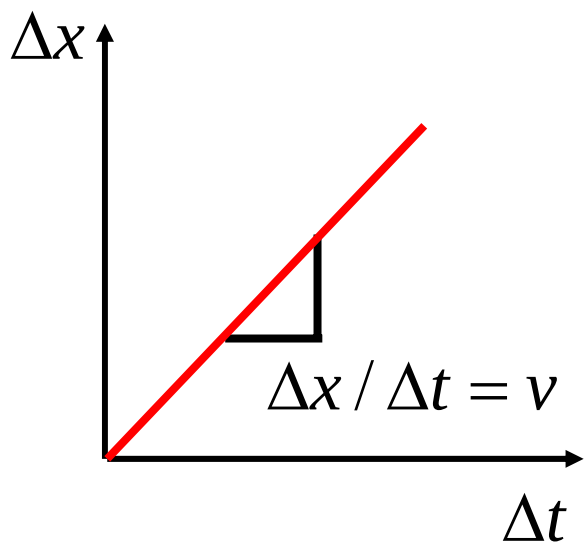
Off-rate = probability times vibrational frequency

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

τ = bond lifetime
(inverse of off-rate)

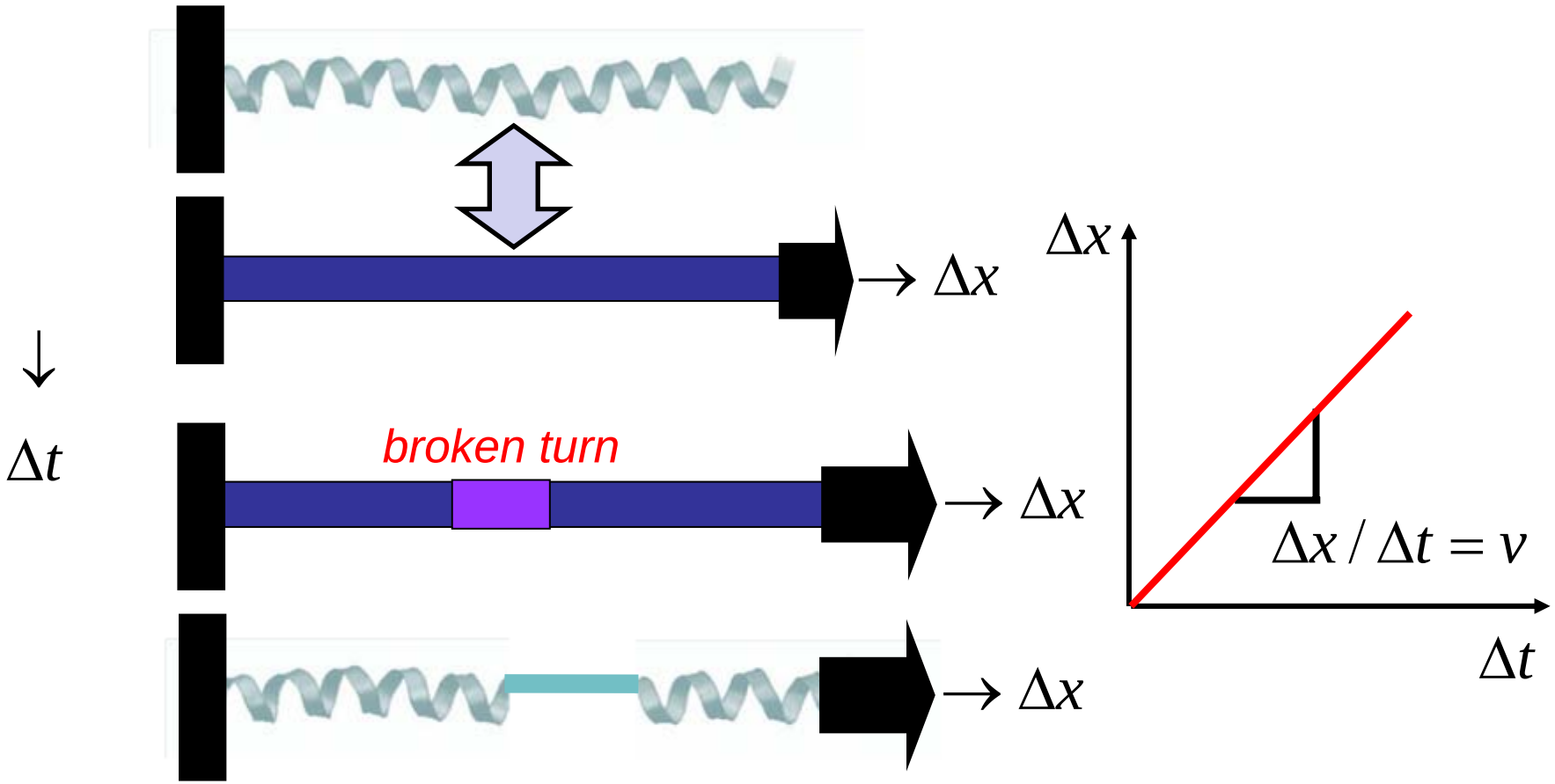
Bell model





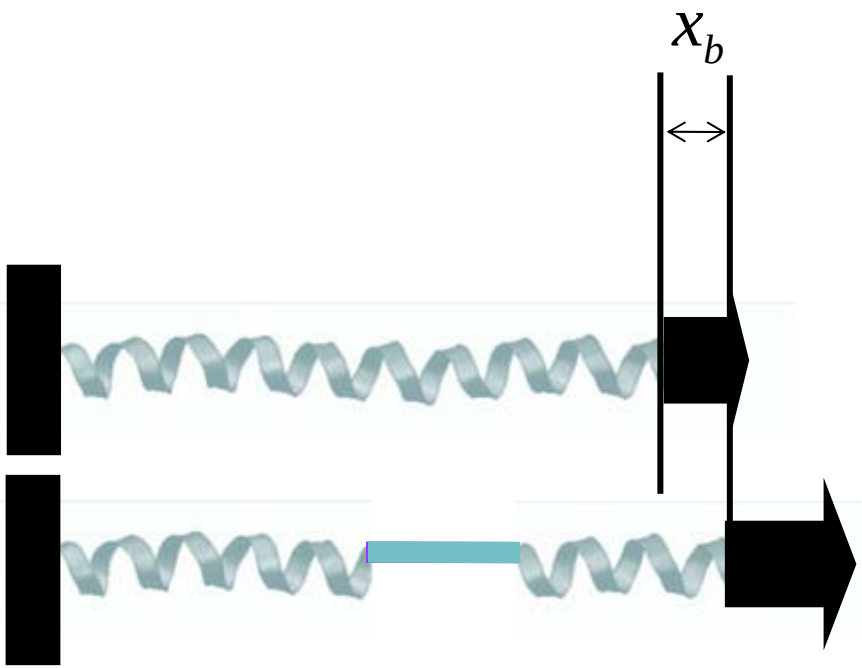
$\Delta x / \Delta t = v$ pulling speed (at end of molecule)

