

1.021, 3.021, 10.333, 22.00 Introduction to Modeling and Simulation
Spring 2018

How to model chemical interactions (cont'd)

Lecture 8

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Massachusetts Institute of Technology

Content overview

I. Fundamentals of particle methods

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

Lectures 1-12

February/March

II. Advanced topics in particle methods

1. Quantum Weirdness: The Theory of Quantum Mechanics
2. The Many-Body Problem: From Many-Body to Single-Particle
3. Quantum modeling of materials
4. From Atoms to Solids
5. Basic properties of materials
6. Advanced properties of materials
7. Materials Informatics

Lectures 13-24

March/April/May

Lecture 8: How to model chemical interactions

Outline:

1. Force fields for proteins (and polymers)
2. Molecular mechanics of proteins
 - 2.1 How to apply load to a molecule

Goal of today's lecture:

- Learn how to develop force fields for proteins and similar materials
- Develop and apply tools in molecular mechanics

Overview: potential energy models

↑ Computational efficiency

— Increased accuracy & “transferability” —

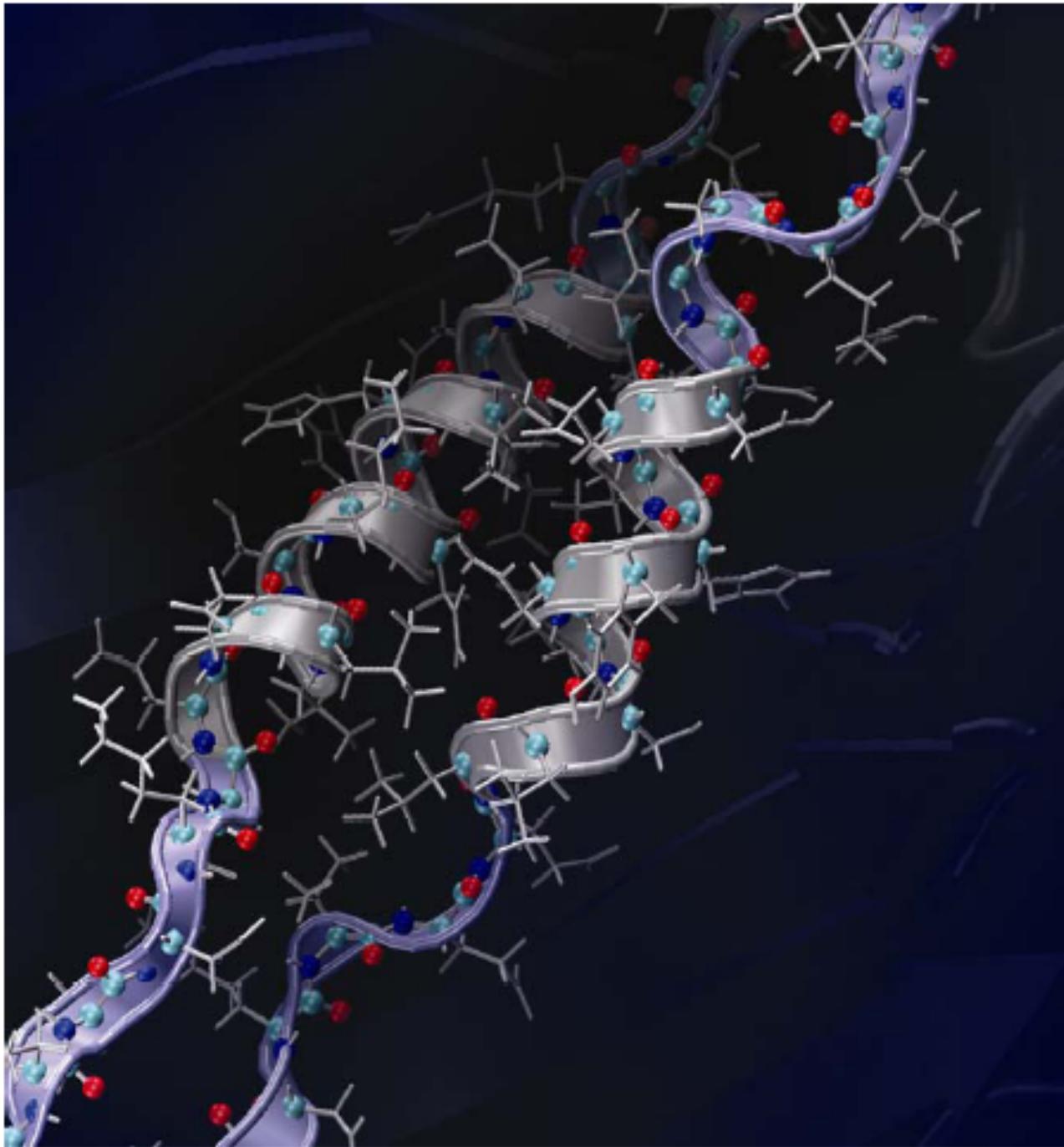
- Empirical models: mathematical functions with parameters (fitted to experiment or quantum mechanics)
 - Pair potentials (LJ, Morse, Buck., harmonic)
 - Embedded atom models/effective medium theories
 - Multi-body potentials (e.g. Tersoff, CHARMM, etc.)
 - Reactive potentials (ReaxFF)
- Semi-empirical models (explicitly note electronic structure)
 - Tight binding
 - MINDO (=Modified Intermediate Neglect of Differential Overlap), NINDO (=Intermediate Neglect of Differential Overlap)
- Quantum mechanical models: Start from Schroedinger's equation (and make approximations to be able to solve it)
 - Quantum chemistry (Hartree-Fock)
 - Density Functional Theory
 - Quantum Monte Carlo



*Energy only
(and positions,
velocities etc.)*

*Energy and
electronic
structure*

1. Force fields for proteins (and polymers)



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**

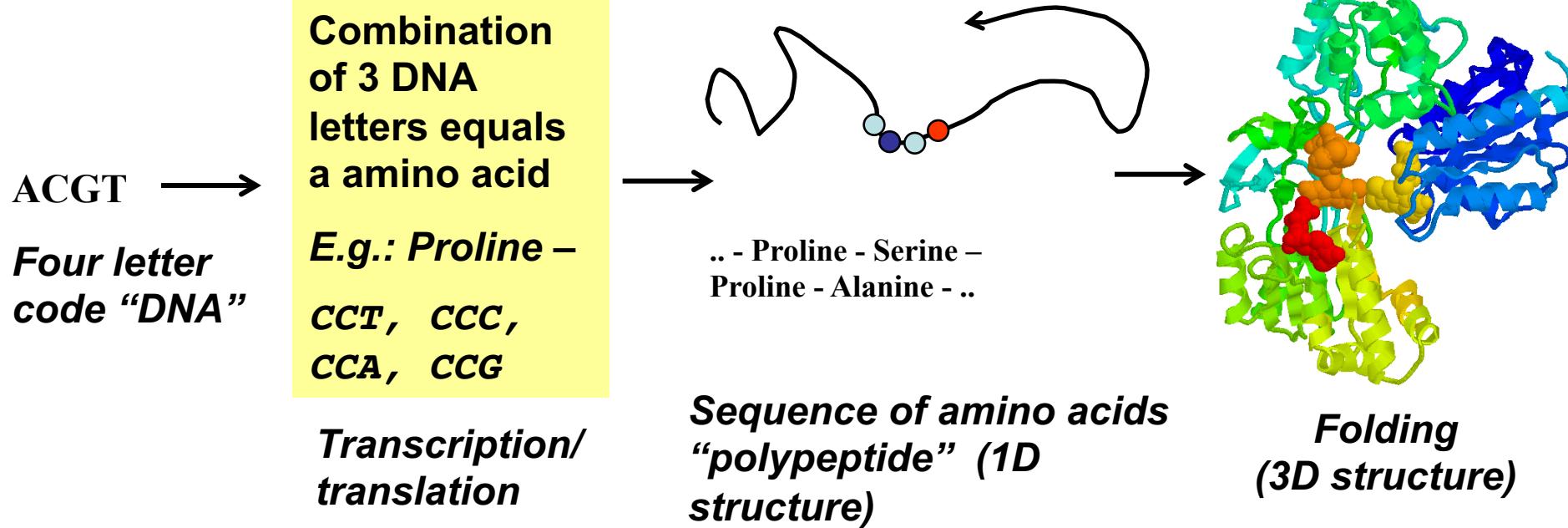
Goal here: To train you in the fundamentals of modeling techniques for proteins, to enable you to carry out protein simulations

Explain the significance of proteins (application)

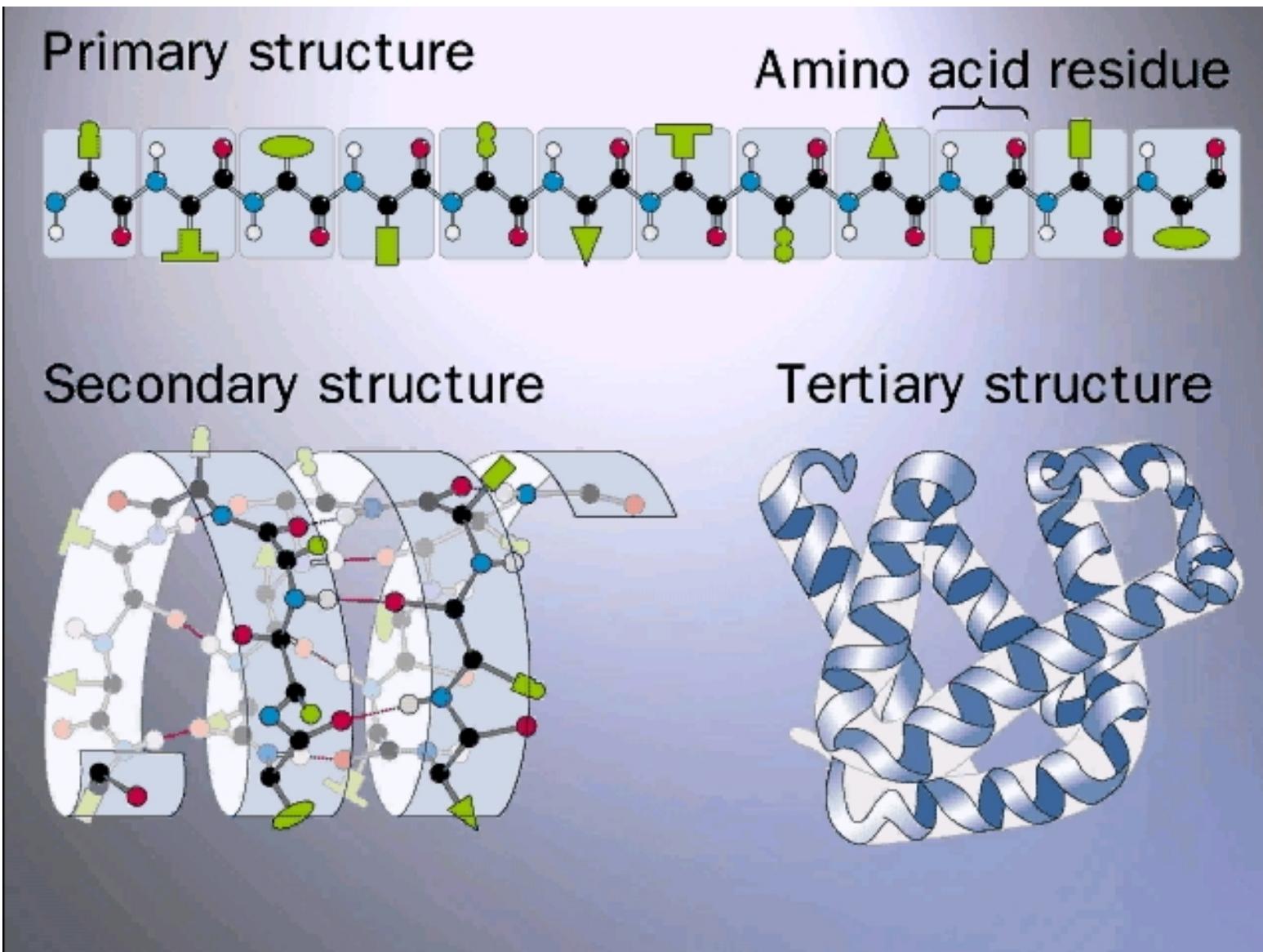
How protein materials are made – the genetic code

- 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



Primary, secondary, tertiary structure



Alpha-helix (abbreviated as AH)

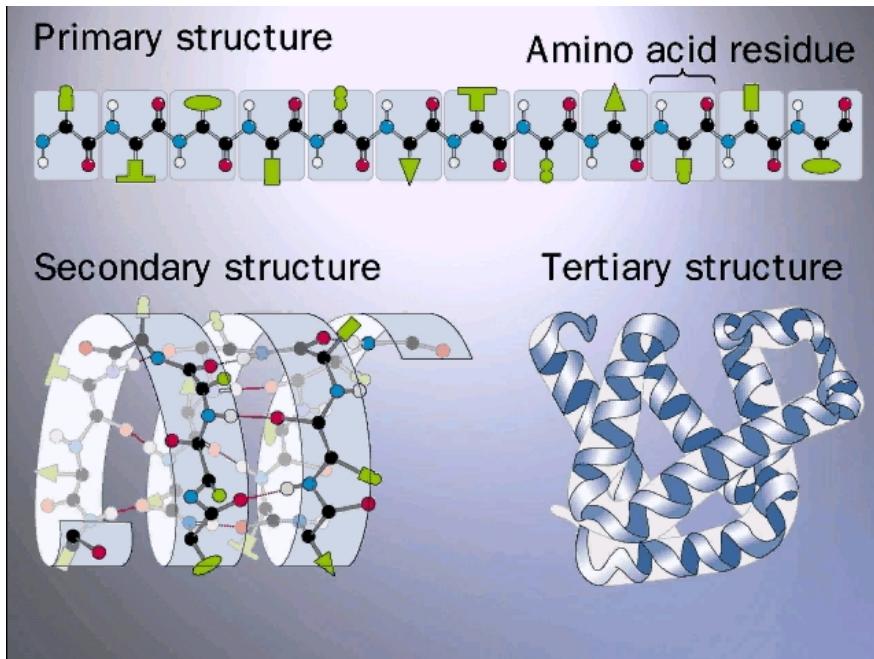
Concept: hydrogen bonding (H-bonding)

e.g. between O and H in H_2O

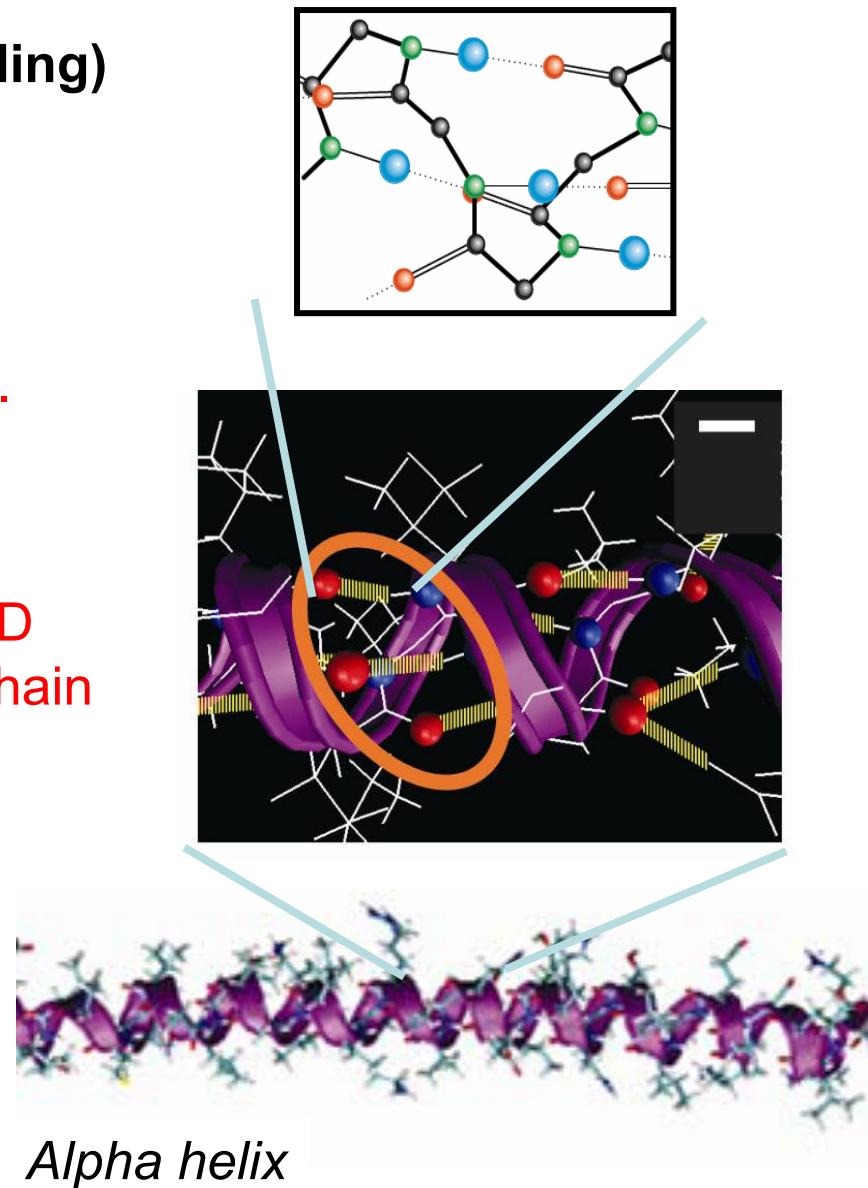
Between N and O in proteins

Drives formation of helical structures

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

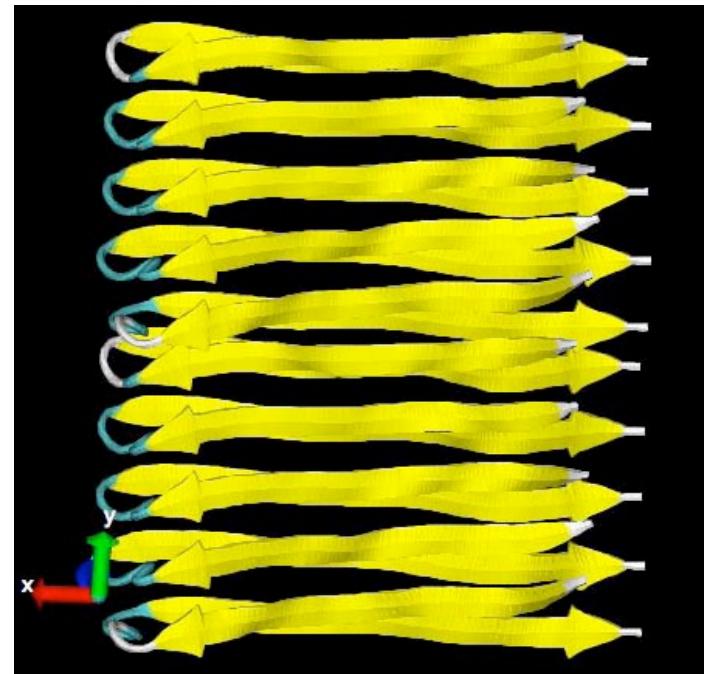
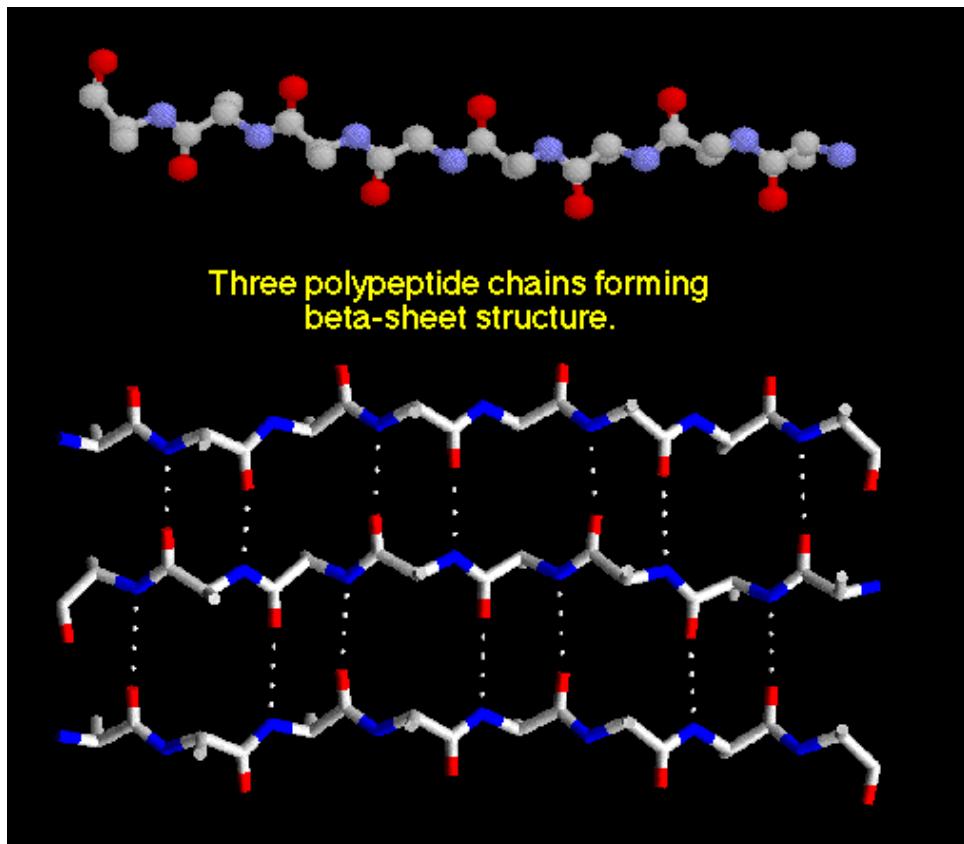


1D
chain



Beta-sheets (abbreviated as BS)