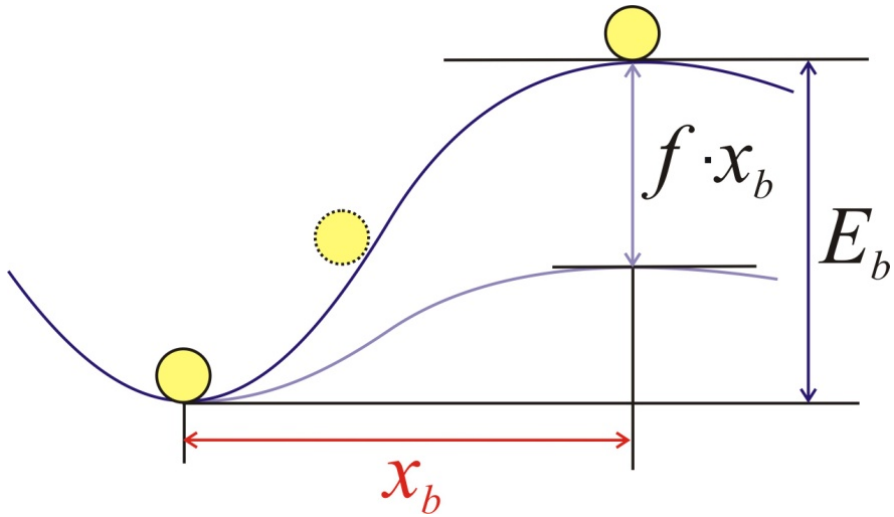
Bell model



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

Structure-energy landscape link

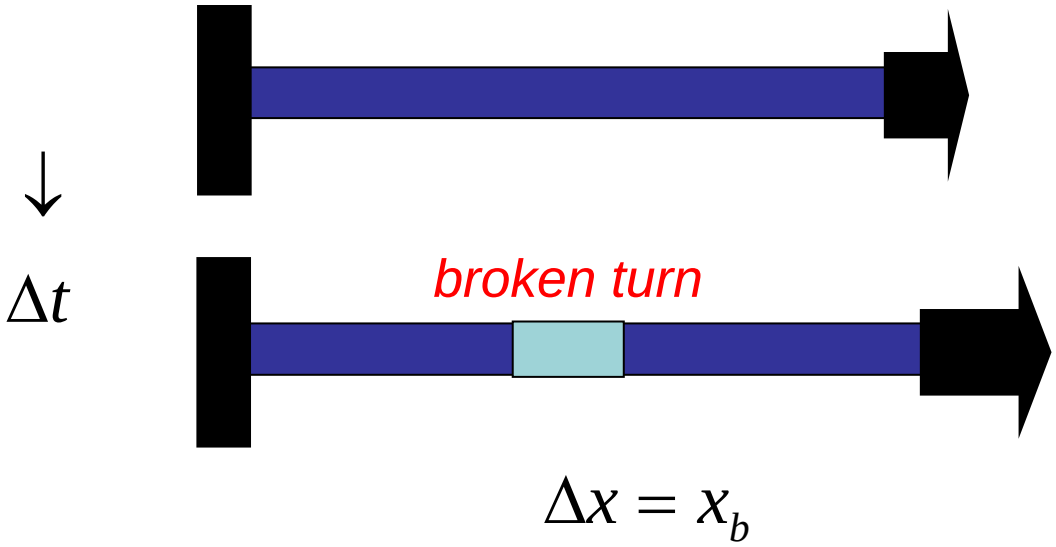


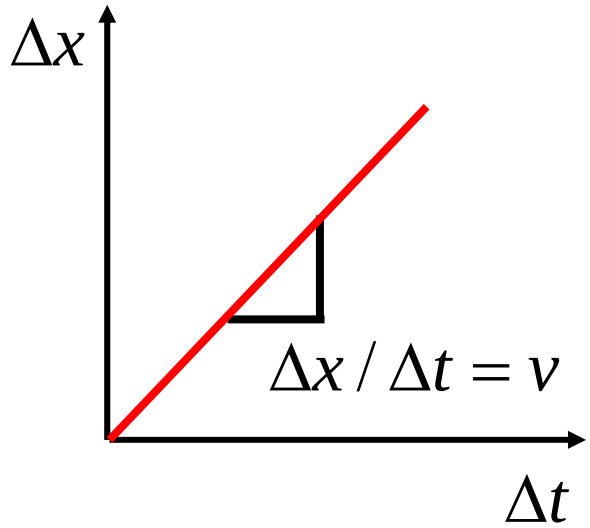


$$\Delta x = x_b$$

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

Bell model





Bond breaking at x_b (lateral applied displacement):

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

$\chi = 1/\tau$

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

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

Solve this expression for f:

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

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

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

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

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

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

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

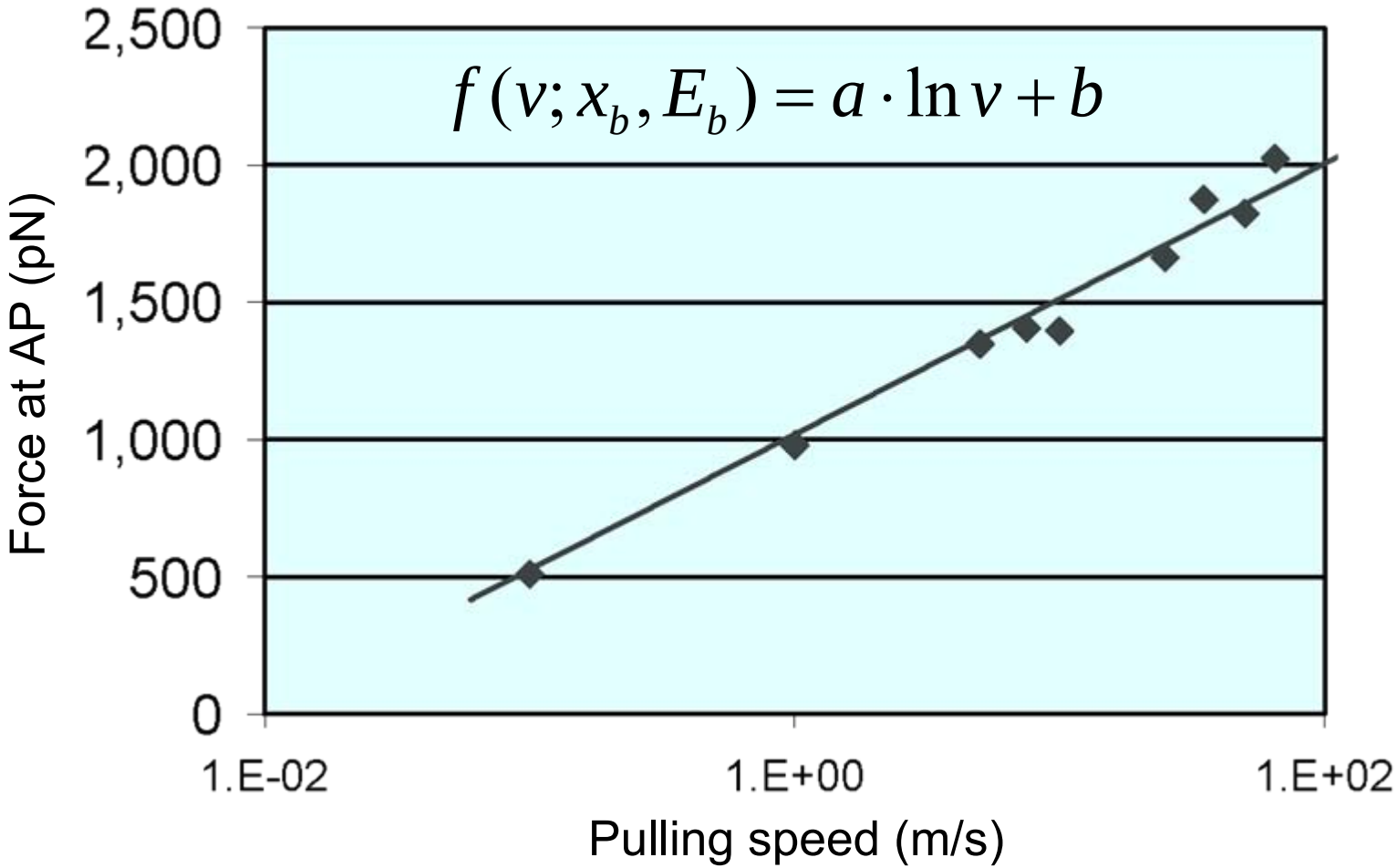
Results in:

$$f(\nu; x_b, E_b) = \frac{k_b \cdot T}{x_b} \cdot \ln \nu - \frac{k_b \cdot T}{x_b} \cdot \ln \nu_0 = a \cdot \ln \nu + b$$