Beta-sheet



Found in many mechanically relevant proteins

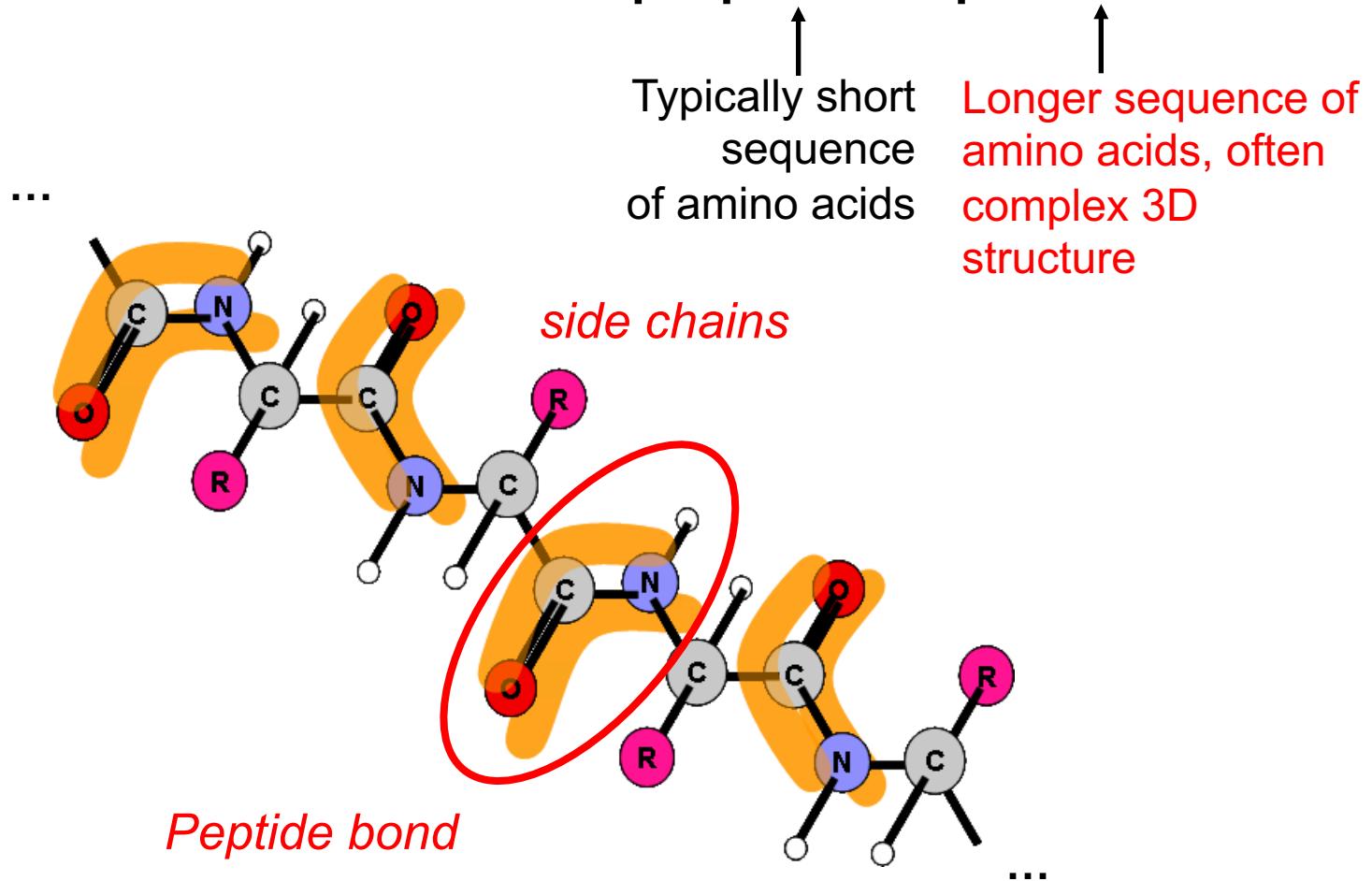
Spider silk

Fibronectin

Titin (muscle tissue)

Amyloids (Alzheimer's disease)

Chemical structure of peptides/proteins

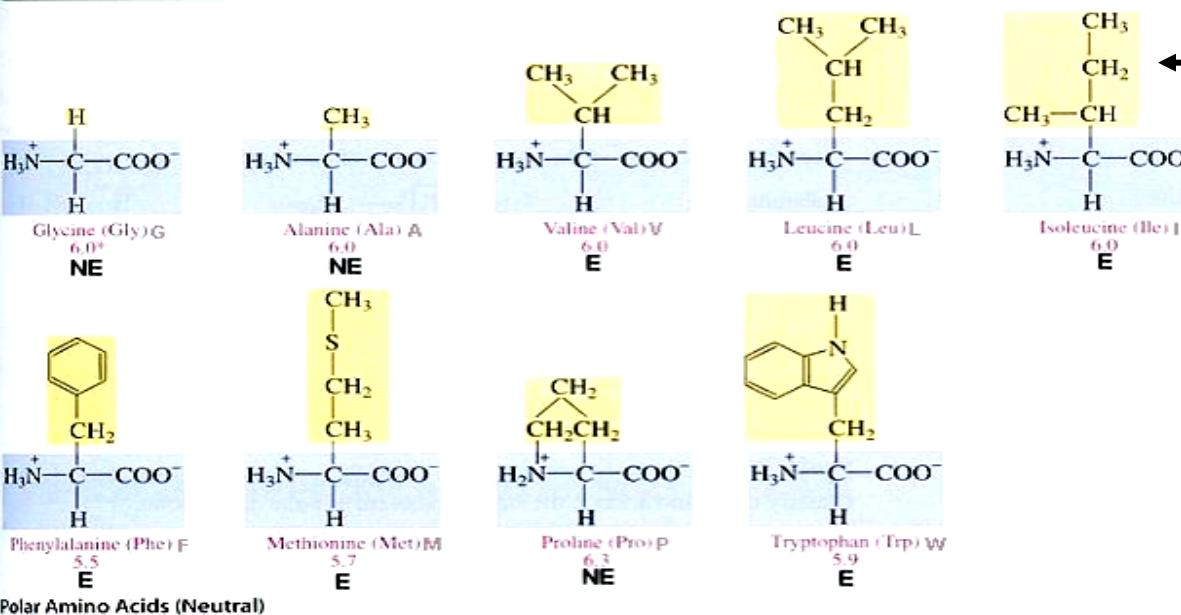


R = side chain, one of the 20 natural amino acids

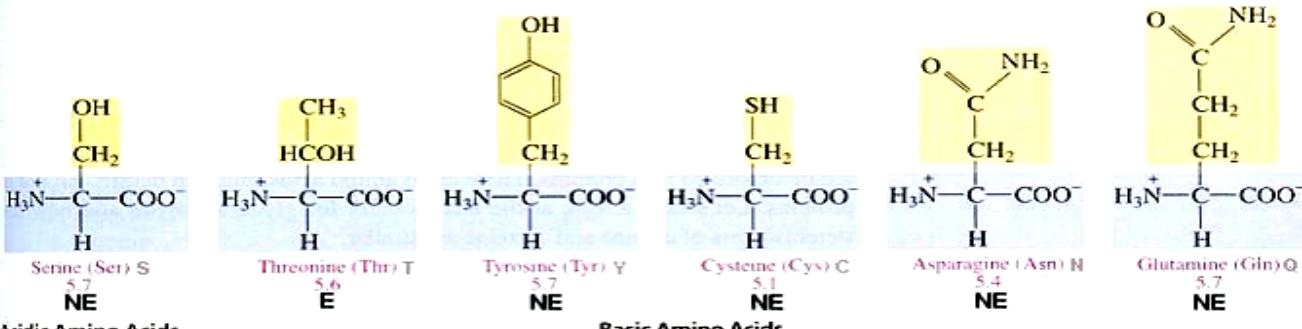
20 natural amino acids differ in their side chain chemistry

Nonpolar Amino Acids

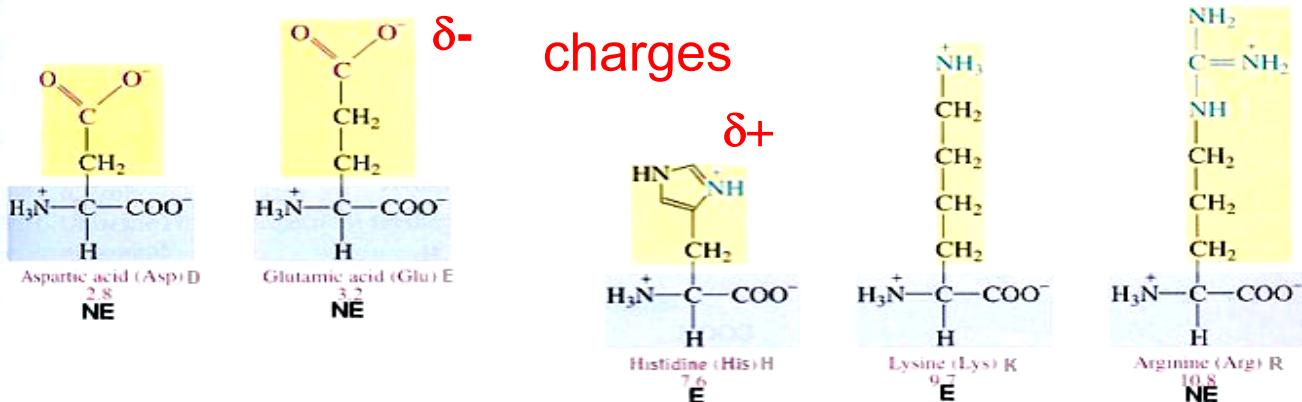
Forms peptide bond



Polar Amino Acids (Neutral)



Acidic Amino Acids



$\delta-$

charges

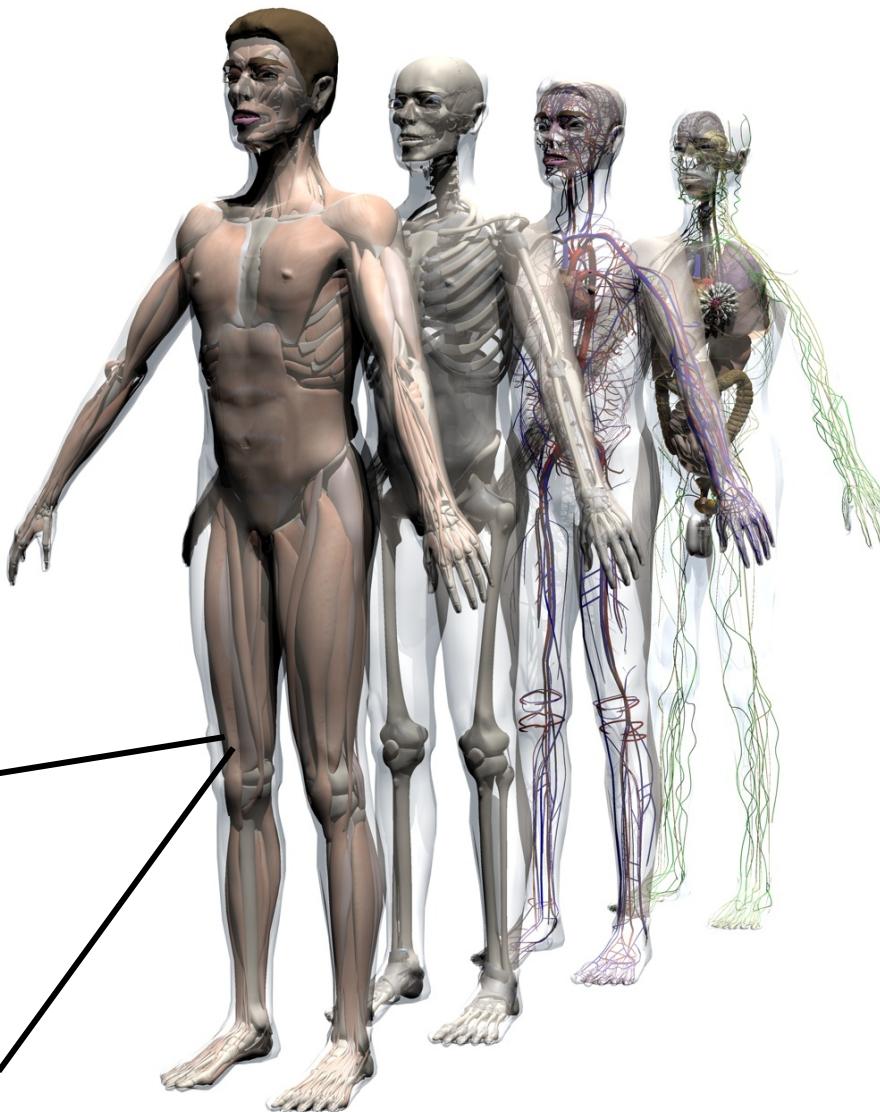
$\delta+$

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)



Muscle tissue
(motor proteins)

Nerve cells

Blood vessels

Tendon
(links bone, muscles)

Cartilage (reduce friction in joints)

Bone (structural stability)

Cellular structure: Protein networks

Cell nucleus

Actin network

Microtubulus
(e.g. cargo)

Vimentin
(extensible,
flexible, provide
strength)

= cytoskeleton

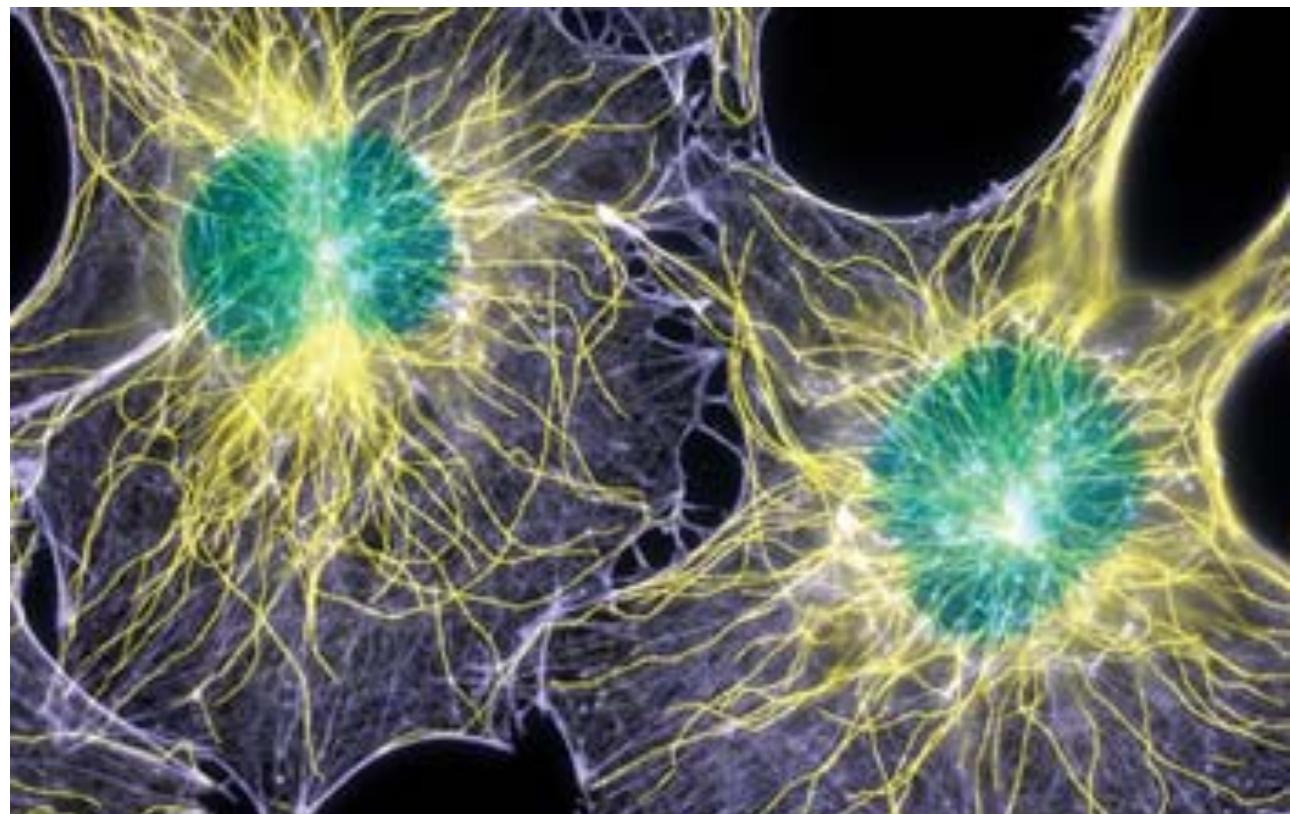
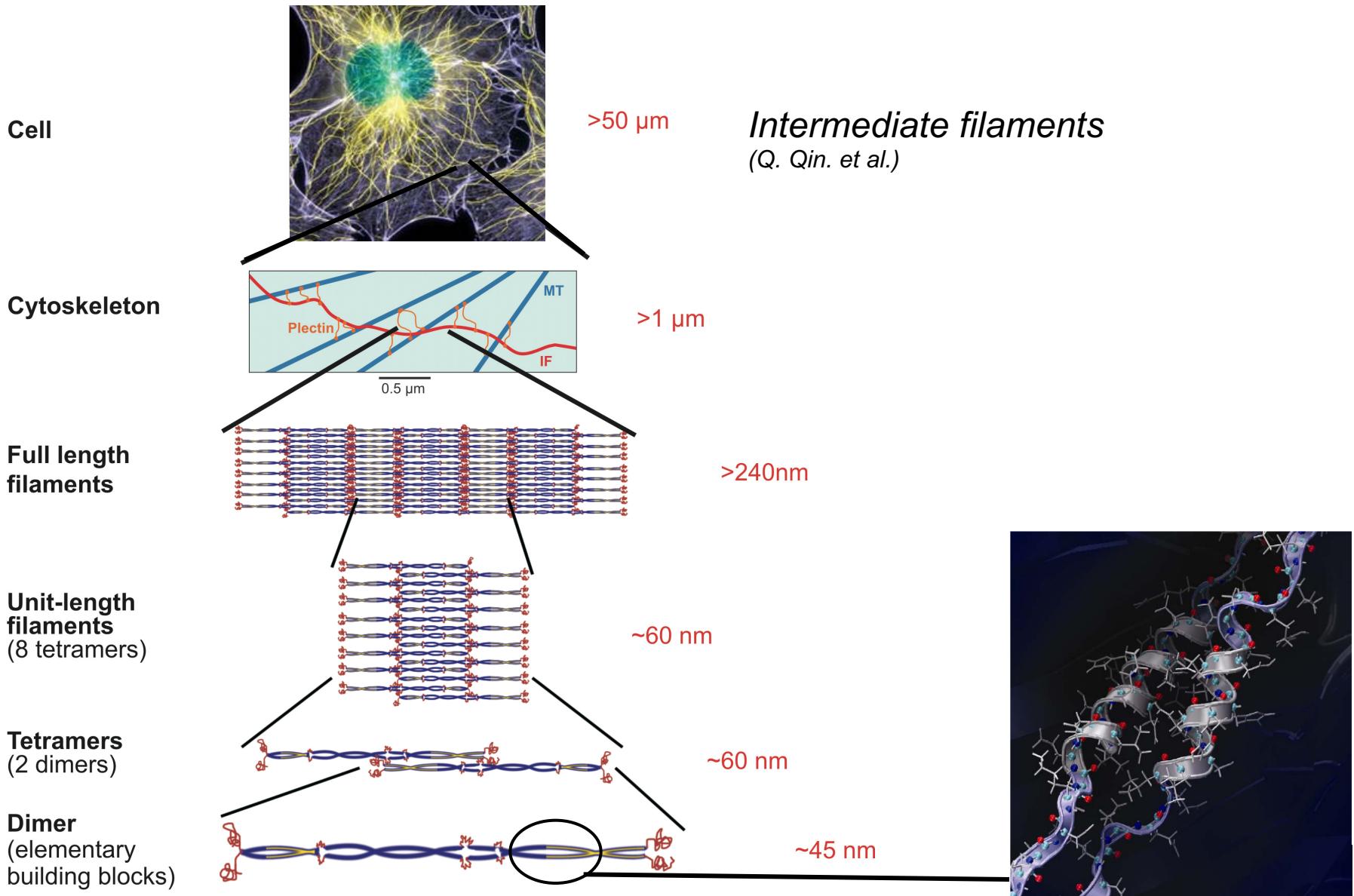
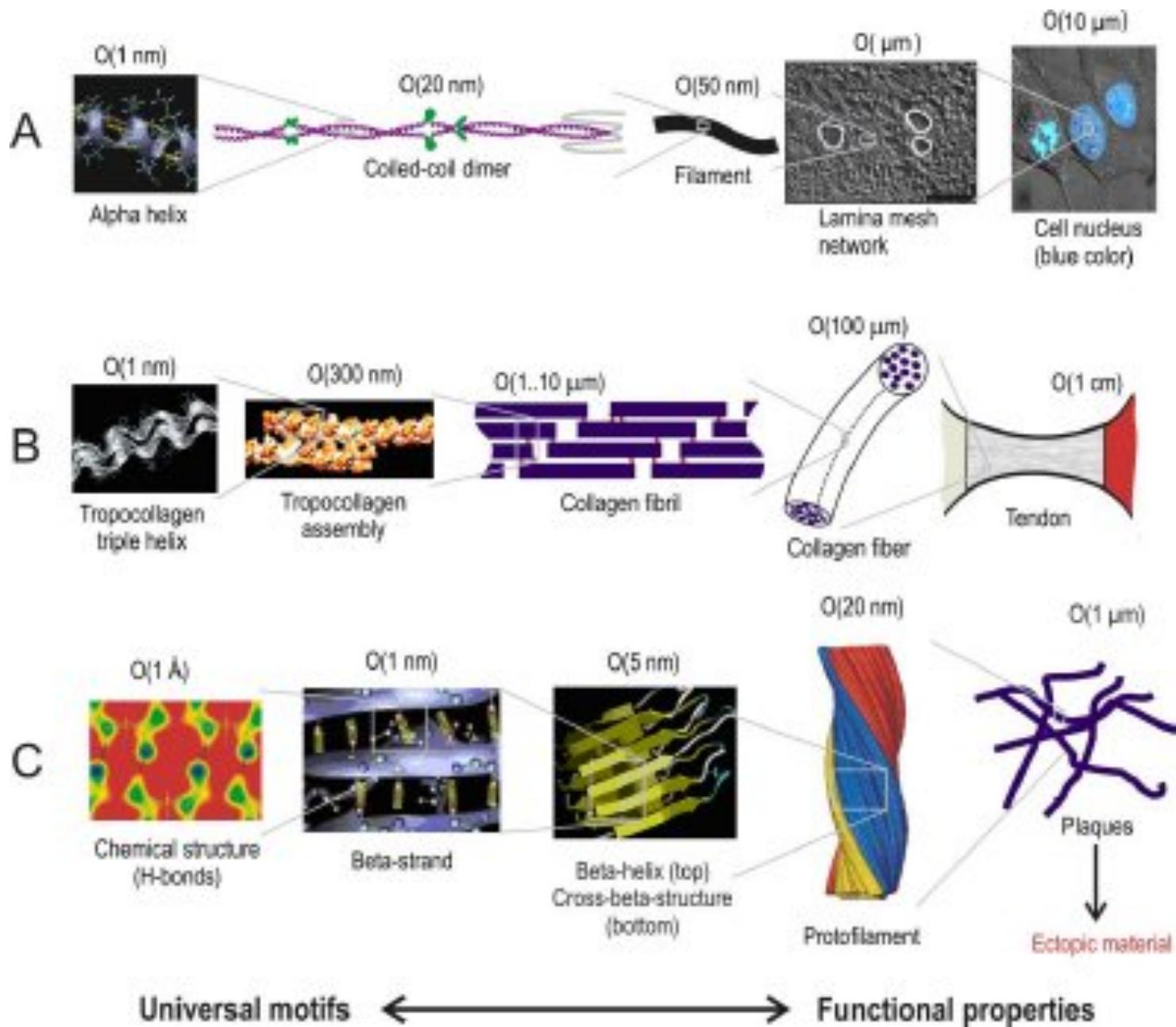


Photo: Torsten Wittmann

Protein structures define the cellular architecture



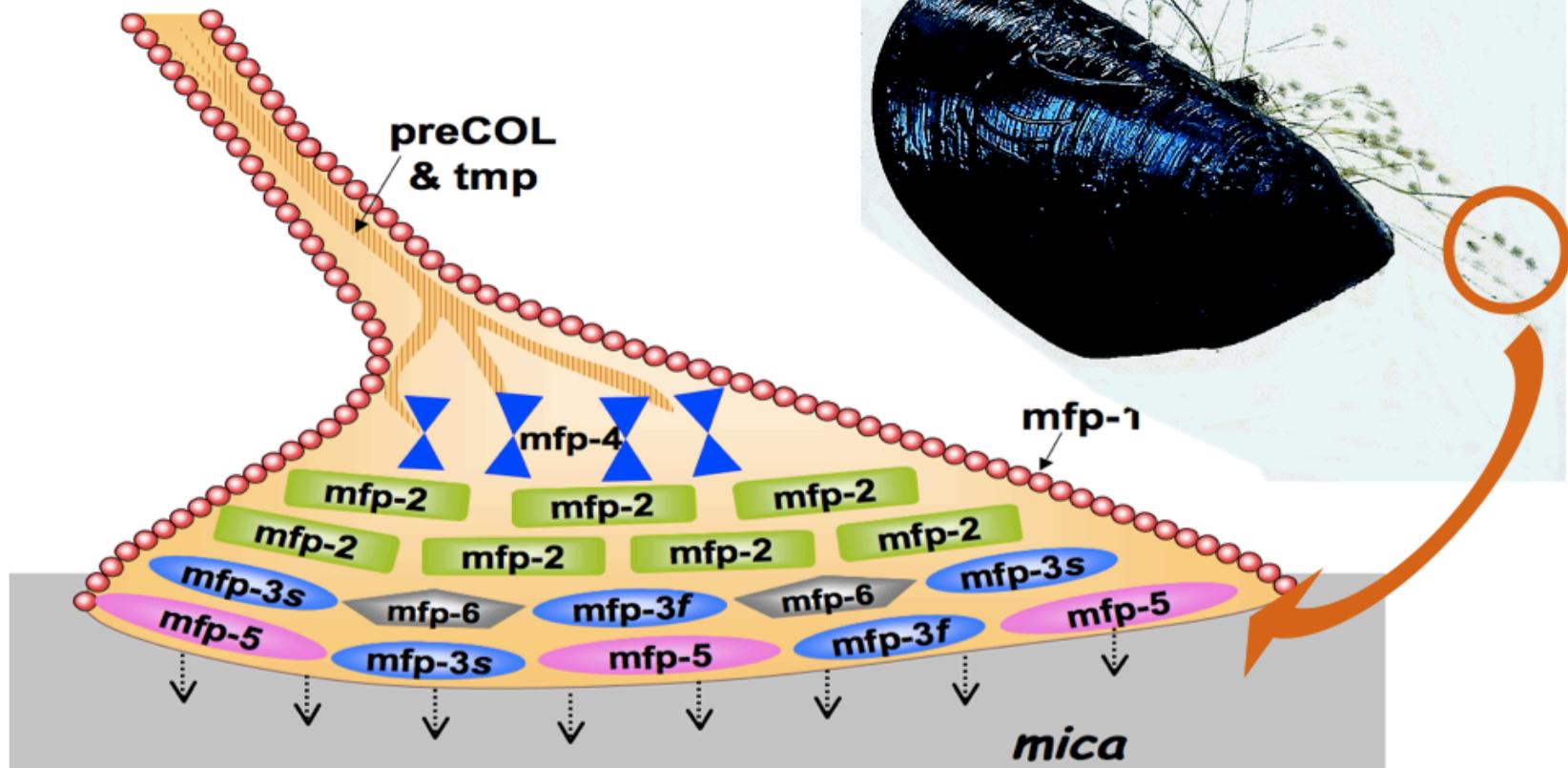


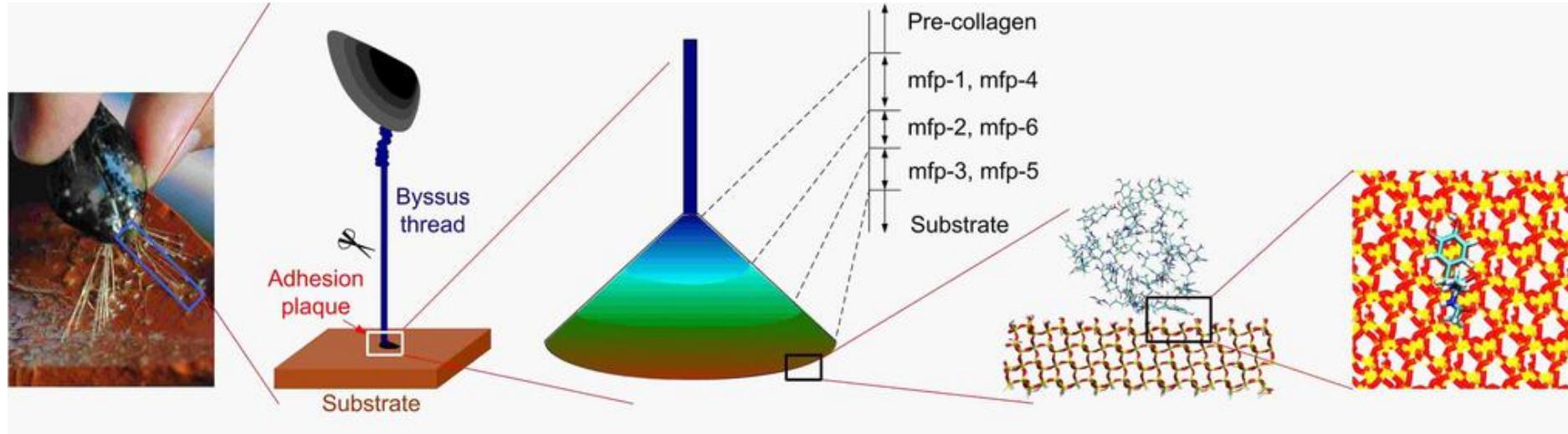
made out of synthetic spider silk



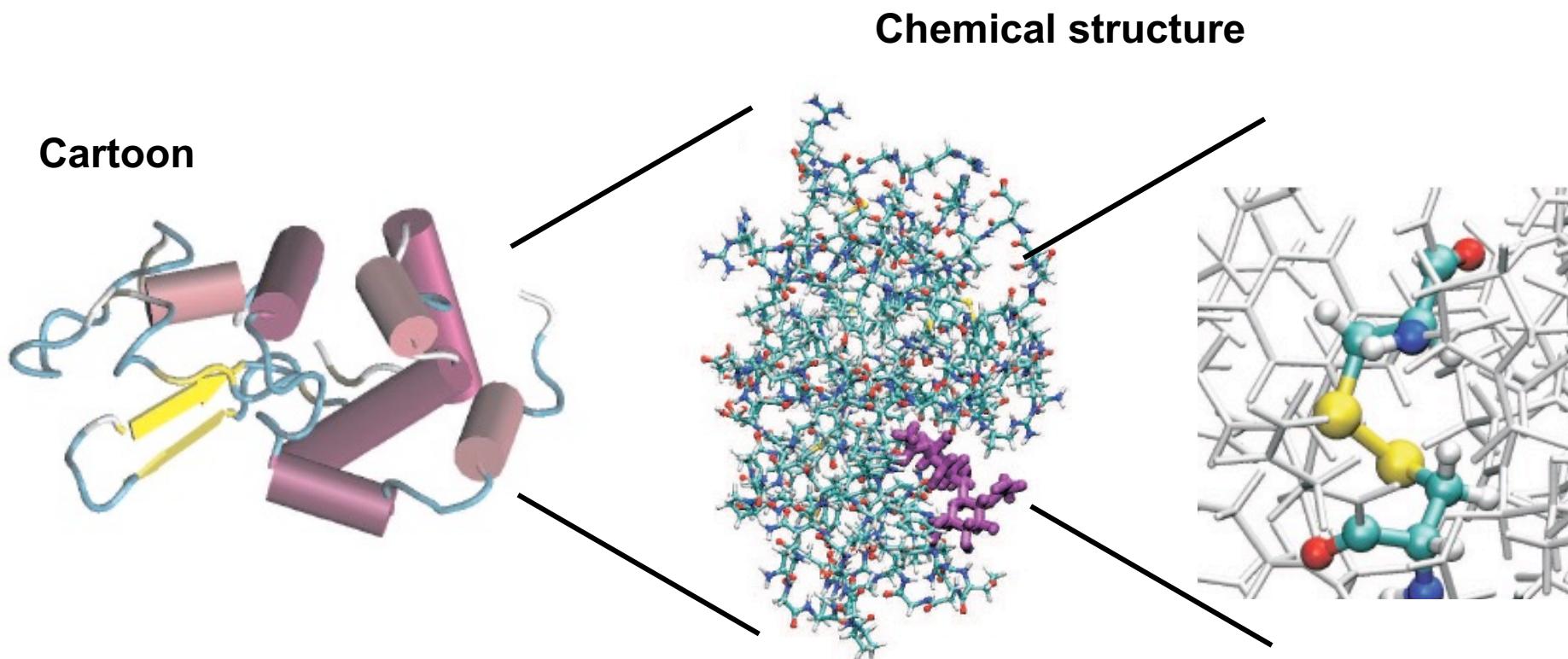
Moon parka (The North Face)





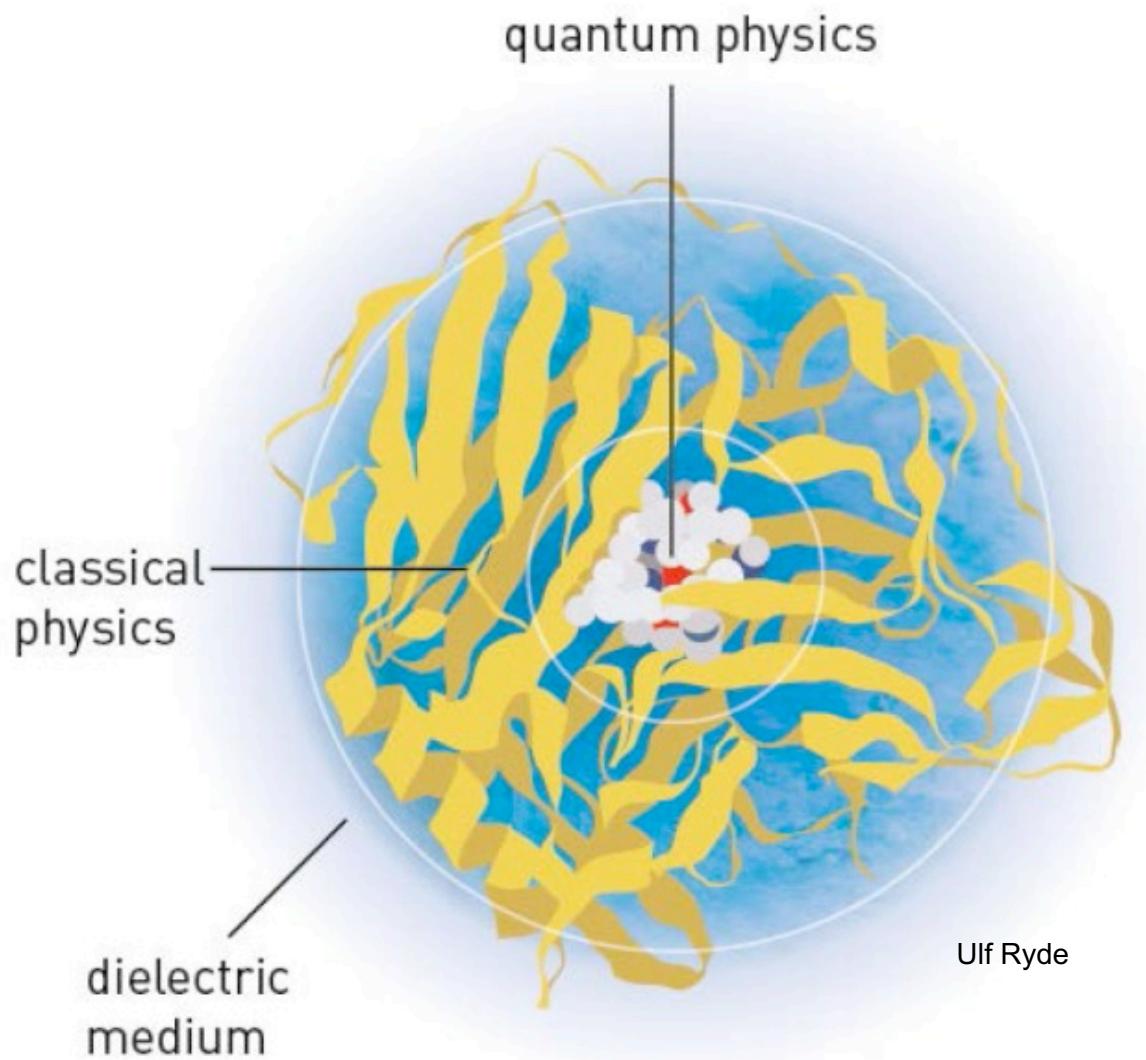


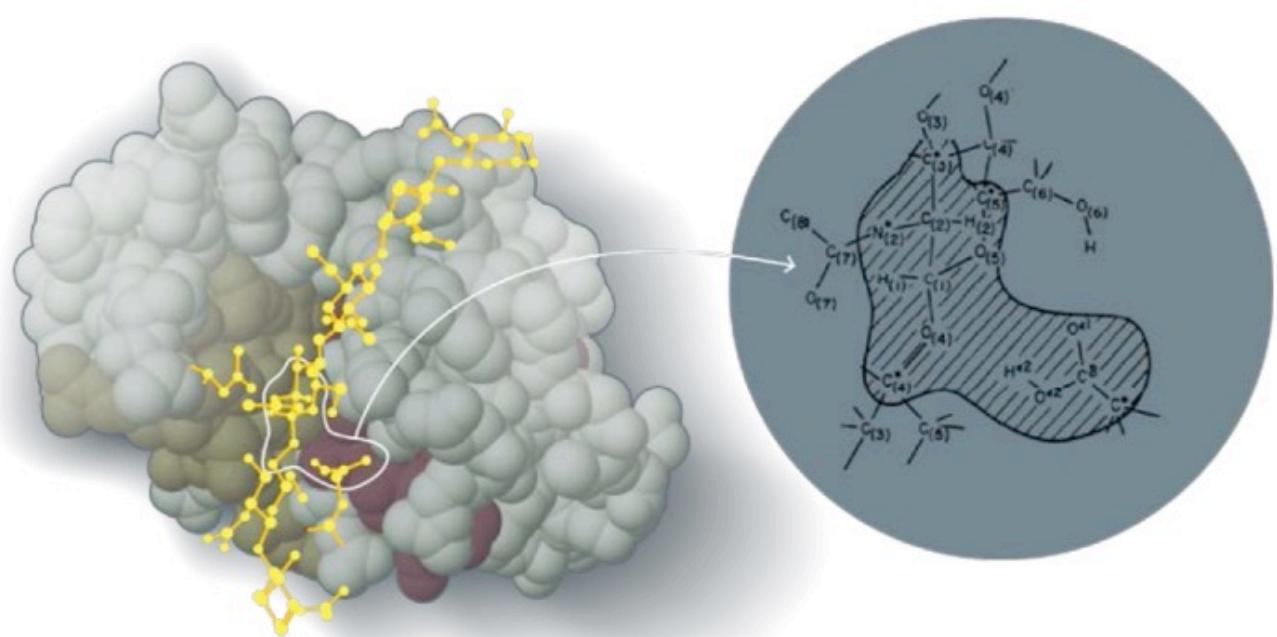
Chemistry, structure and properties are linked



Presence of various chemical bonds (chemical complexity):

- 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)







Nobelpriset 2013

The Nobel



The Nobel Prize in Chemistry 2013



Martin Karplus
Université de Strasbourg,
France and Harvard
University, Cambridge,
MA, USA



Michael Levitt
Stanford University School of
Medicine, CA, USA



Arieh Warshel
University of Southern
California, Los Angeles, CA,
USA

"För utvecklandet av flerskalemodeller för komplexa kemiska system."

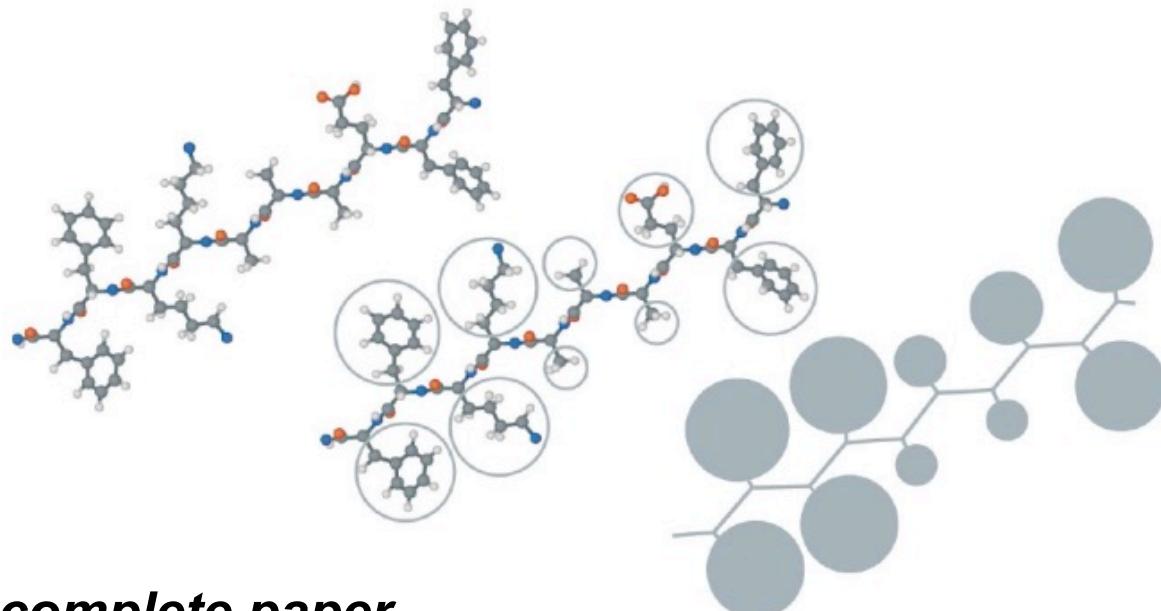
"For the development of multiscale models for complex chemical systems."

© Kungl. Ve



Scientific Background on the Nobel Prize in Chemistry 2013

DEVELOPMENT OF MULTISCALE MODELS FOR COMPLEX CHEMICAL SYSTEMS

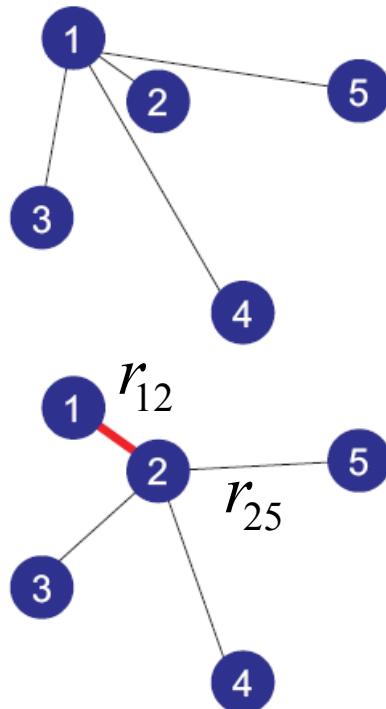


See *Stellar* for complete paper

1.1 CHARMM force field

Pair potential: total energy

“simply” the sum of all energies of pairs of atoms



two “loops” over pairs of all particles

$$U_{total} = \frac{1}{2} \sum_{i=1, i \neq j}^N \sum_{j=1}^N \phi(r_{ij})$$

with $\phi_{ij} = \phi(r_{ij})$

$$U_{total} = \frac{1}{2} (\phi_{12} + \phi_{13} + \phi_{14} + \phi_{1N} \dots + \phi_{21} + \phi_{23} + \dots + \phi_{2N} + \dots + \phi_{N-1,N})$$

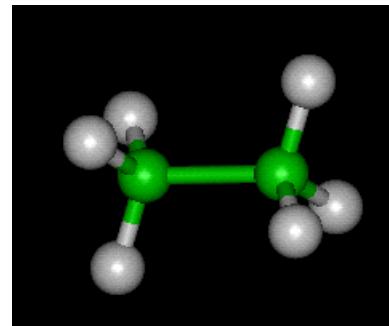
Review: atomic interactions – different types of chemical bonds

- **Primary bonds (“strong”)**
 - Ionic (ceramics, quartz, feldspar - **rocks**)
 - Covalent (**silicon**)
 - Metallic (copper, nickel, **gold**, silver)
(high melting point, 1000-5,000K)
- **Secondary bonds (“weak”)**
 - Van der Waals (**wax**, low melting point)
 - Hydrogen bonds (proteins, **spider silk**)
(melting point 100-500K)
- Ionic: Non-directional (point charges interacting)
- Covalent: Directional (bond angles, torsions matter)
- Metallic: Non-directional (electron gas concept)

Difference of material properties originates from different atomic Interactions: Concept: add different contributions (linear addition...)