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

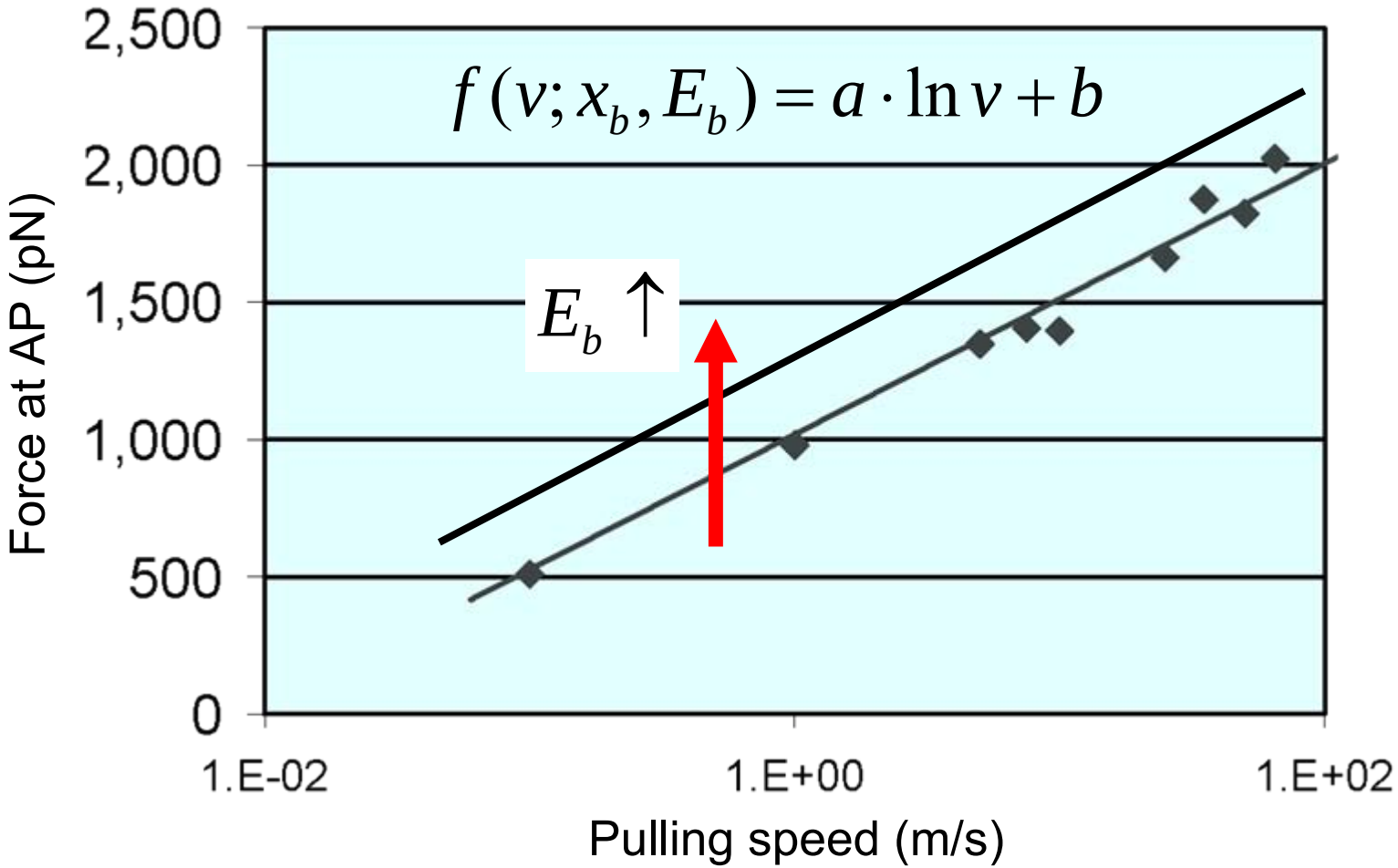
$$b = -\frac{k_B \cdot T}{x_b} \cdot \ln \nu_0$$