Generalization: split energy contributions due to different chemical bonds

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



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**”

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

Force fields for organics: Basic approach

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

=0 for proteins

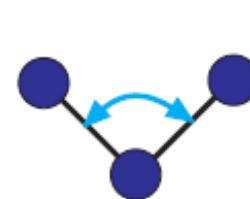
$$U_{Covalent} = U_{stretch} + U_{bend} + U_{rot}$$

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



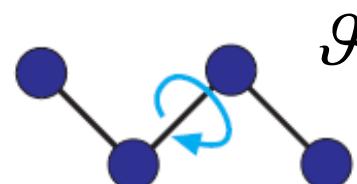
bond stretching

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



angle bending

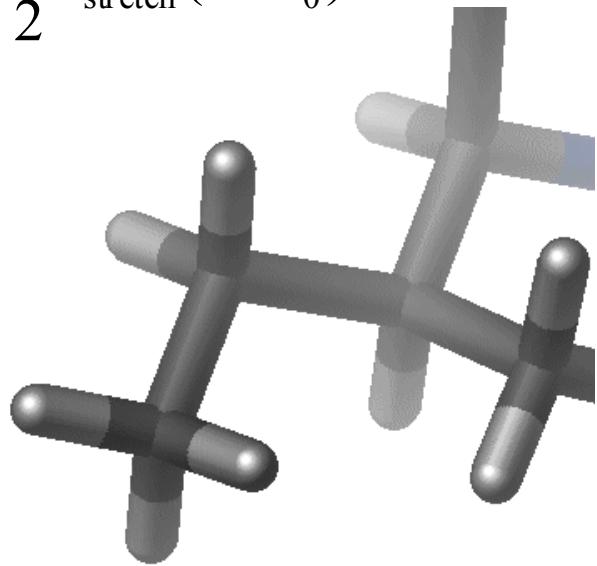
$$\begin{cases} \phi_{rot} = \frac{1}{2} k_{rot} (1 - \cos(\vartheta)) \\ U_{rot} = \sum_{quadruplets} \phi_{rot} \end{cases}$$



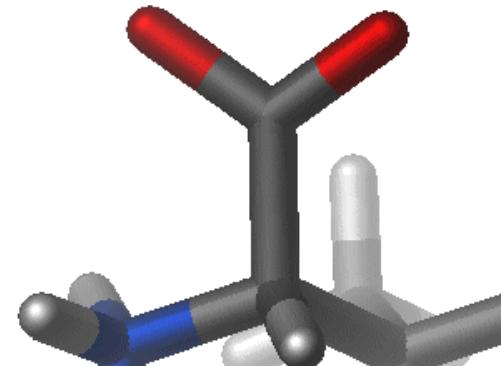
bond rotation

Model for covalent bonds

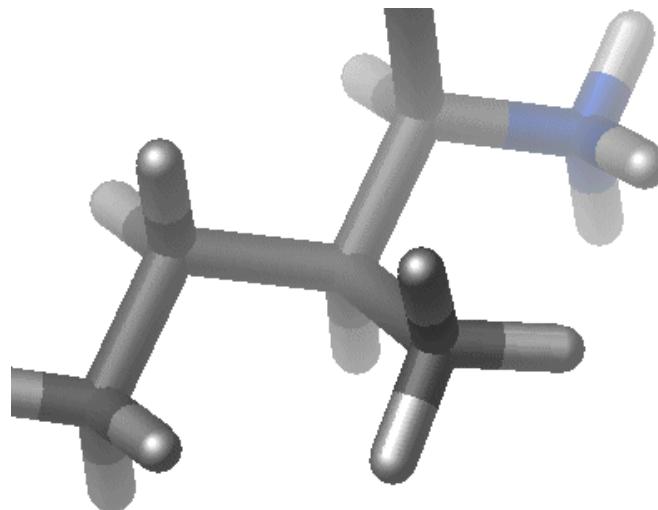
$$\phi_{\text{stretch}} = \frac{1}{2} k_{\text{stretch}} (r - r_0)^2$$



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

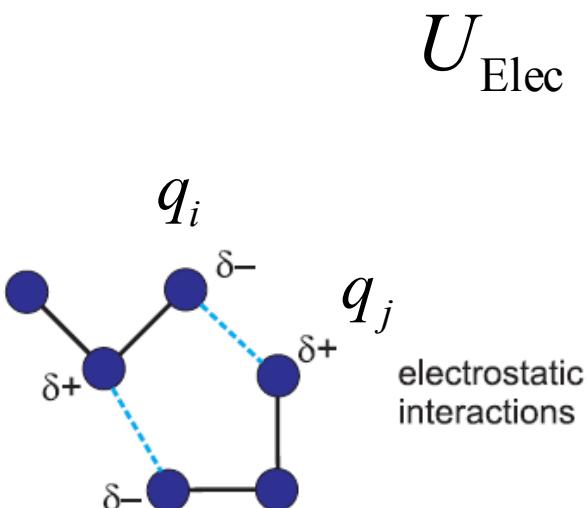


$$\phi_{\text{rot}} = \frac{1}{2} k_{\text{rot}} (1 - \cos(\vartheta))$$



Force fields for organics: Basic approach

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



U_{Elec} :

Coulomb potential $\phi(r_{ij}) = \frac{q_i q_j}{\epsilon_1 r_{ij}}$

electrostatic constant

ϵ_1

distance

$$\text{Coulomb forces } F(r_{ij}) = -\frac{q_i q_j}{\epsilon_1 r_{ij}^2}$$

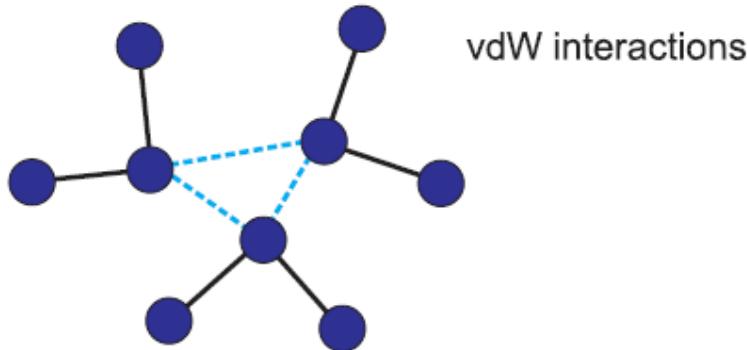
$$\epsilon_1 = 4\pi\epsilon_0 \quad \epsilon_0 = 1.602 \times 10^{-19} \text{ C}$$

Force fields for organics: Basic approach

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

=0 for proteins

U_{vdW}



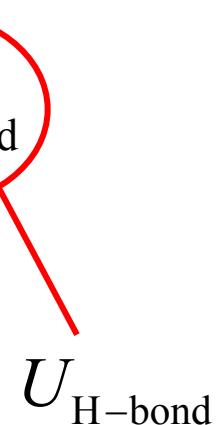
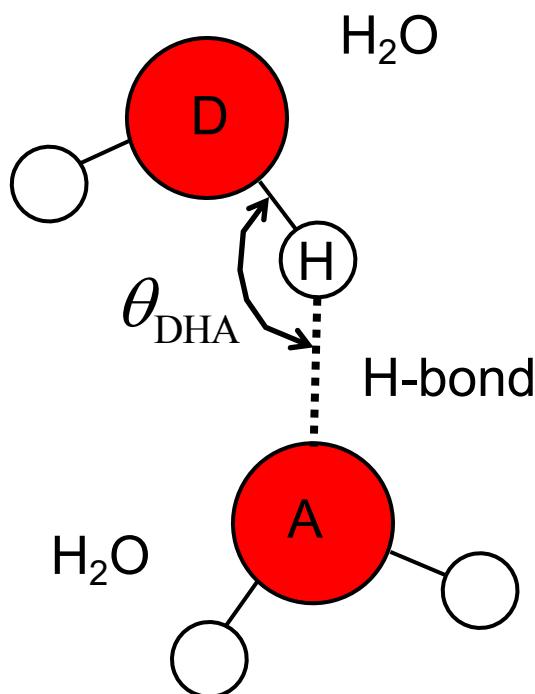
$$U_{vdW} : \text{ LJ potential } \phi(r_{ij}) = 4\epsilon \left[\left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^6 \right]$$

LJ potential is particularly good model for vdW interactions (Argon) ³⁴

H-bond model

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

=0 for proteins



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

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

r_{ij} = distance between D-A

Summary

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

=0 for proteins

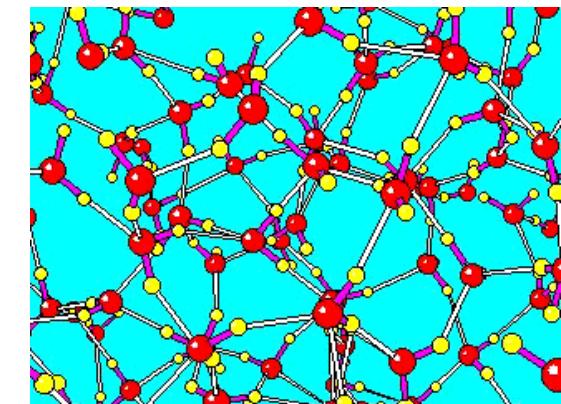
U_{Elec} : Coulomb potential $\phi(r_{ij}) = \frac{q_i q_j}{\epsilon_1 r_{ij}}$

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

$$\left\{ \begin{array}{l} \phi_{stretch} = \frac{1}{2} k_{stretch} (r - r_0)^2 \\ \phi_{bend} = \frac{1}{2} k_{bend} (\theta - \theta_0)^2 \\ \phi_{rot} = \frac{1}{2} k_{rot} (1 - \cos(\vartheta)) \end{array} \right.$$

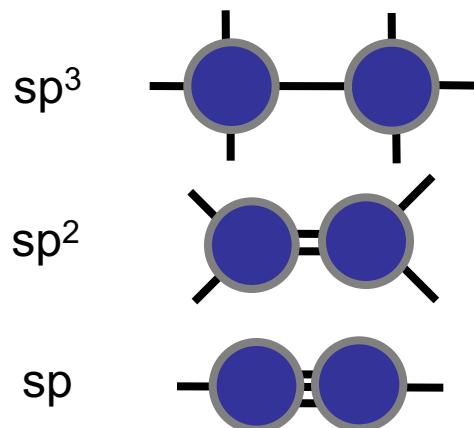
U_{vdW} : LJ potential $\phi(r_{ij}) = 4\epsilon \left[\left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^6 \right]$

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



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 **sp³**, **sp²**, **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, ...

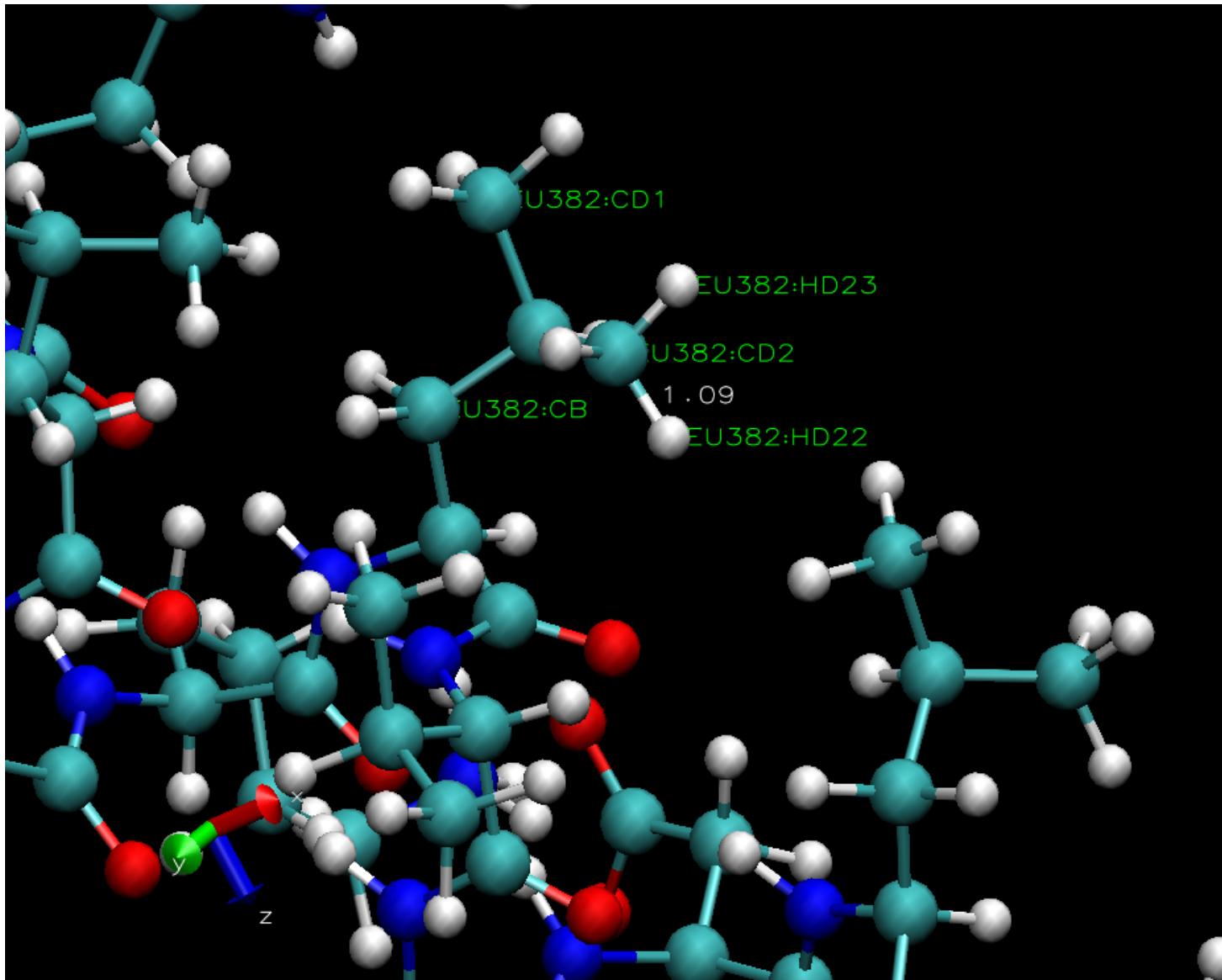


Atom typing in CHARMM

Example of the RTF for the Alanine residue:

```
RESI ALA0.00
GROUP
ATOM N NH1 -0.47 ! | |
ATOM H N HN 0.31 : HN-N
ATOM C A CT1 0.07 ! | | HB1
ATOM H A HB 0.09 ! | | /
GROUP ! HA-CA--CB-HB2
ATOM C B CT3 -0.27 ! | | \
ATOM H B1 HA 0.09 ! | | HB3
ATOM H B2 HA 0.09 O=C
ATOM H B3 HA 0.09 ! | |
GROUP !
ATOM C C 0.51
ATOM O O-0.51
BOND CB 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
- 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

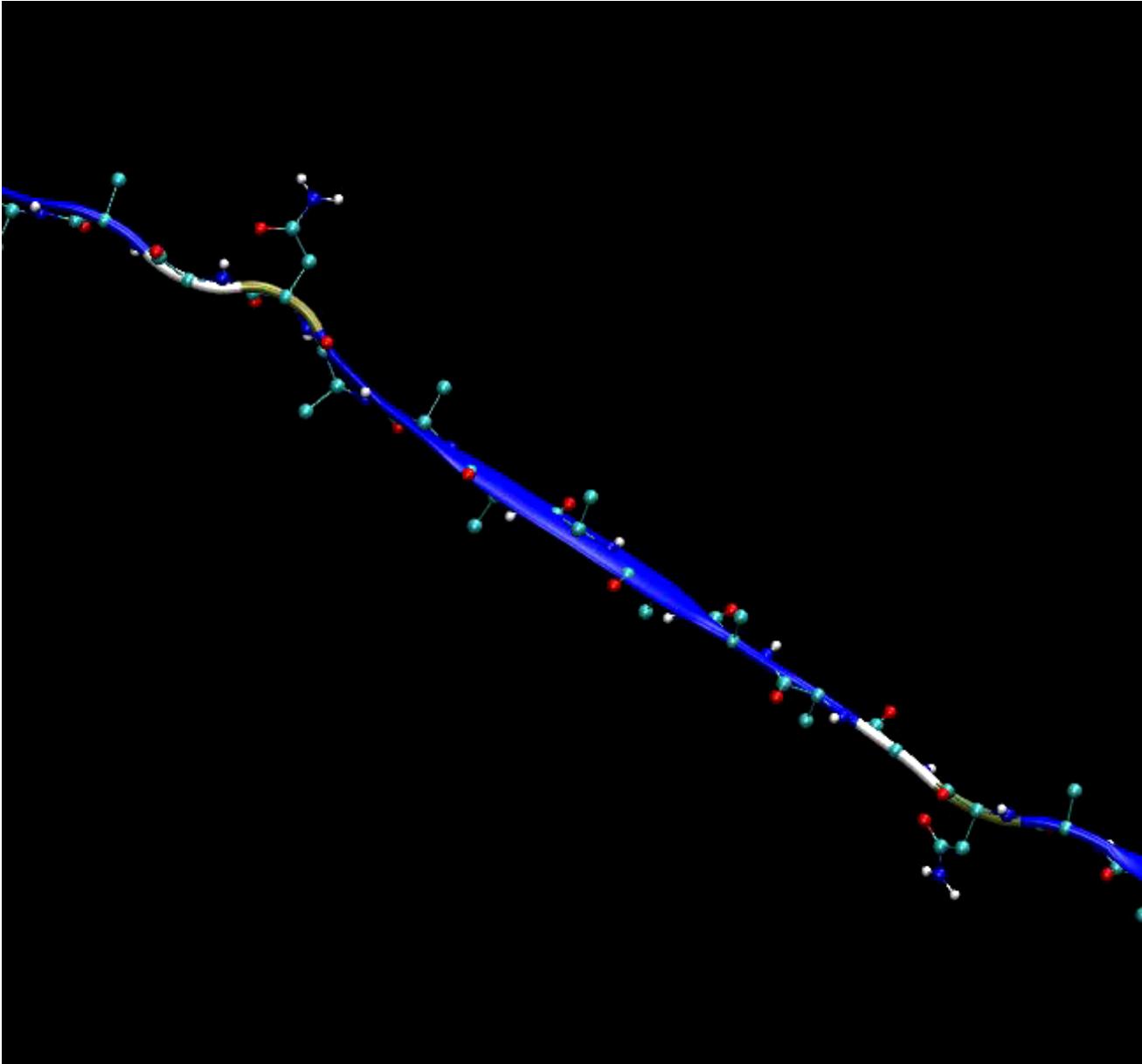
*Include anharmonic
terms
Derived from QM,
more general*

CHARMM force field

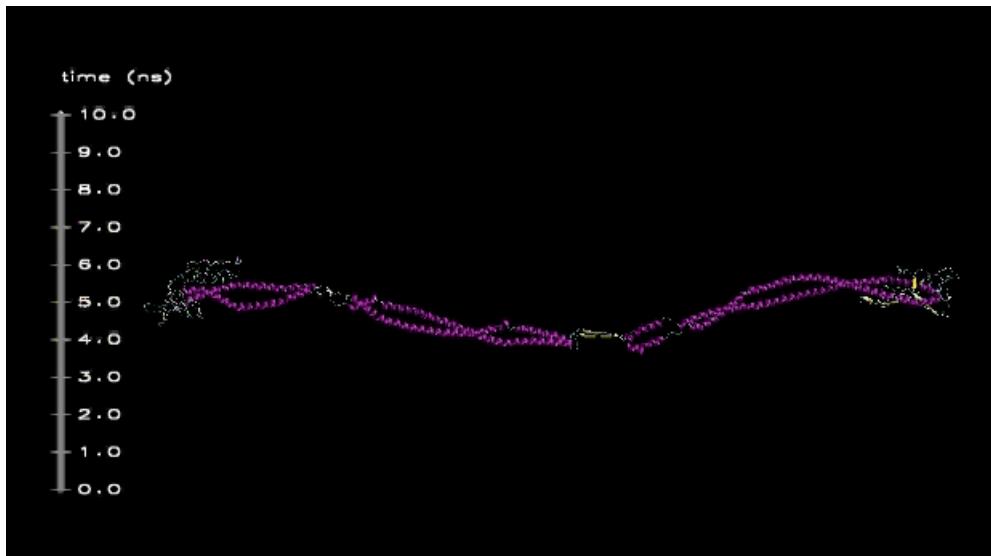
- Widely used and accepted model for protein structures
- Programs such as NAMD have implemented the CHARMM force field

nanoHUB stretchmol module, study of a protein domain that is part of human vimentin intermediate filaments, collagen molecules, etc...

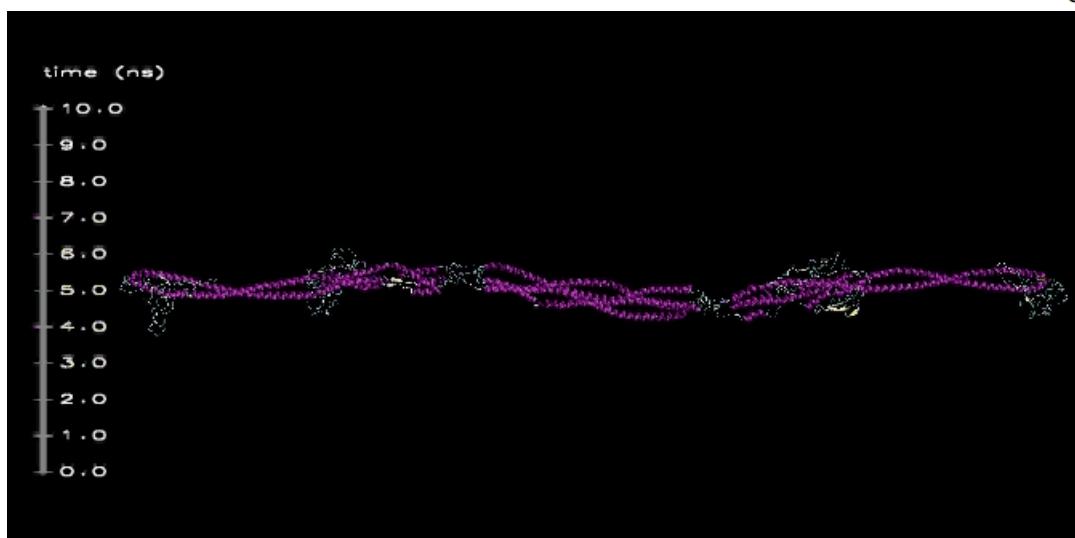
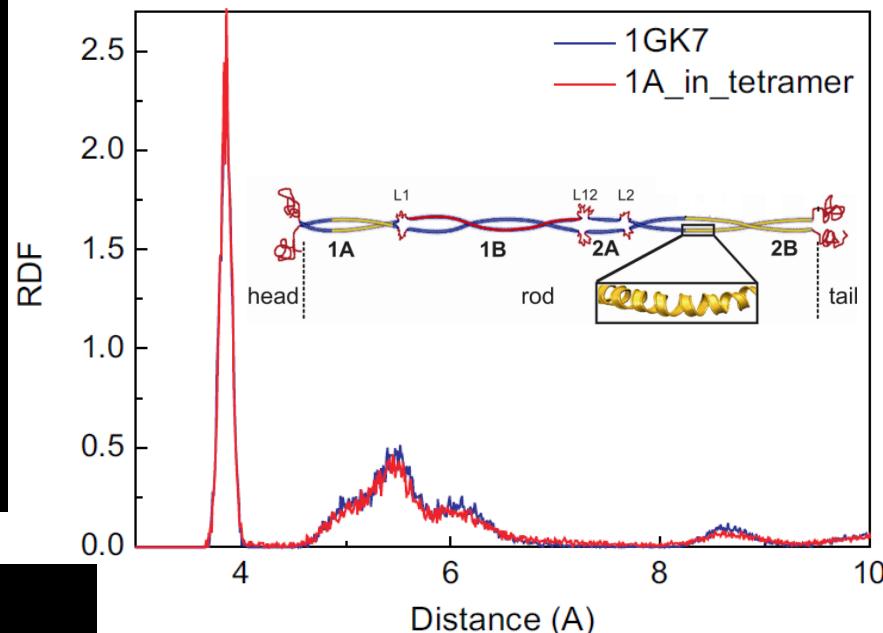
Movie: protein folding with CHARMM



Movies in equilibrium (temperature 300 K)



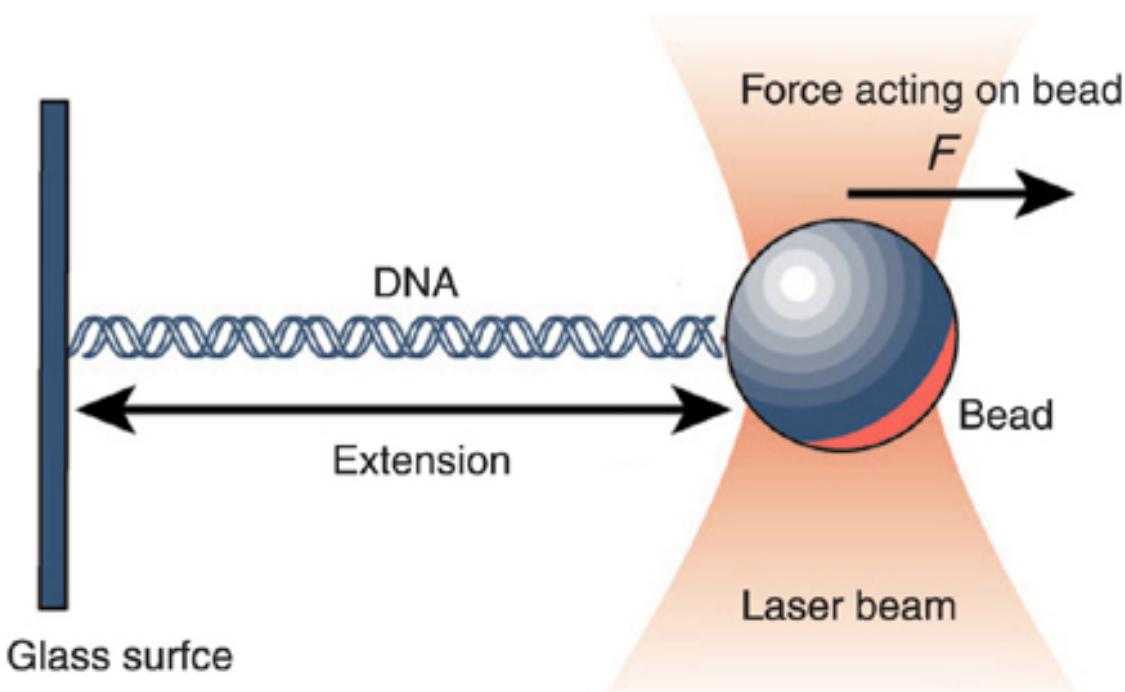
Dimer



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

2. Molecular mechanics of proteins

How proteins deform and ultimately fail...**physiologically and in disease**



Cooking spaghetti



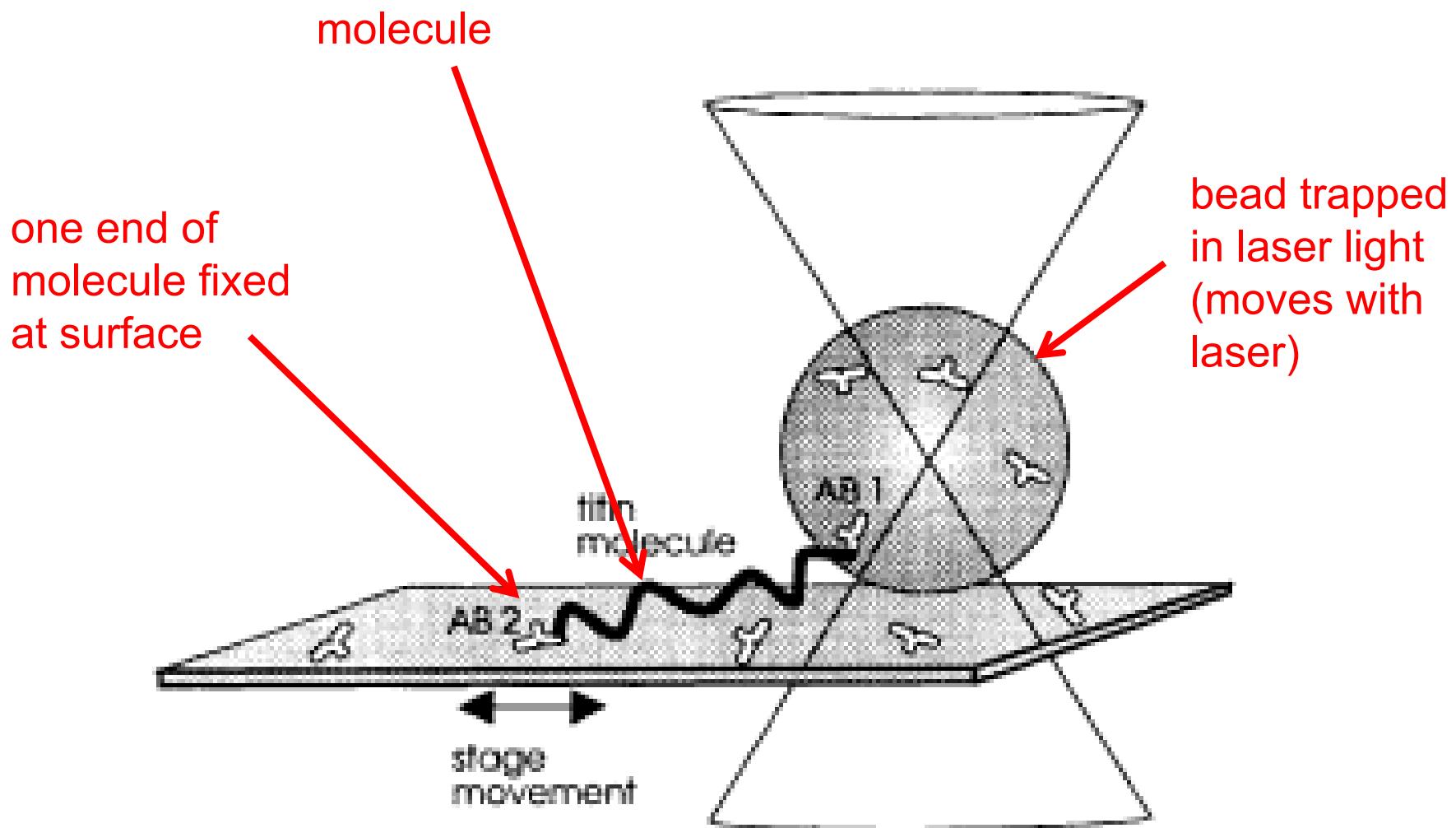
stiff rods

cooking



*soft, flexible rods
(like many protein molecules)*

Single molecule tensile test – “optical tweezer”



Example 1: Elasticity of tropocollagen molecules

*Entropic elasticity
leads to strongly
nonlinear elasticity*

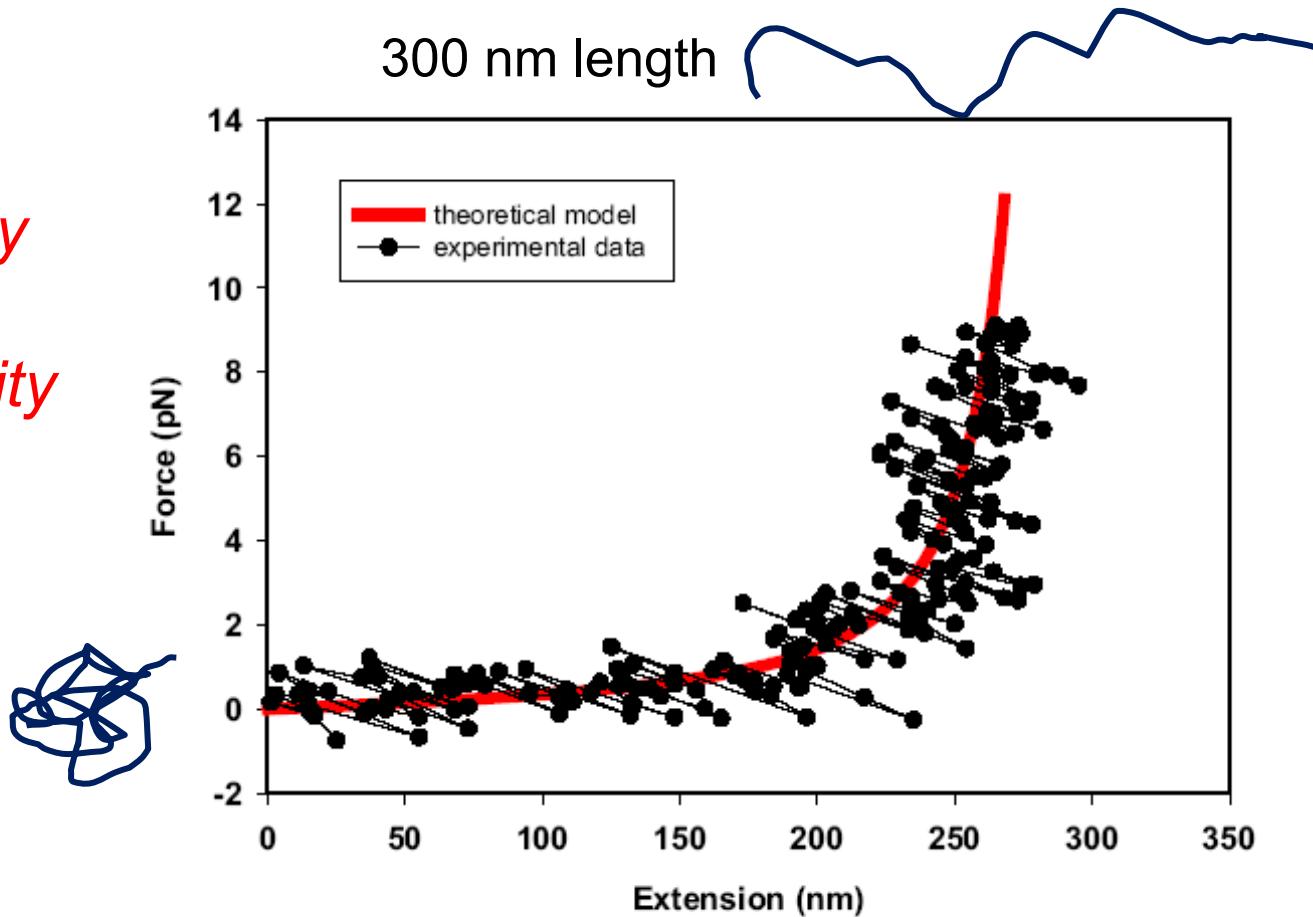
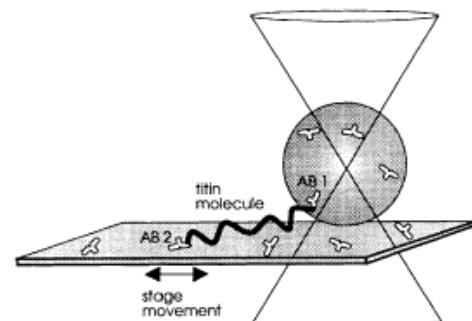


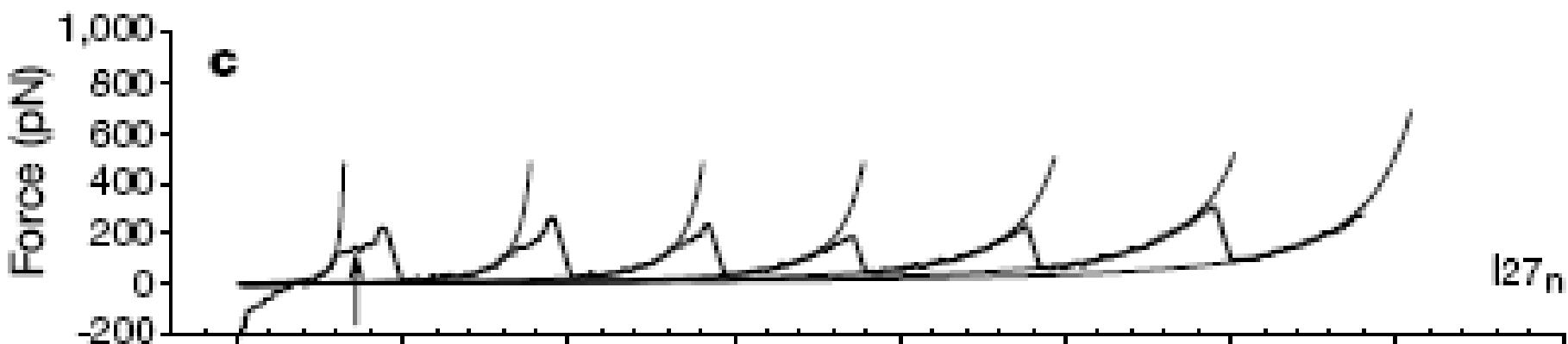
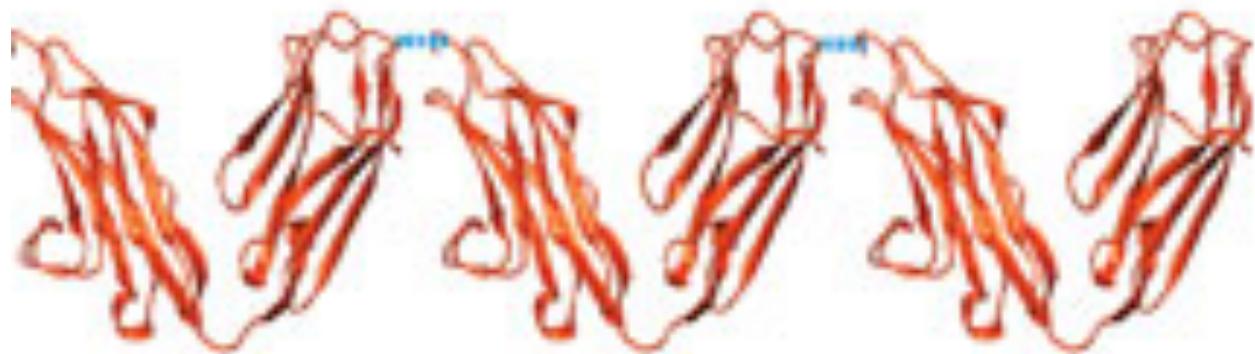
Fig. 2. The force-extension curve for stretching a single type II collagen molecule. The data were fitted to Marko-Siggia entropic elasticity model. The molecule length and persistence length of this sample is 300 and 7.6 nm, respectively.

Example 2: Single protein molecule mechanics