$f \sim \ln v$ behavior of strength



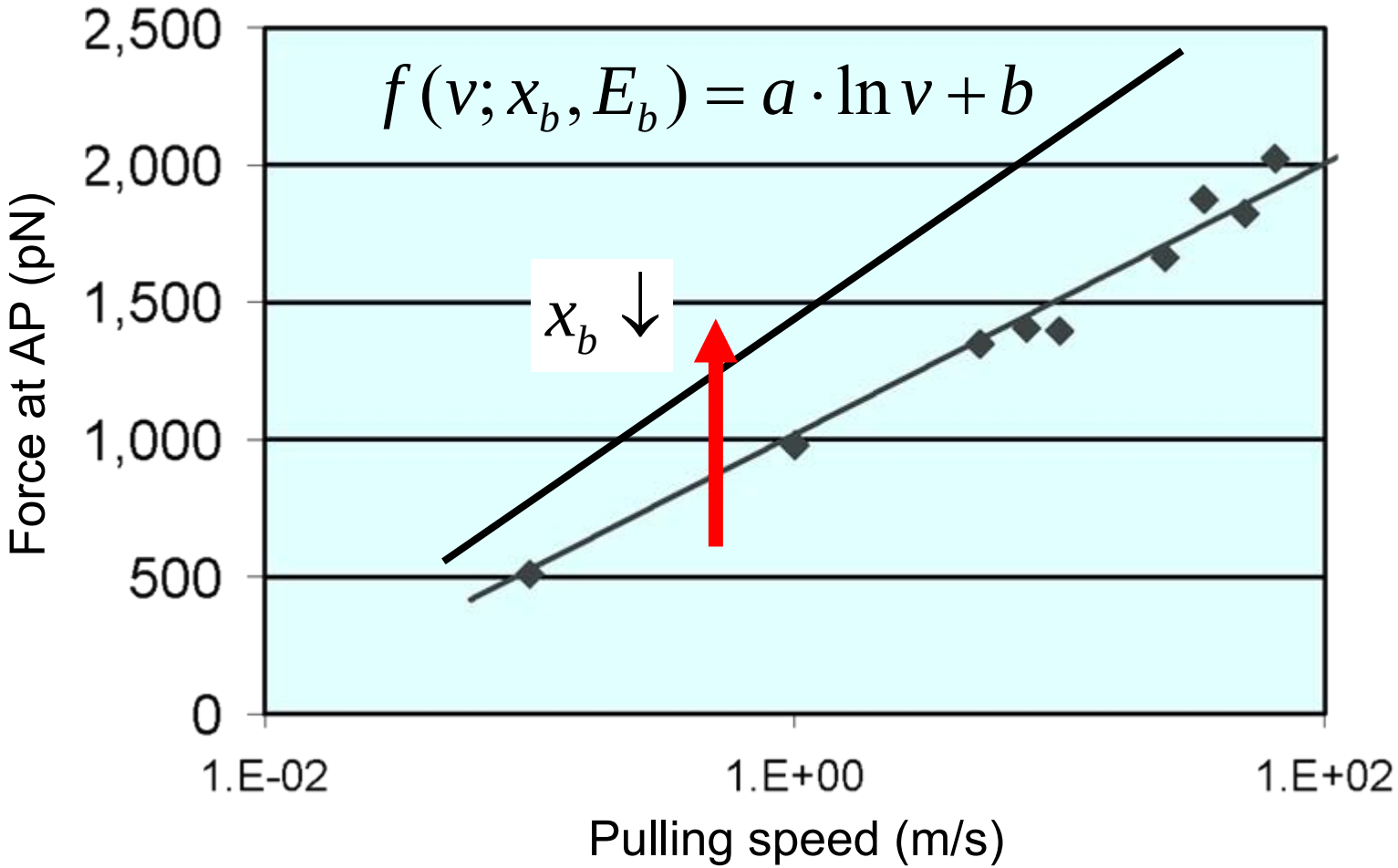
E_b= 5.6 kcal/mol and x_b= 0.17 Å (results obtained from fitting to the simulation data)

Scaling with E_b: shifts curve



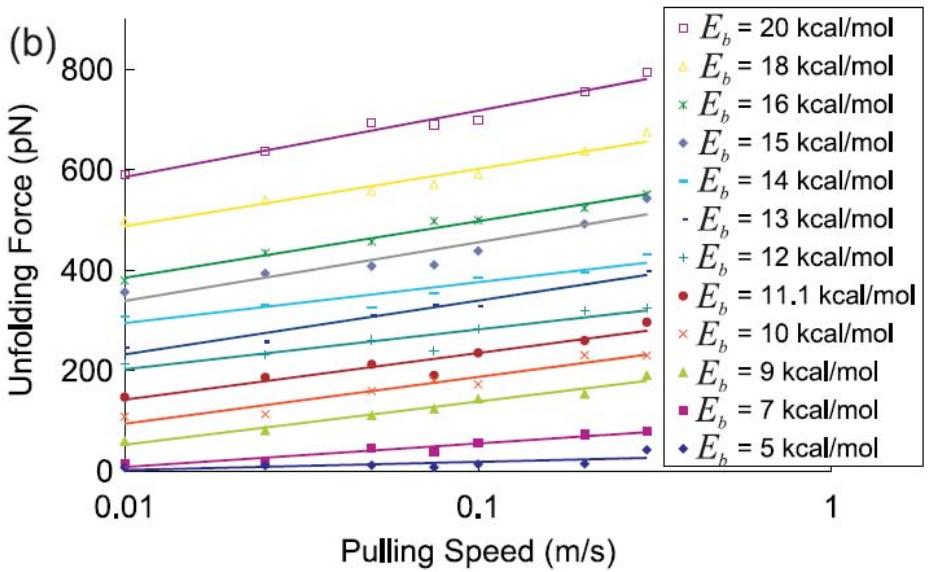
$$a = \frac{k_B \cdot T}{x_b} \qquad b = -\frac{k_B \cdot T}{x_b} \cdot \ln \nu_0 \qquad \nu_0 = \omega_0 \cdot x_b \cdot \exp\left(-\frac{E_b}{k_b \cdot T}\right)$$

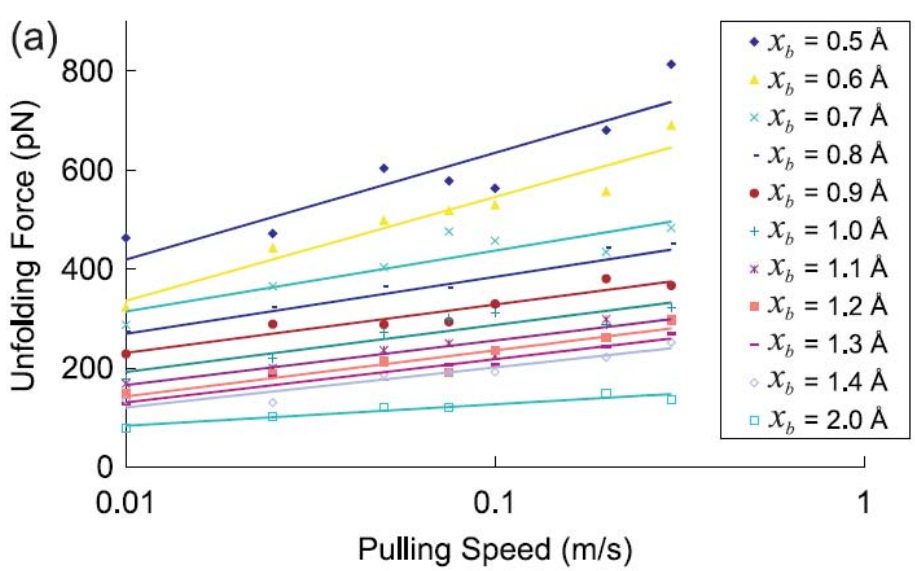
Scaling with x_b: changes slope

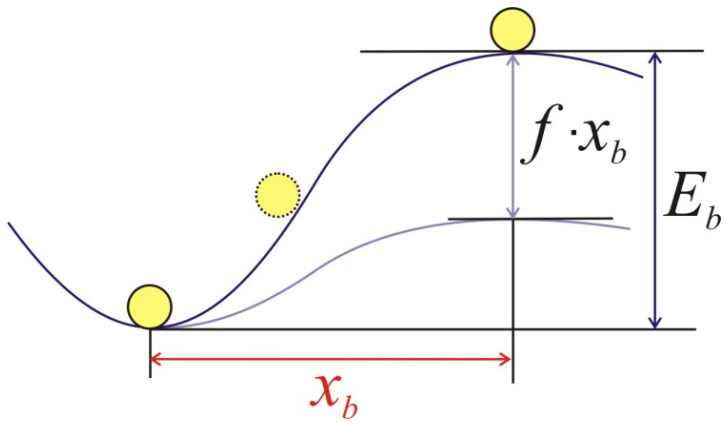


$$a = \frac{k_B \cdot T}{x_b} \qquad b = -\frac{k_B \cdot T}{x_b} \cdot \ln v_0 \qquad v_0 = \omega_0 \cdot x_b \cdot \exp\left(-\frac{E_b}{k_b \cdot T}\right)$$

Simulation results





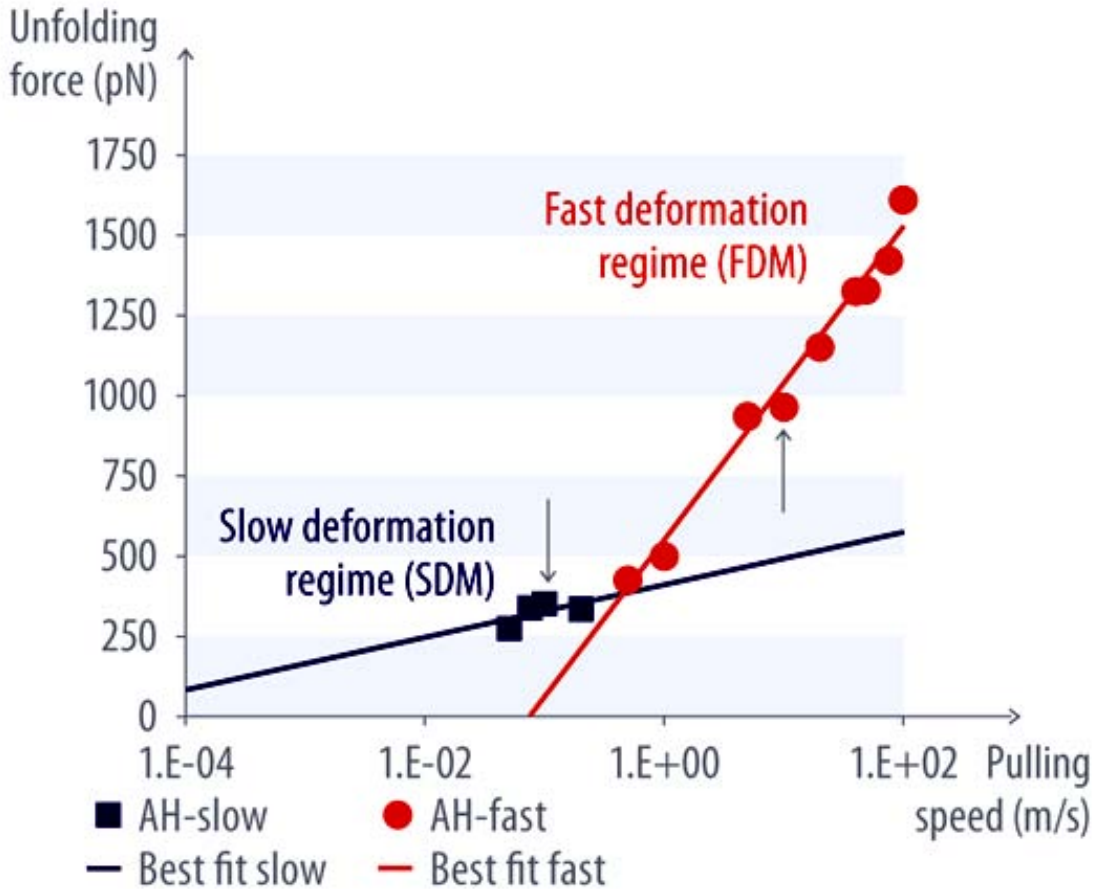


Bertaud, Hester, Jimenez, and Buehler, *J. Phys. Cond. Matt.,* 2010

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)