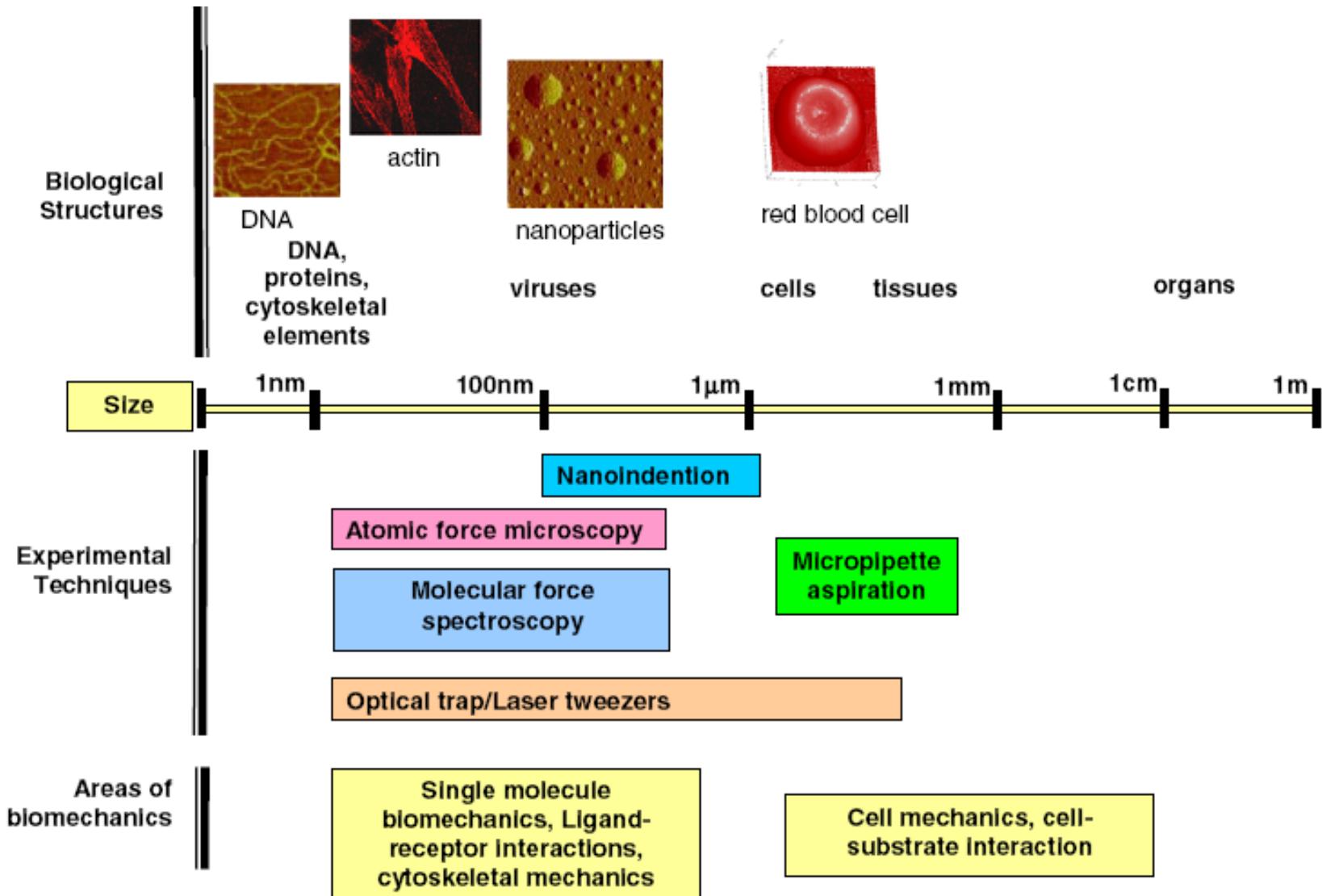
Optical tweezers experiment



Protein structure (I27 multidomain titin in muscle)



Experimental techniques

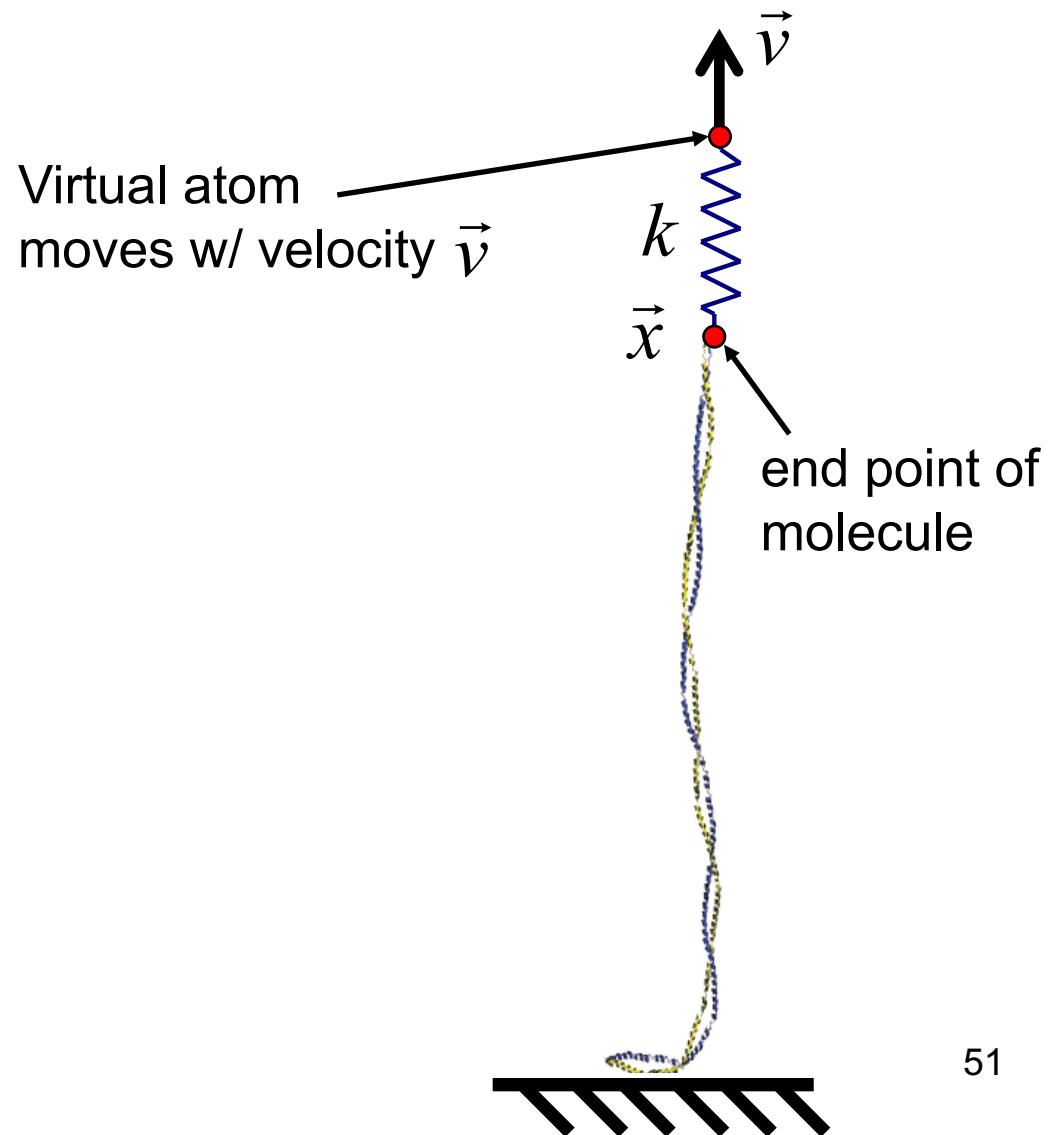


2.1 How to apply load to a molecule

*(in molecular dynamics
simulations)*

Steered molecular dynamics (SMD)

Steered molecular dynamics used to apply forces to protein structures



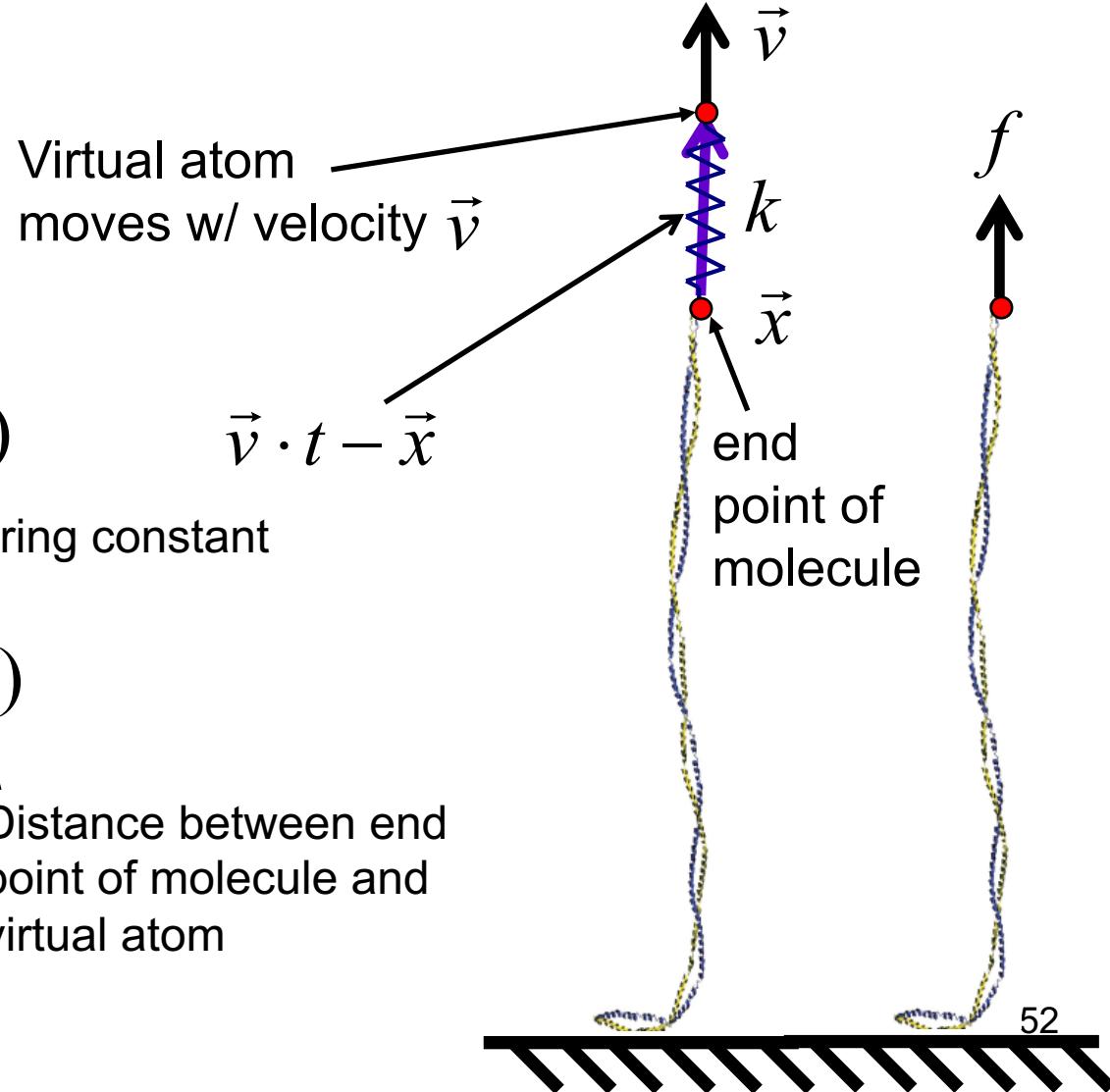
Steered molecular dynamics (SMD)

Steered molecular dynamics used to apply forces to protein structures

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

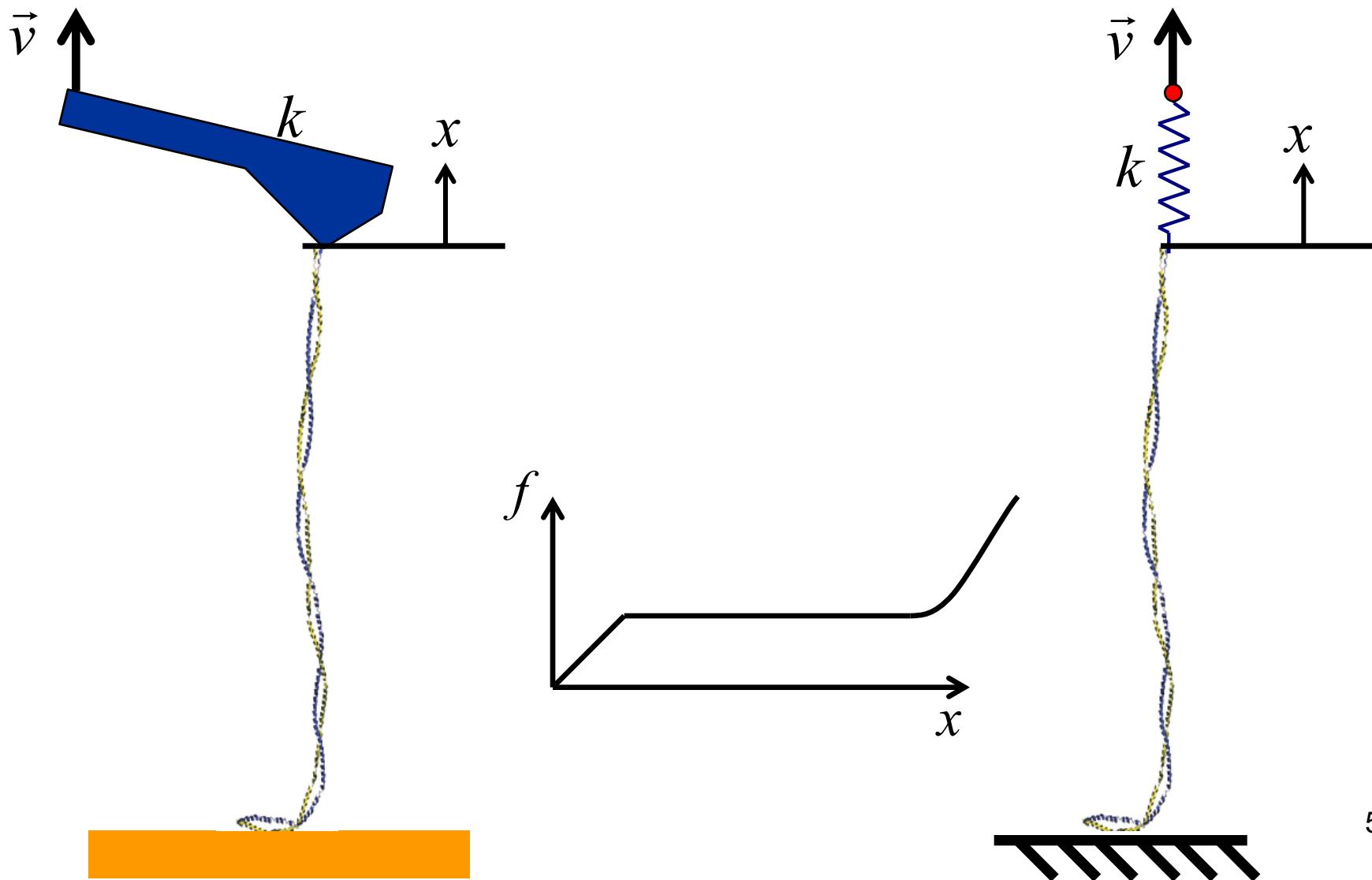
SMD deformation speed vector

time



SMD mimics AFM single molecule experiments

Atomic force microscope



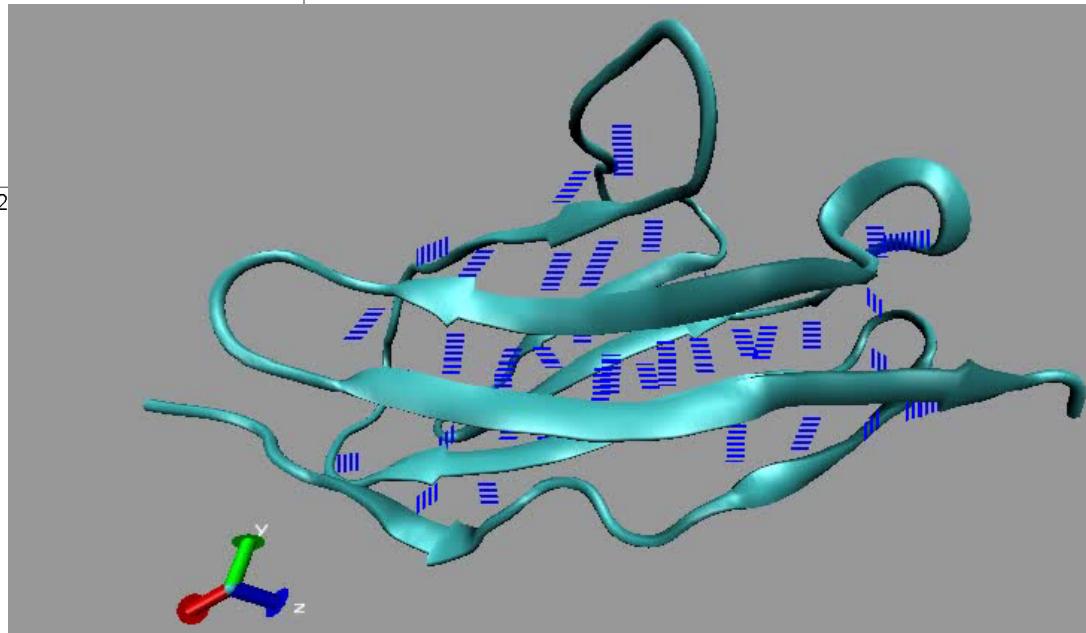
SMD is a useful approach to probe the nanomechanics of proteins (elastic deformation, “plastic” – permanent deformation, etc.)

Example: titin unfolding (CHARMM force field)

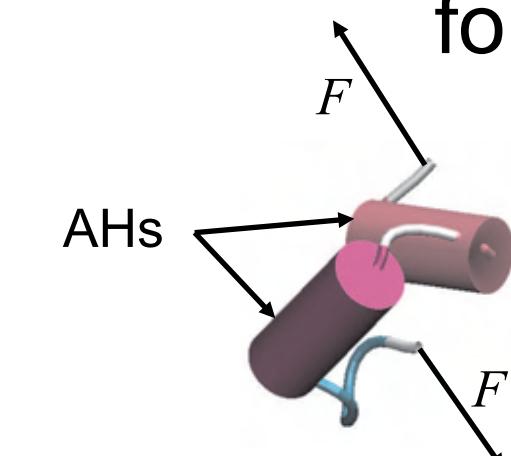
Unfolding of titin molecule



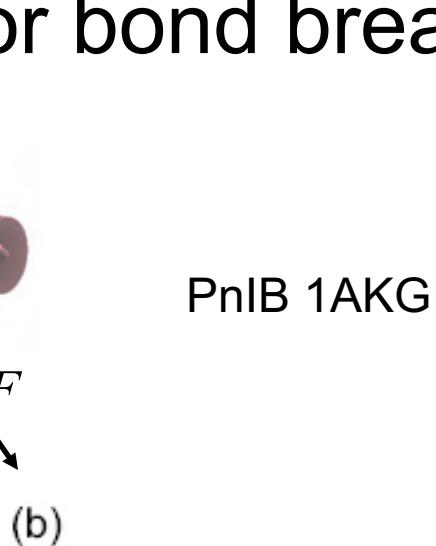
Titin I27 domain: Very
resistant to unfolding due to
parallel H-bonded strands



Protein unfolding – reactive model (allows for bond breaking)

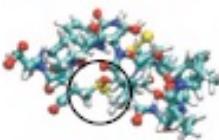


(a)

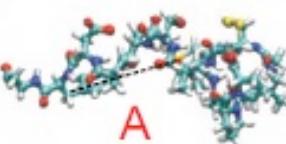


PnIB 1AKG

(b)



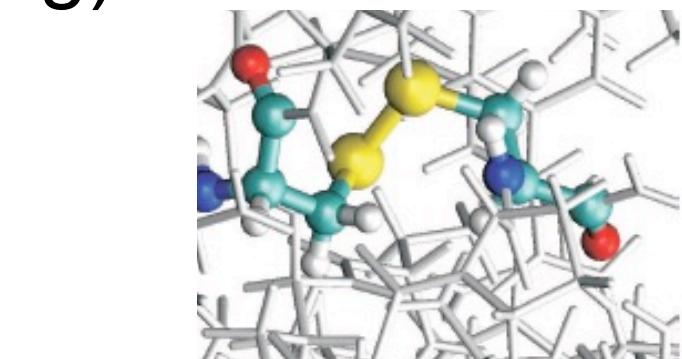
(d)



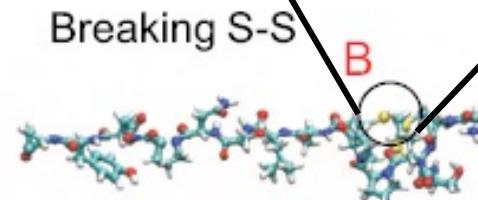
Breaking C-S



ReaxFF modeling

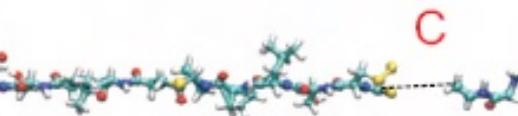


(c)



Breaking S-S

B

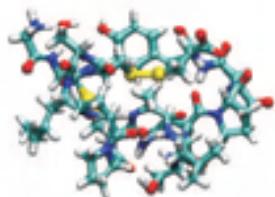


C

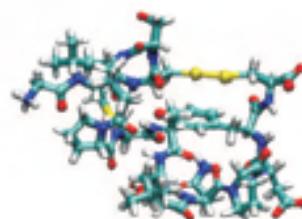
Breaking C-C

Protein unfolding - CHARMM

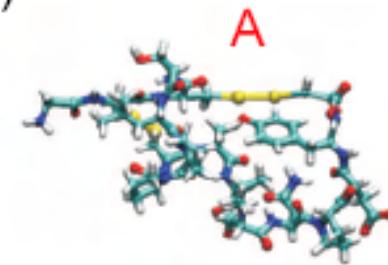
(a)



(b)

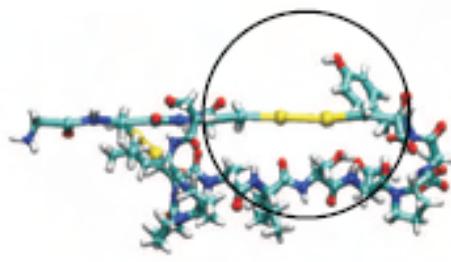


(c)

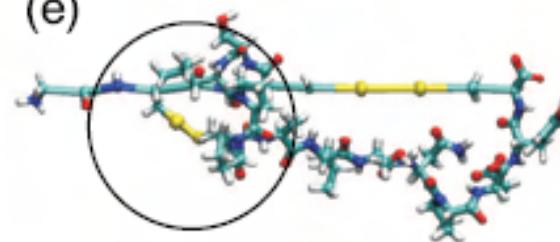


Covalent bonds don't break

(d)

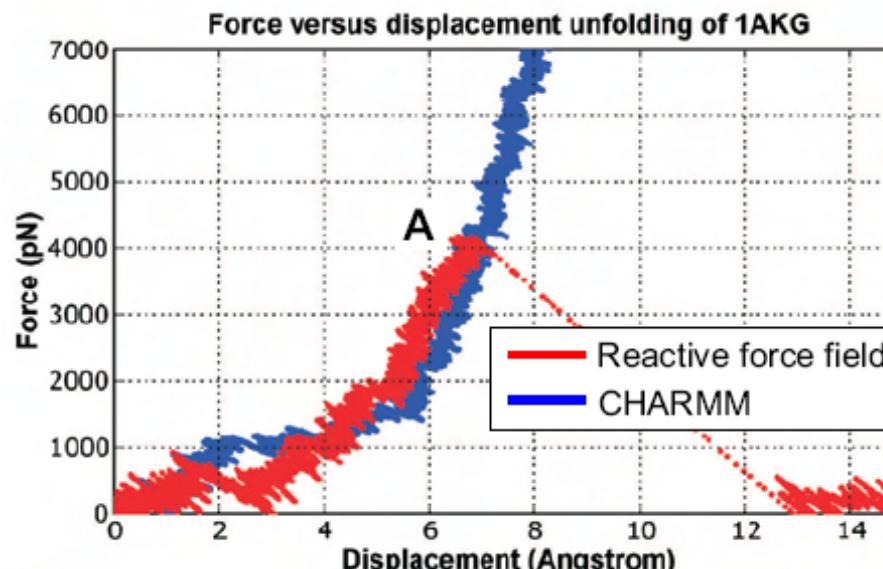
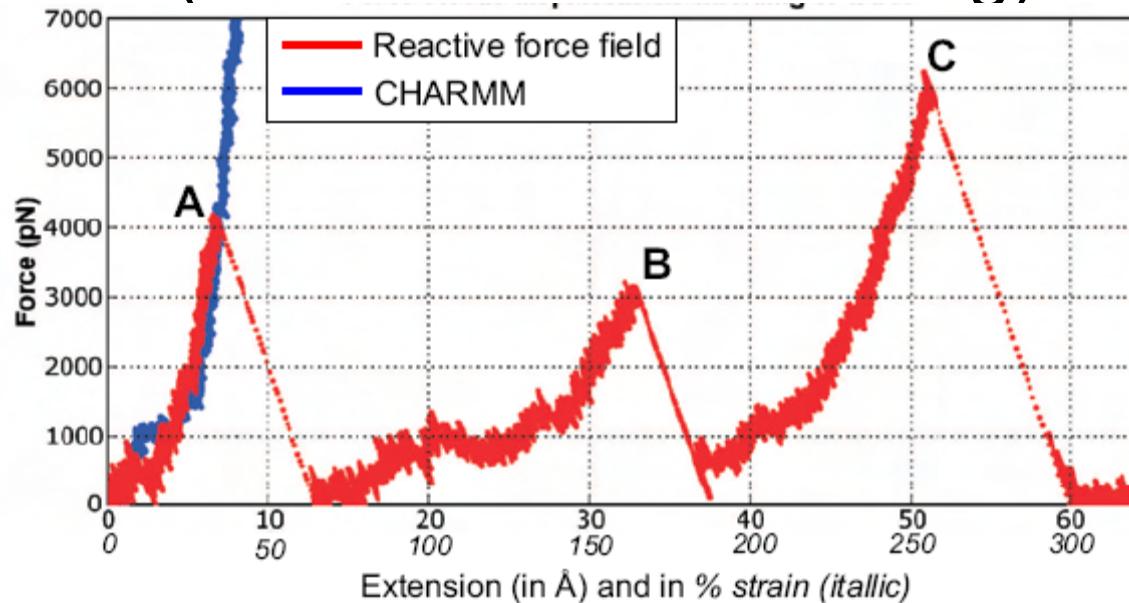


(e)



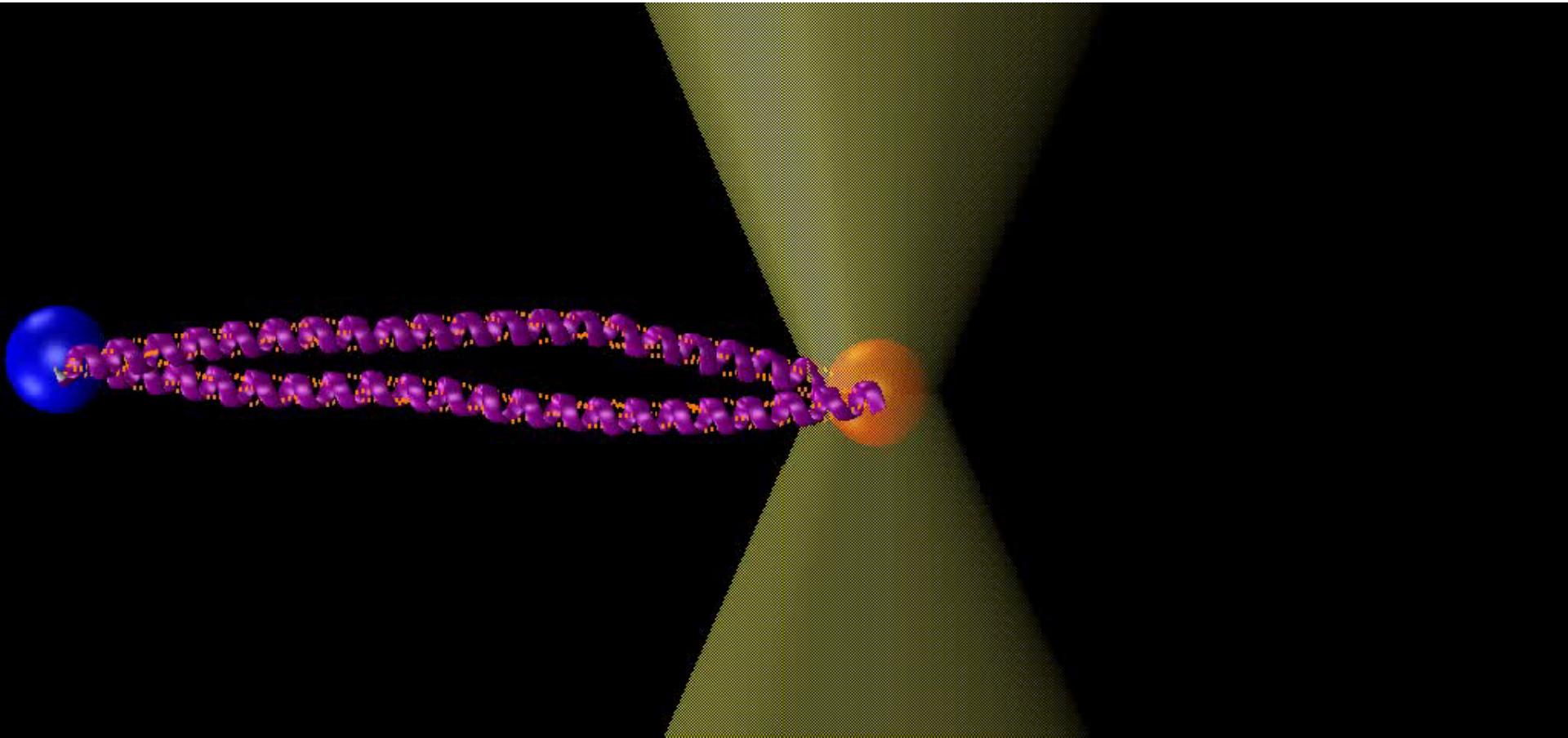
CHARMM modeling

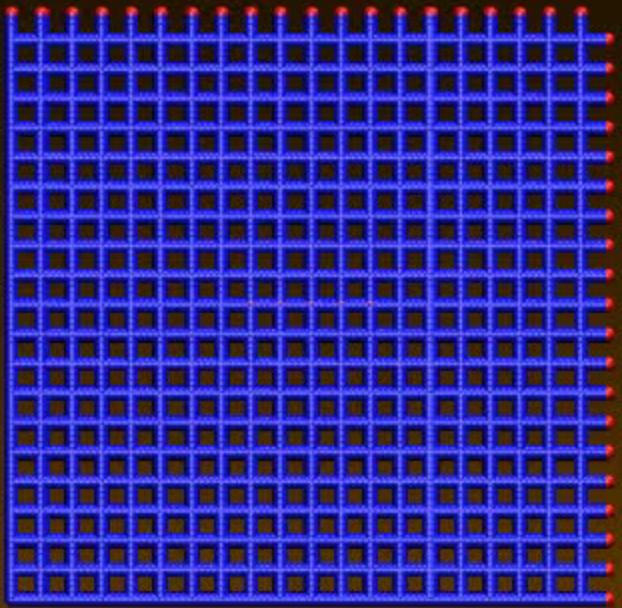
Comparison – CHARMM vs. reactive model (allows for bond breaking)