Analysis of energy landscape parameters

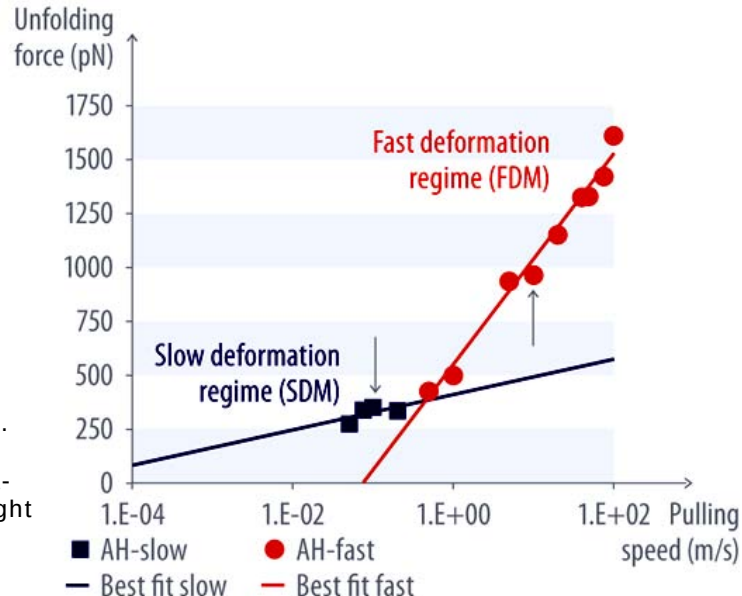
Table 1. Summary of the differences between the SDM and FDM, for AH1, AH2, and BS

	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

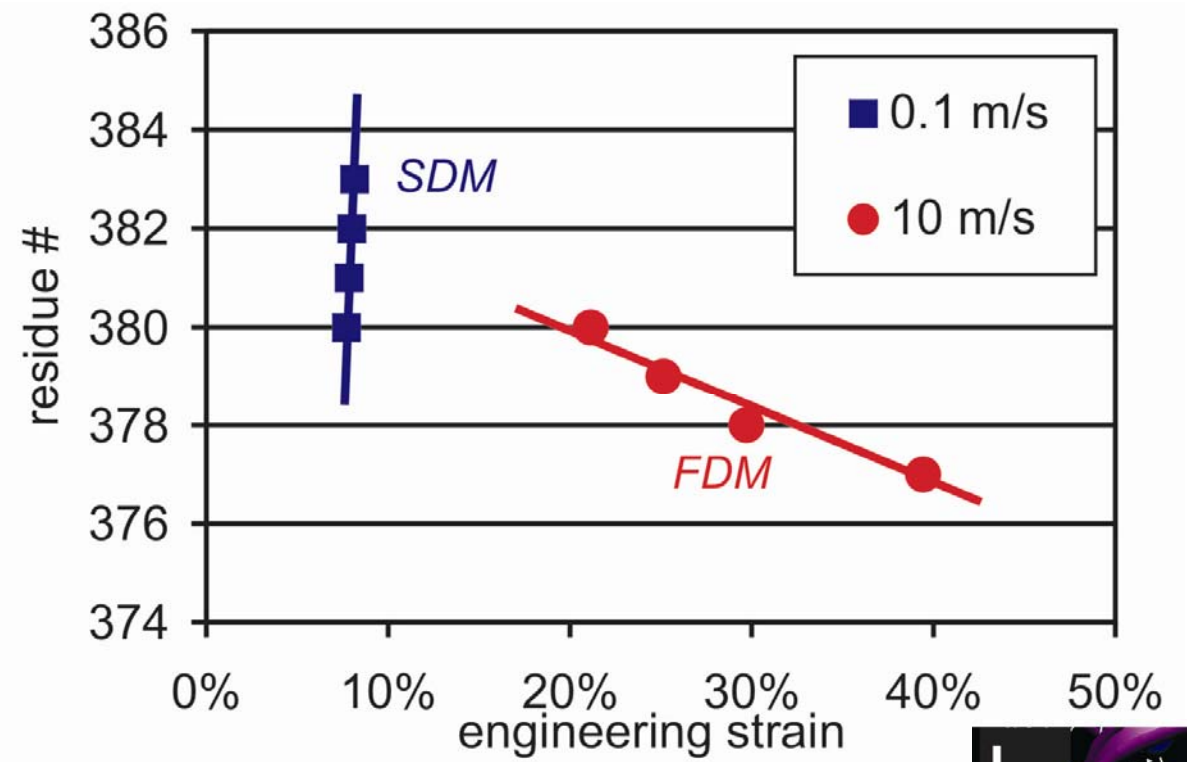
The values in parentheses in the AH columns represent the results for AH2.