Case study: From nanoscale filaments to micrometer meshworks

Movie: MD simulation of AH coiled coil



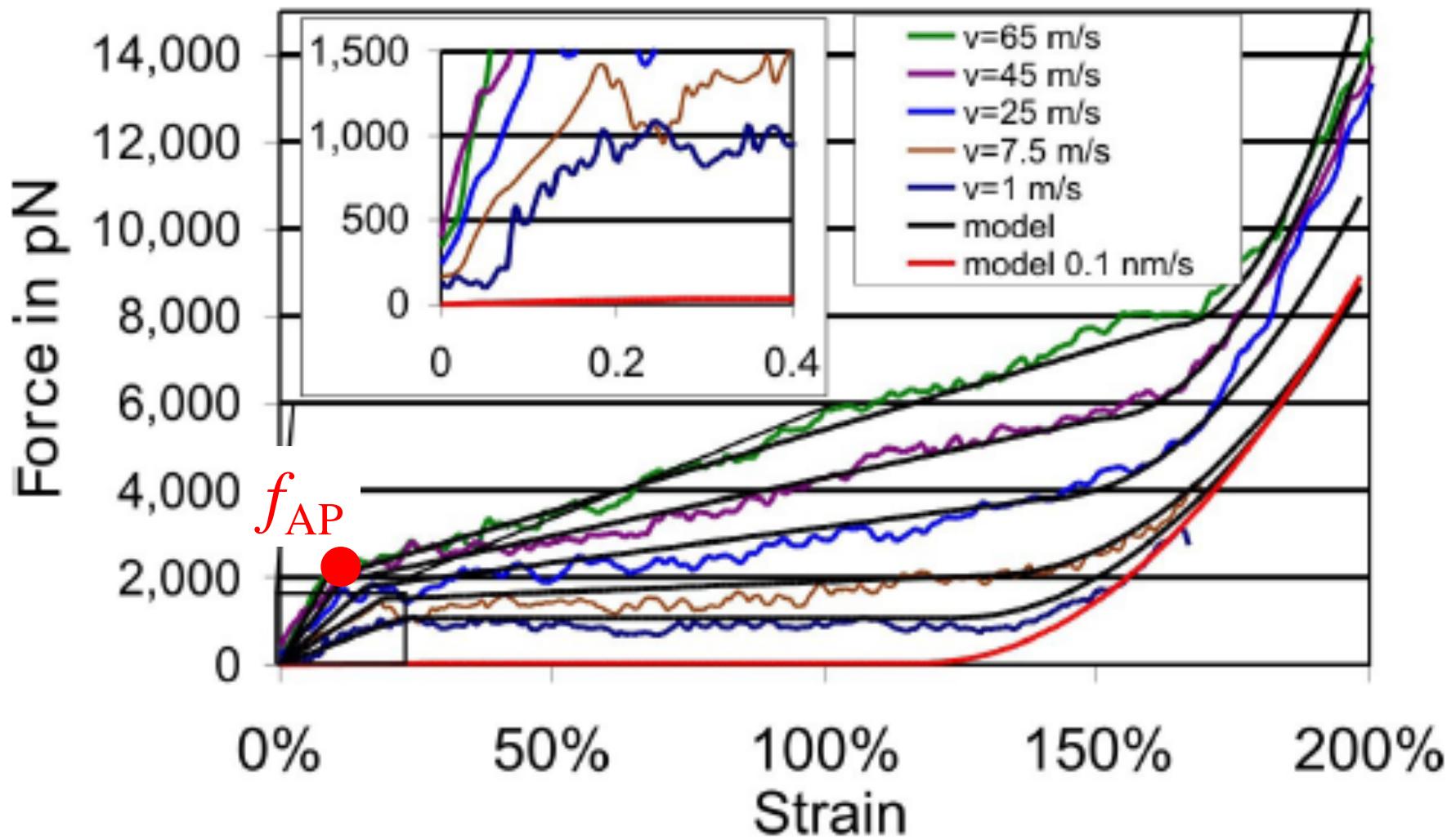


Supersonic fracture in cellular protein meshwork

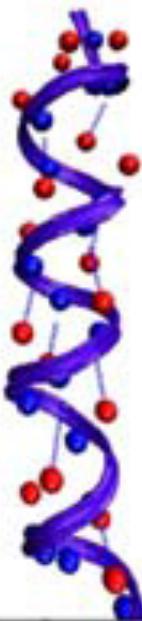
What about varying pulling speeds?

*Changing the time-scale of
observation of fracture*

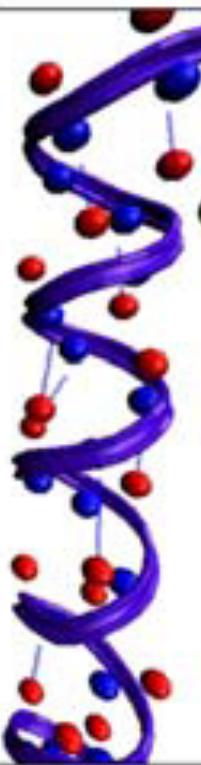
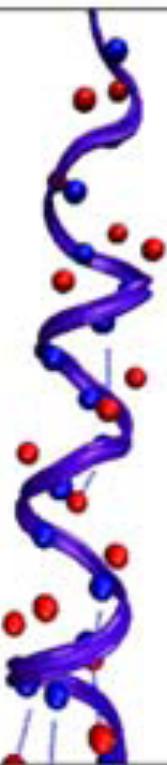
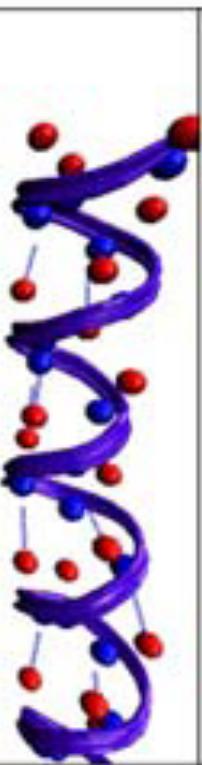
Variation of pulling speed



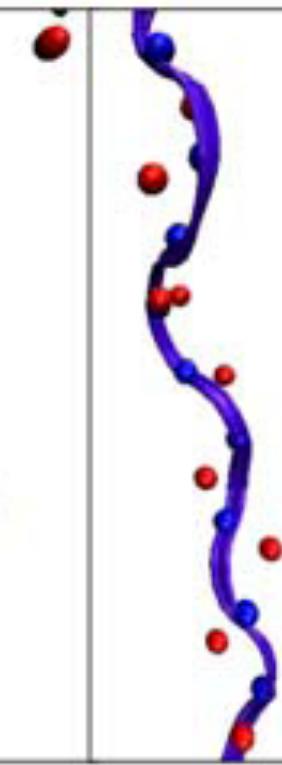
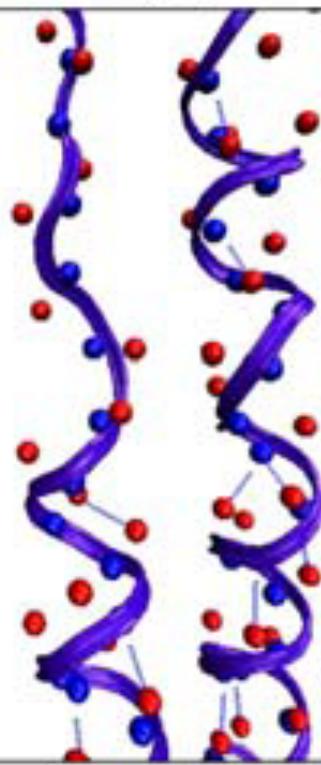
(a)



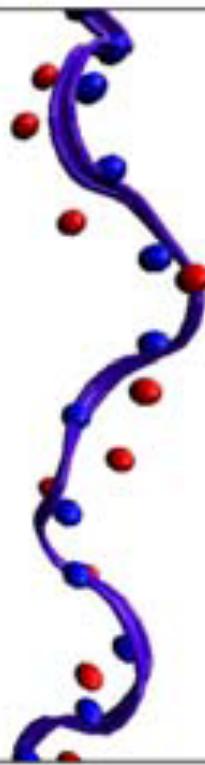
(b)



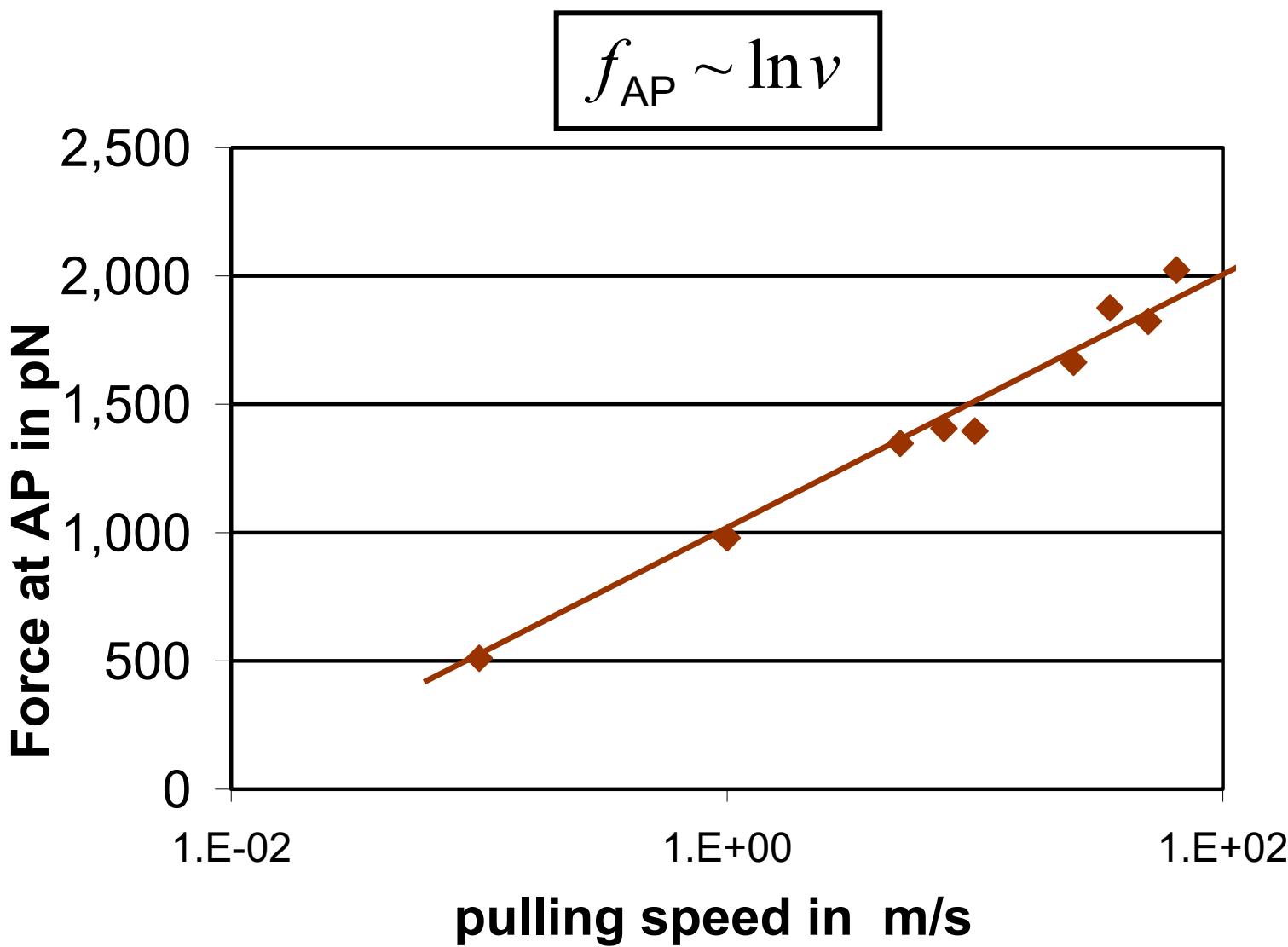
(c)



(d)

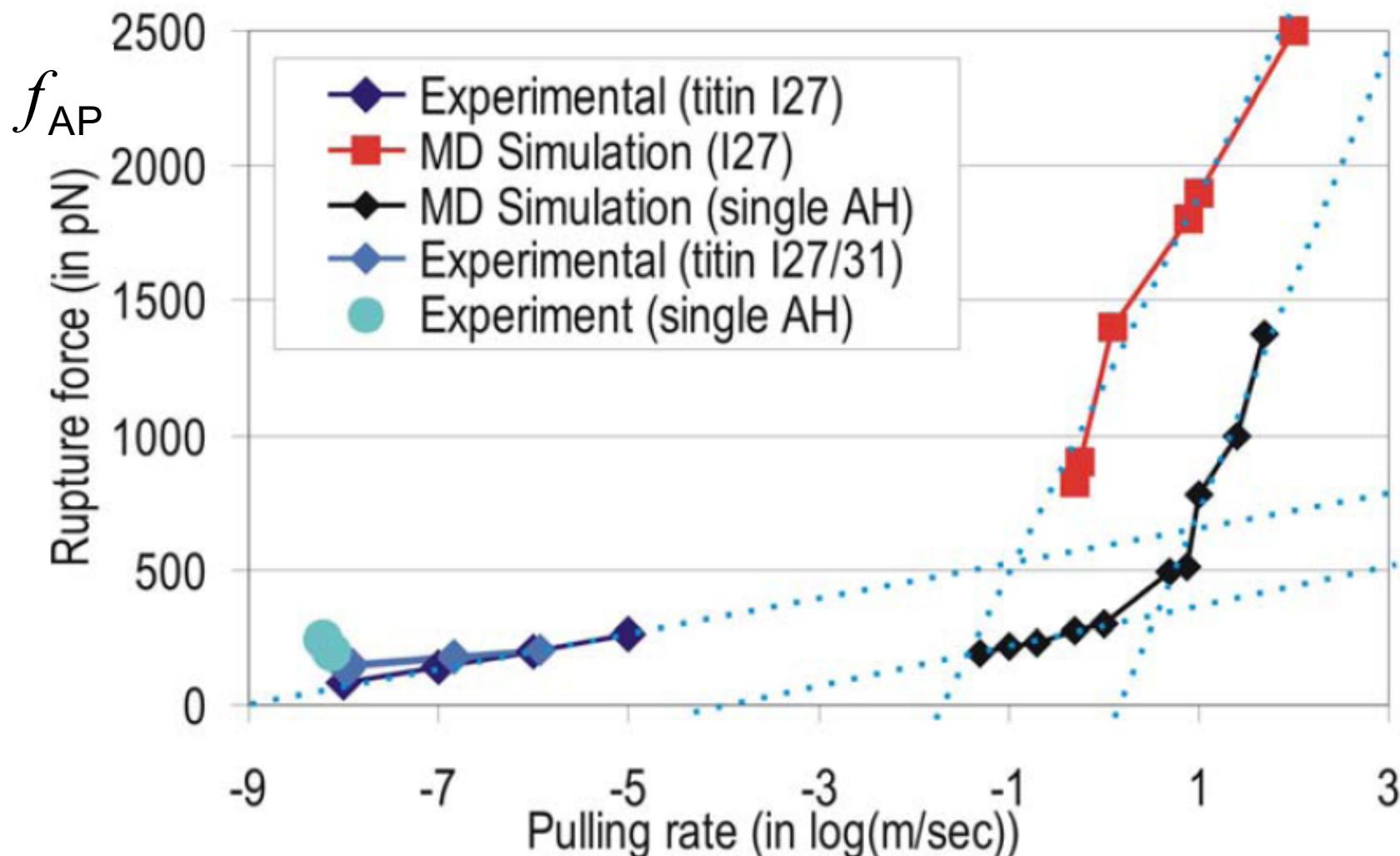


Force at angular point f_{AP} =fracture force



General results...

Rupture force vs. pulling speed



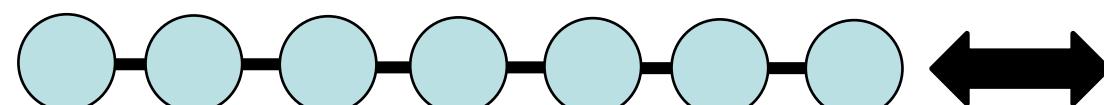
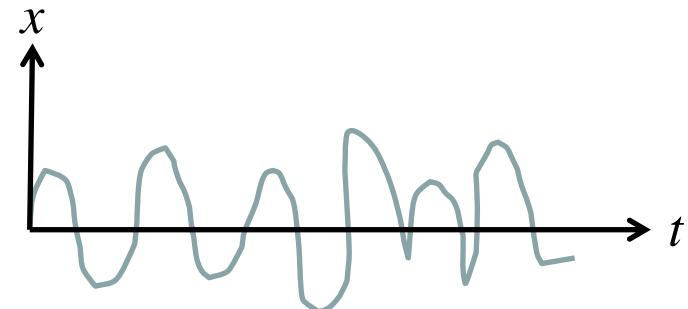
How to make sense of these results?

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

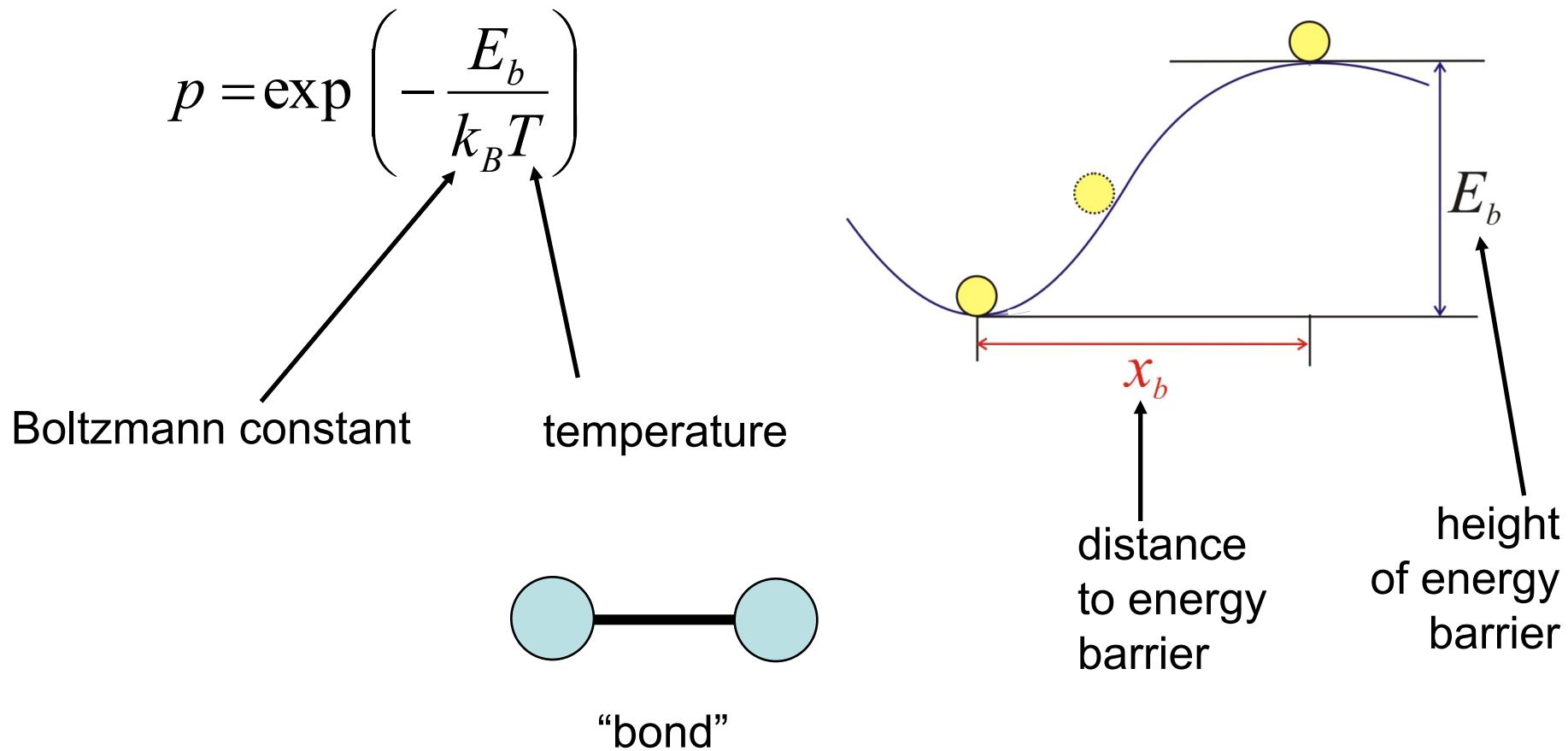
$$p = \exp\left(-\frac{E_b}{k_B T}\right)$$

- All bonds **vibrate at frequency ω**



Bell model

Probability for bond rupture (Arrhenius relation)



Bell model

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

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

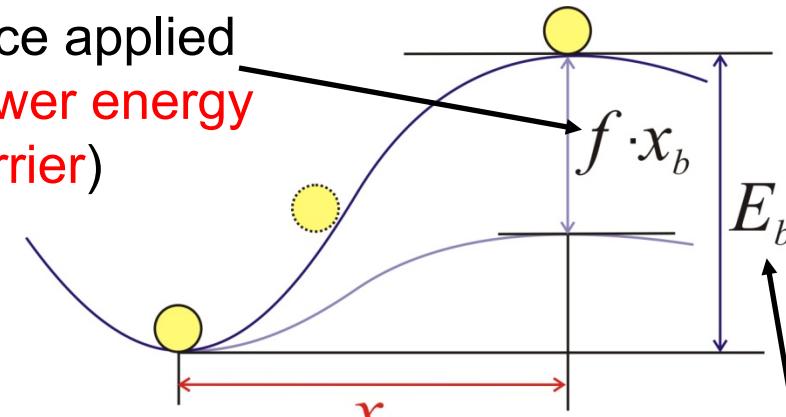
Boltzmann constant

temperature



“bond”

force applied
(lower energy
barrier)



distance
to energy
barrier

height
of energy
barrier

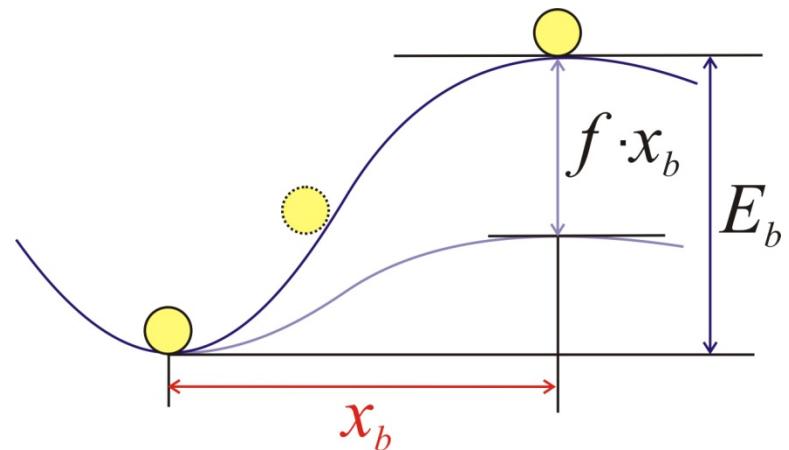
Bell model

Probability for bond rupture (Arrhenius relation)

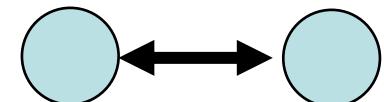
$$p = \exp\left(-\frac{E_b - f \cdot x_B}{k_B T}\right)$$

Off-rate = probability times
vibrational frequency

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



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



bond vibrations 3

Bell model

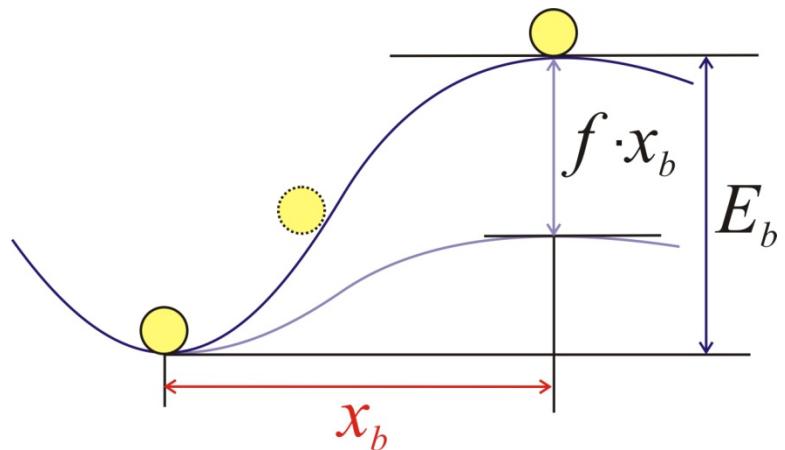
Probability for bond rupture (Arrhenius relation)

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

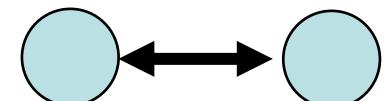