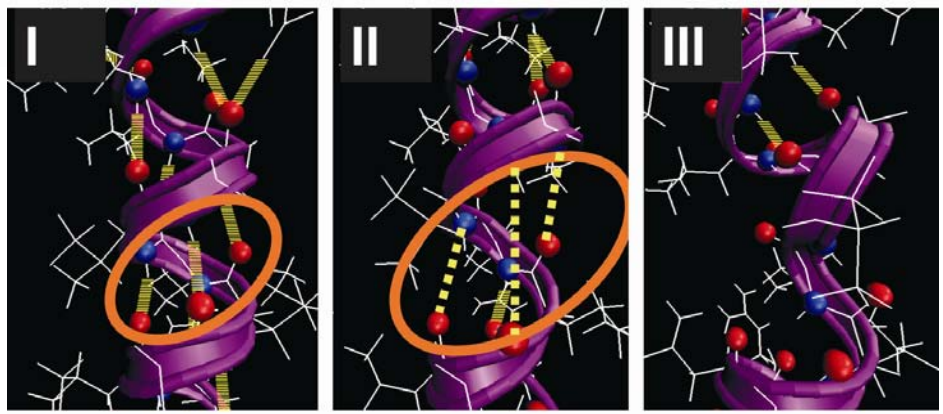
Energy single H-bond: ≈3-4 kcal/mol

What does this mean???

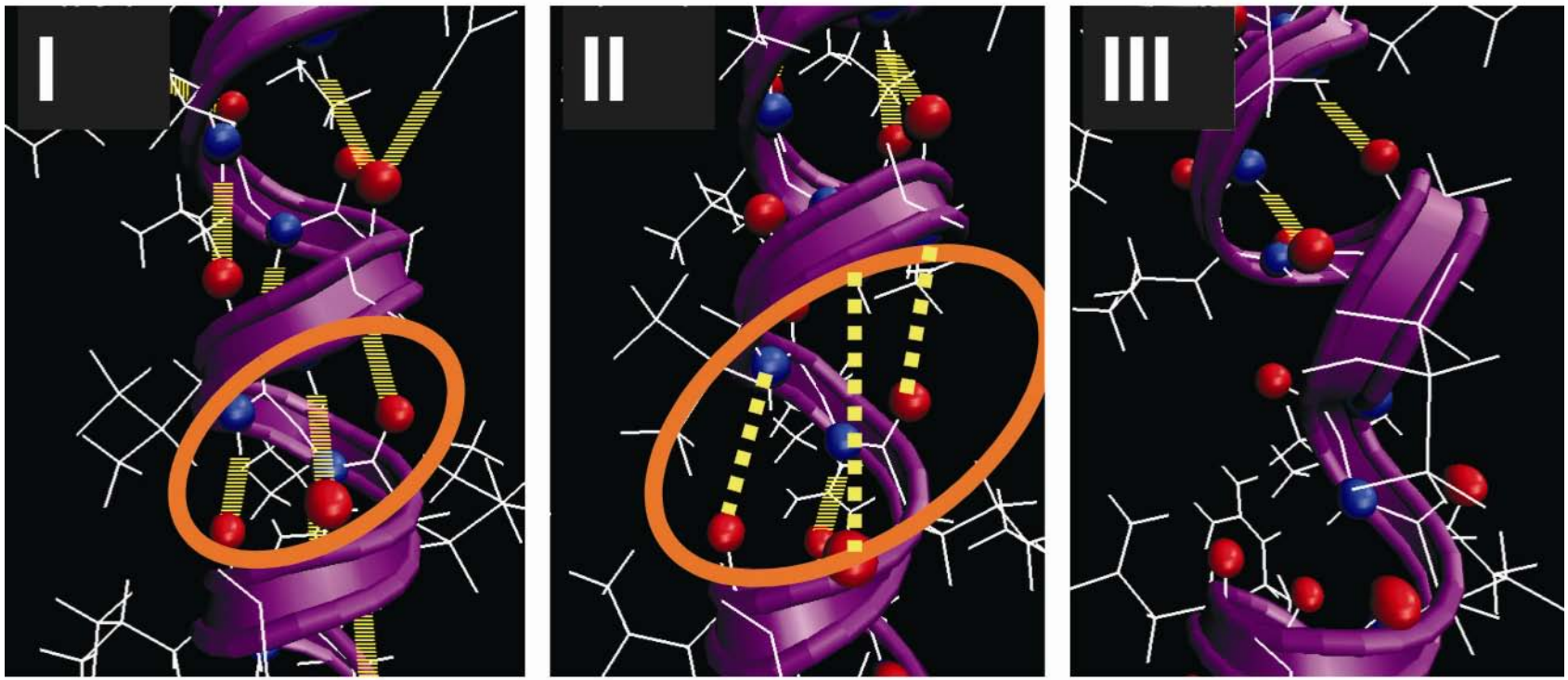


H-bond rupture dynamics: mechanism





H-bond rupture dynamics: mechanism



I: All HBs are intact

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

III: Rest of the AH relaxes – slower deformation…

3.021J / 1.021J / 10.333J / 18.361J / 22.00J Introduction to Modeling and Simulation
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