Off-rate = probability times
vibrational frequency

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

“How often bond breaks per unit time”



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

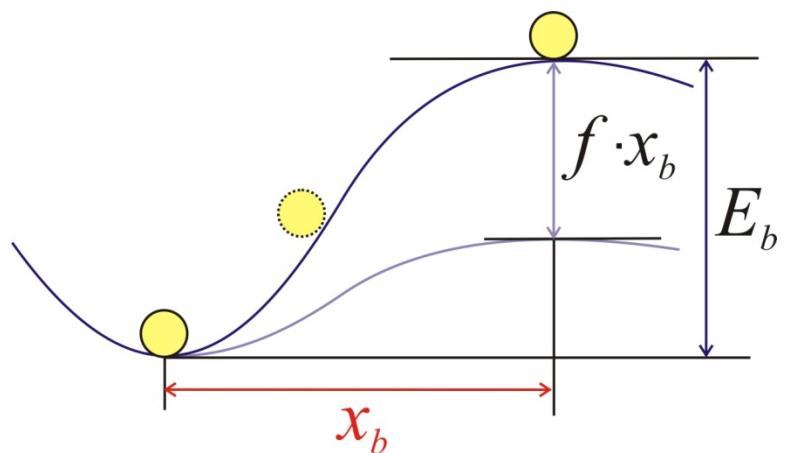


bond vibrations

Bell model

Probability for bond rupture (Arrhenius relation)

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

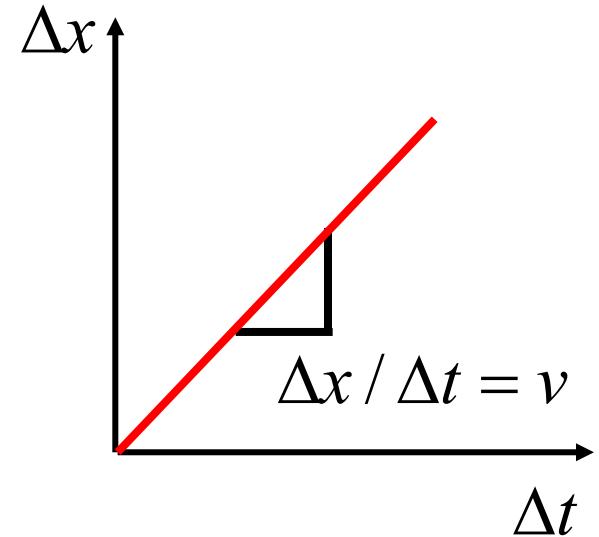
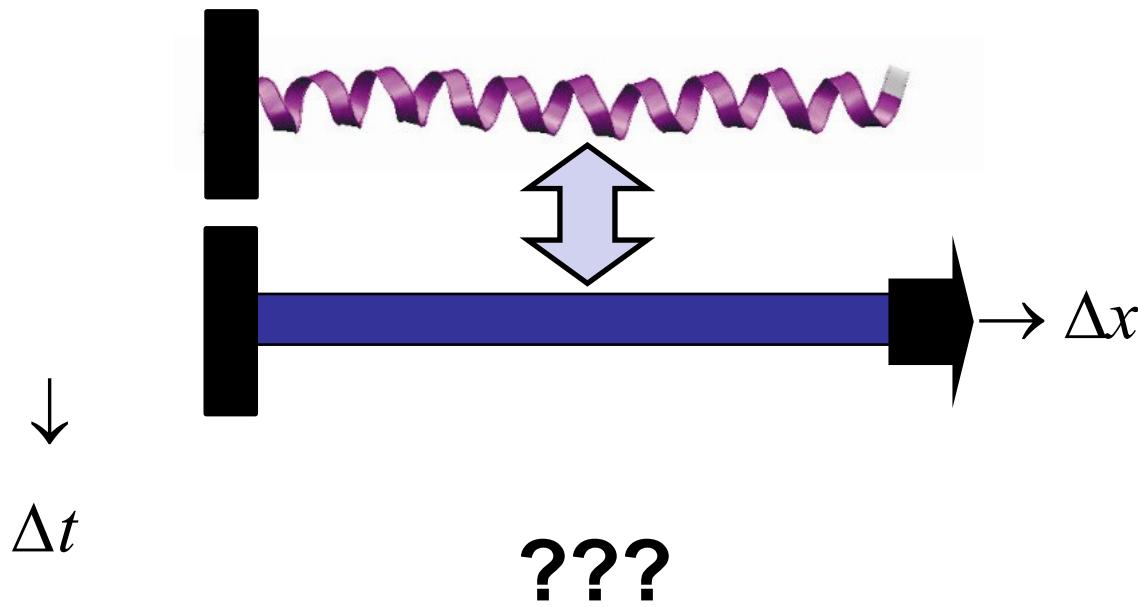


Off-rate = probability times
vibrational frequency

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

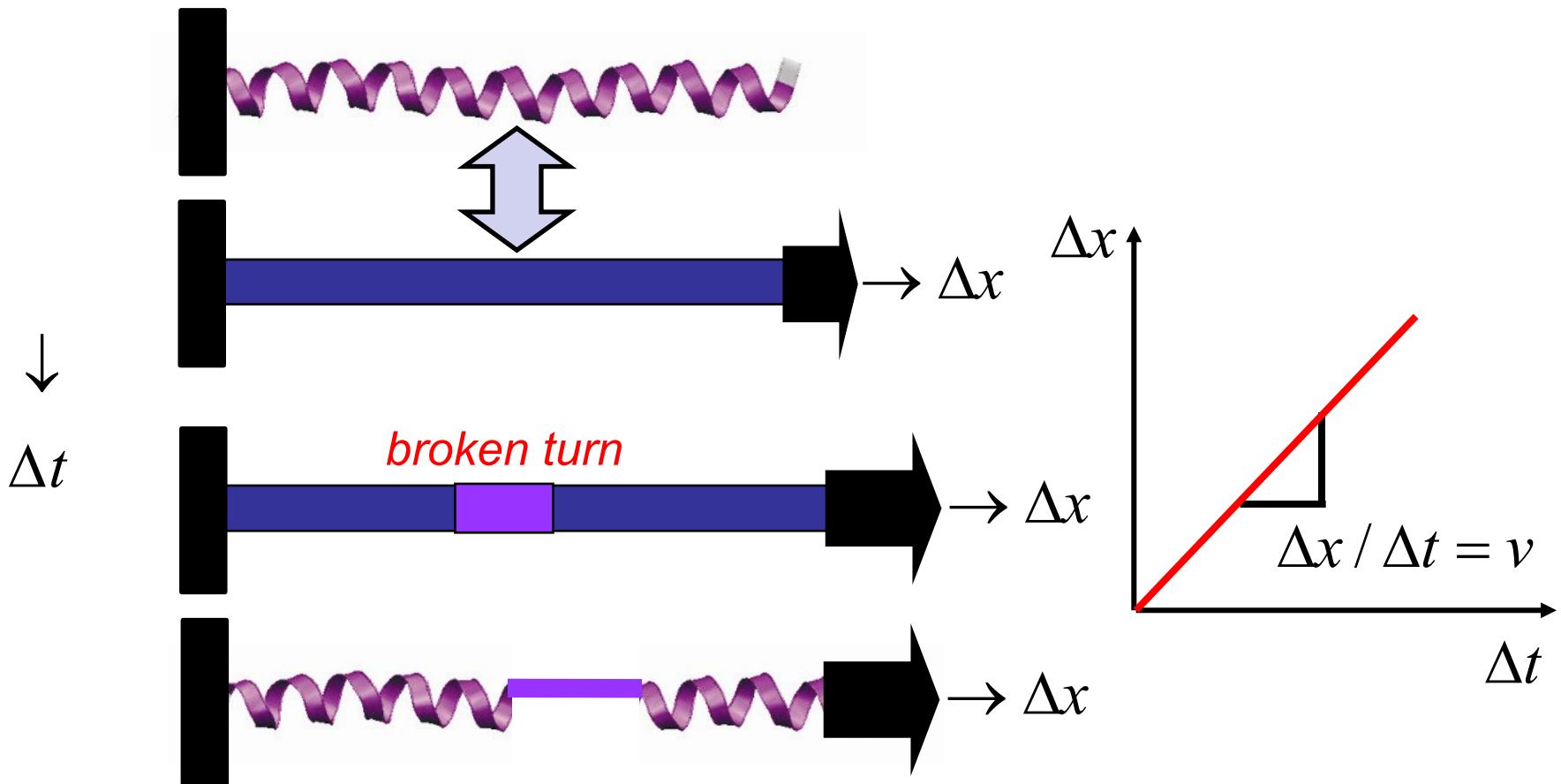
τ = bond lifetime
(inverse of off-rate)⁷⁵

Bell model



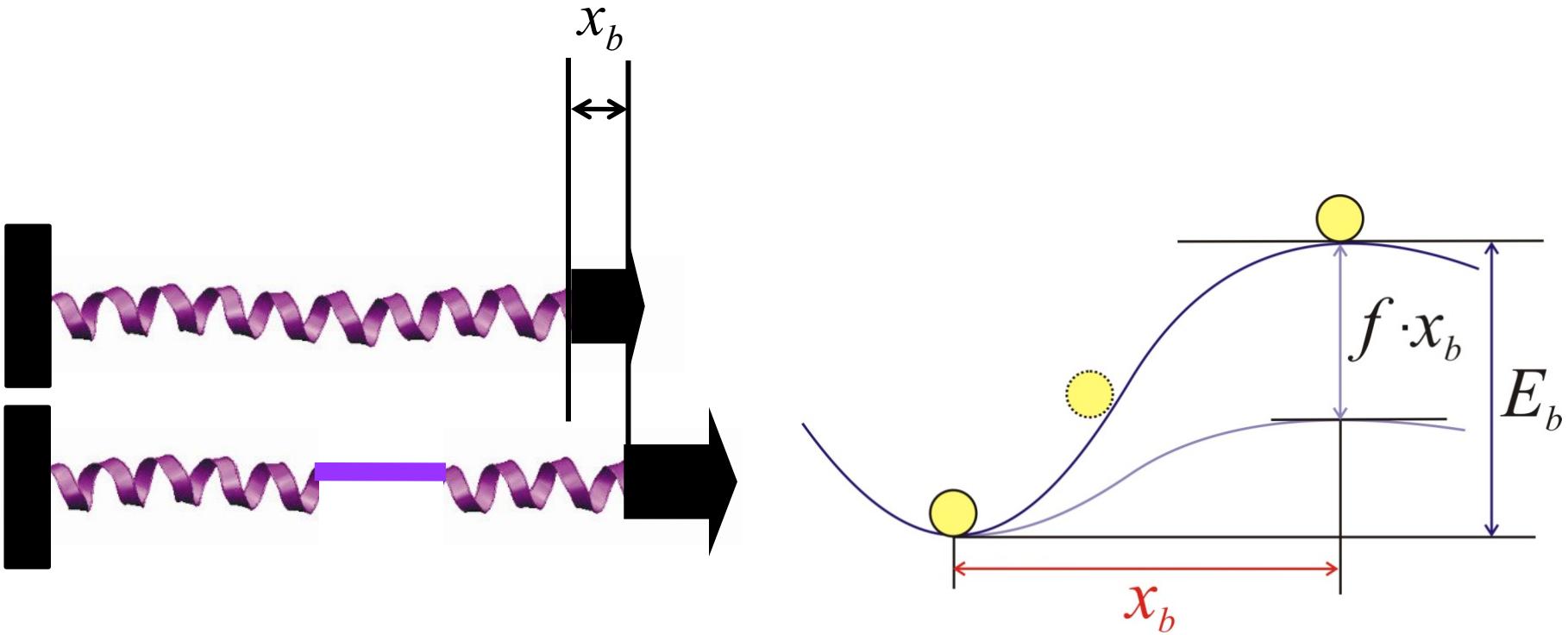
$\Delta x / \Delta t = v$ pulling speed (at end of molecule)

Bell model



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

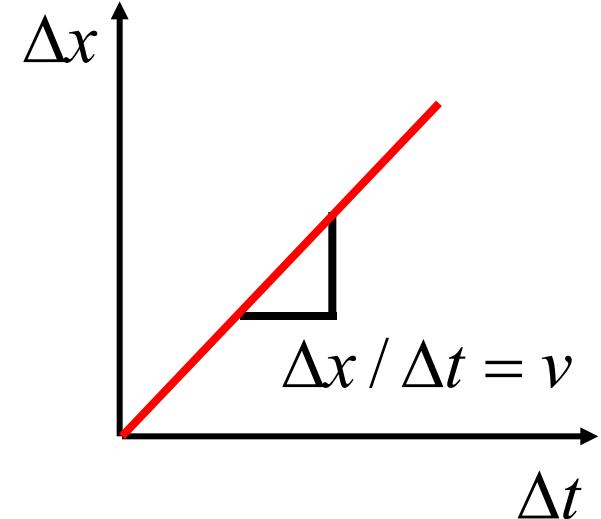
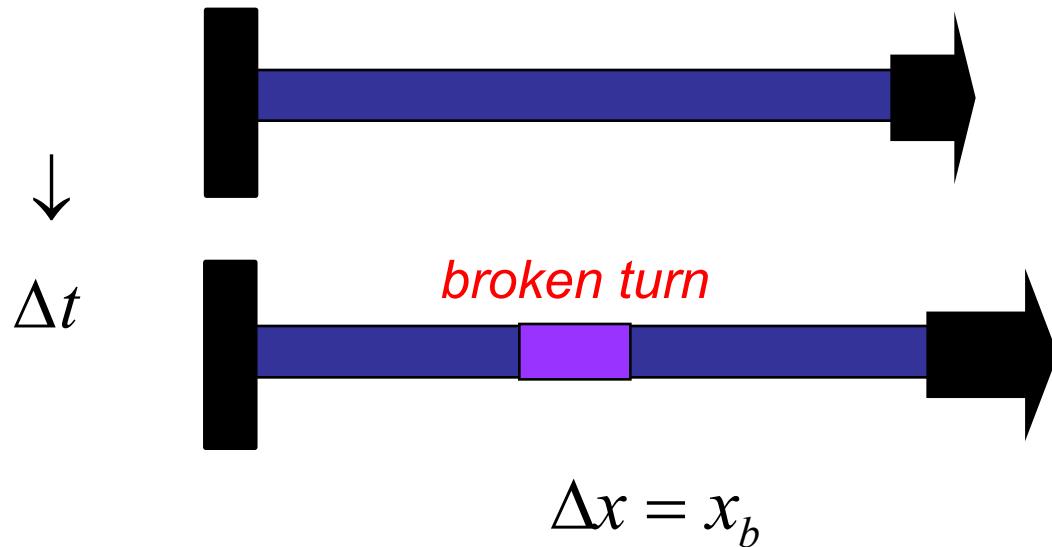
Structure-energy landscape link



$$\Delta x = x_b$$

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

Bell model



Bond breaking at x_b (lateral applied displacement):

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

\Downarrow
 $= 1/\tau$

↑
pulling speed ⁷⁹

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 :

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

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

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

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

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

Simplification by grouping of variables

*Only system parameters,
[distance/length]*

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

Bell model

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

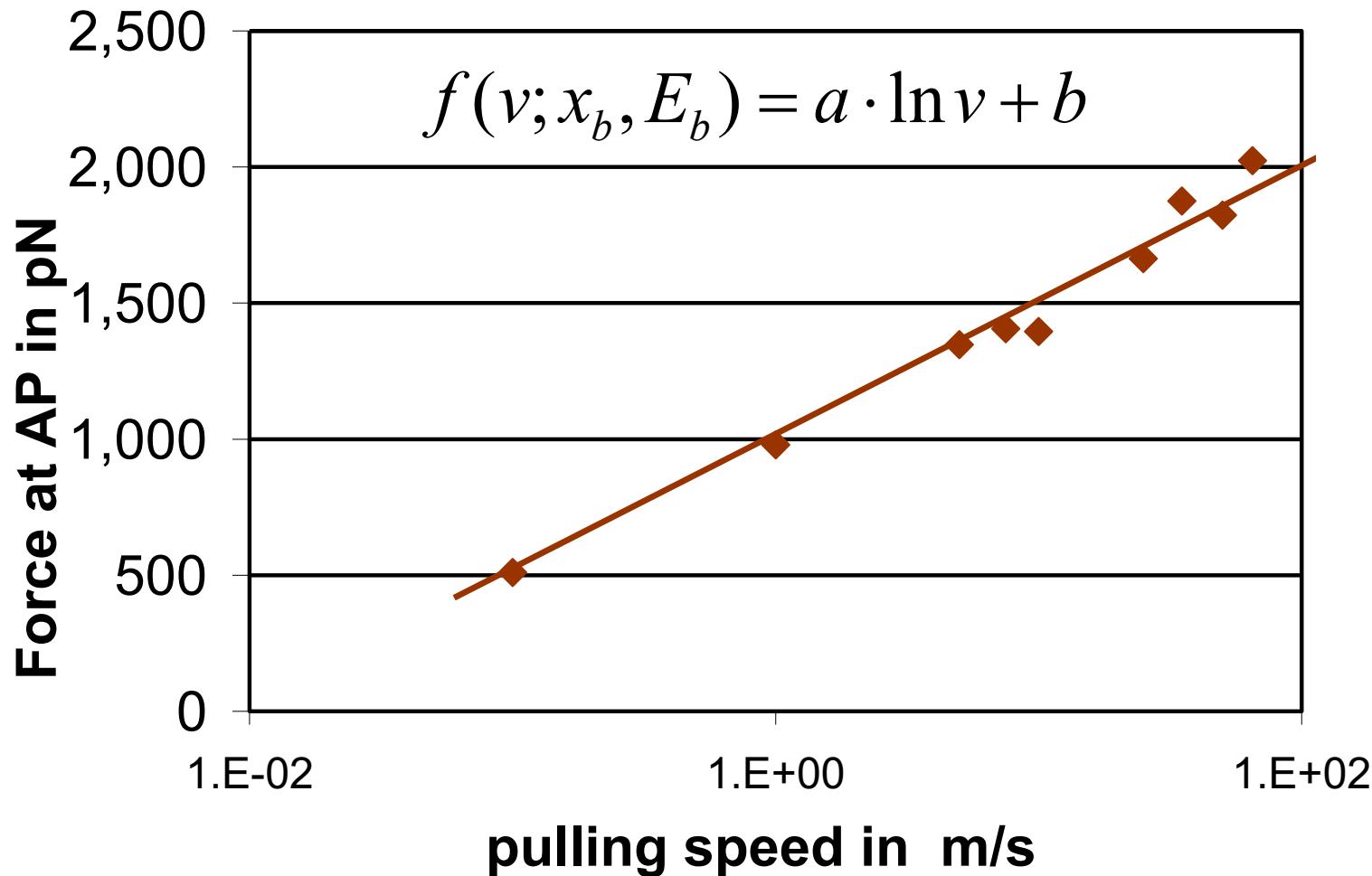
Results in:

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

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

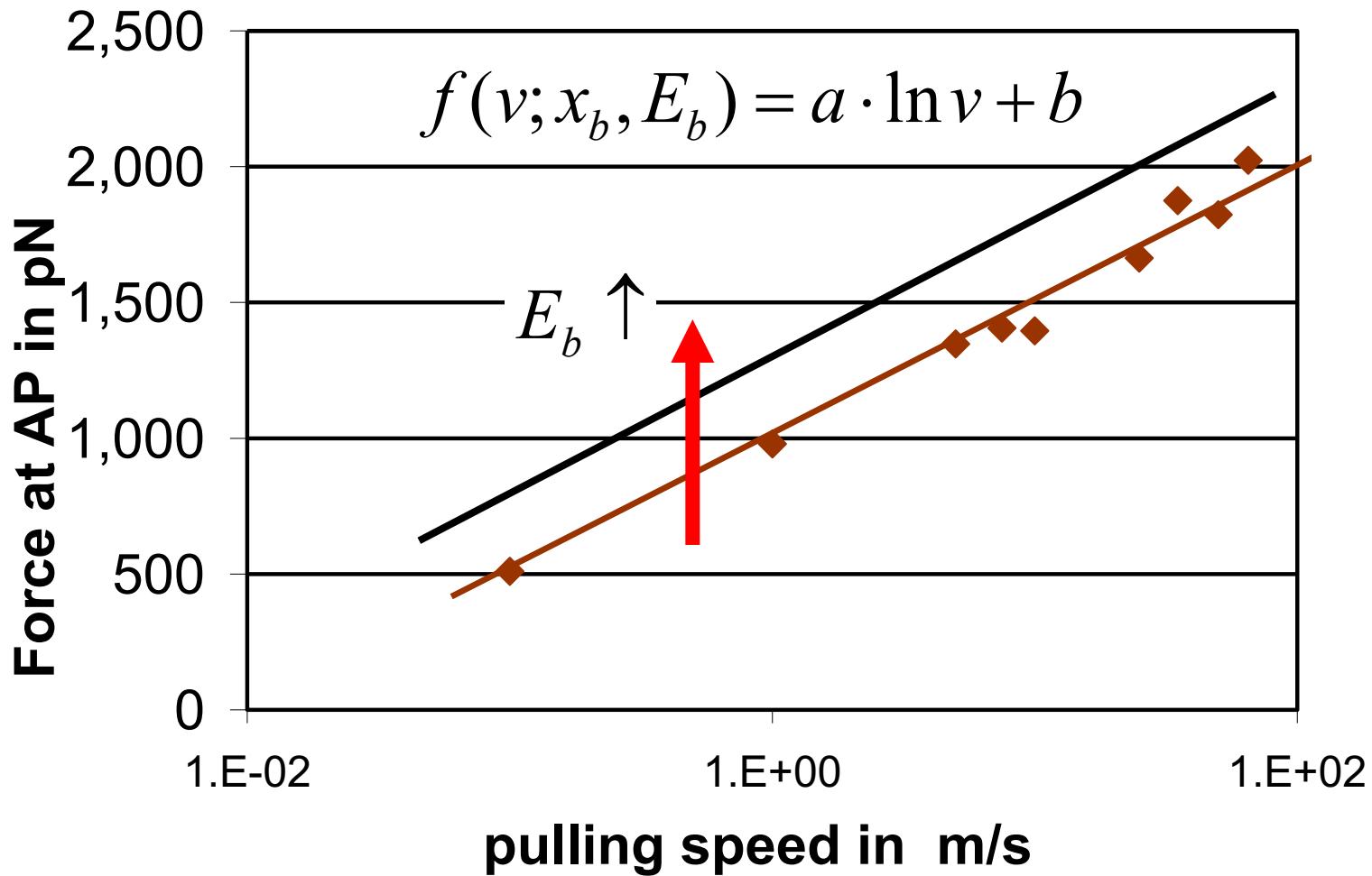
$$b = -\frac{k_B \cdot T}{x_b} \cdot \ln v_0$$

$f \sim \ln \nu$ 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

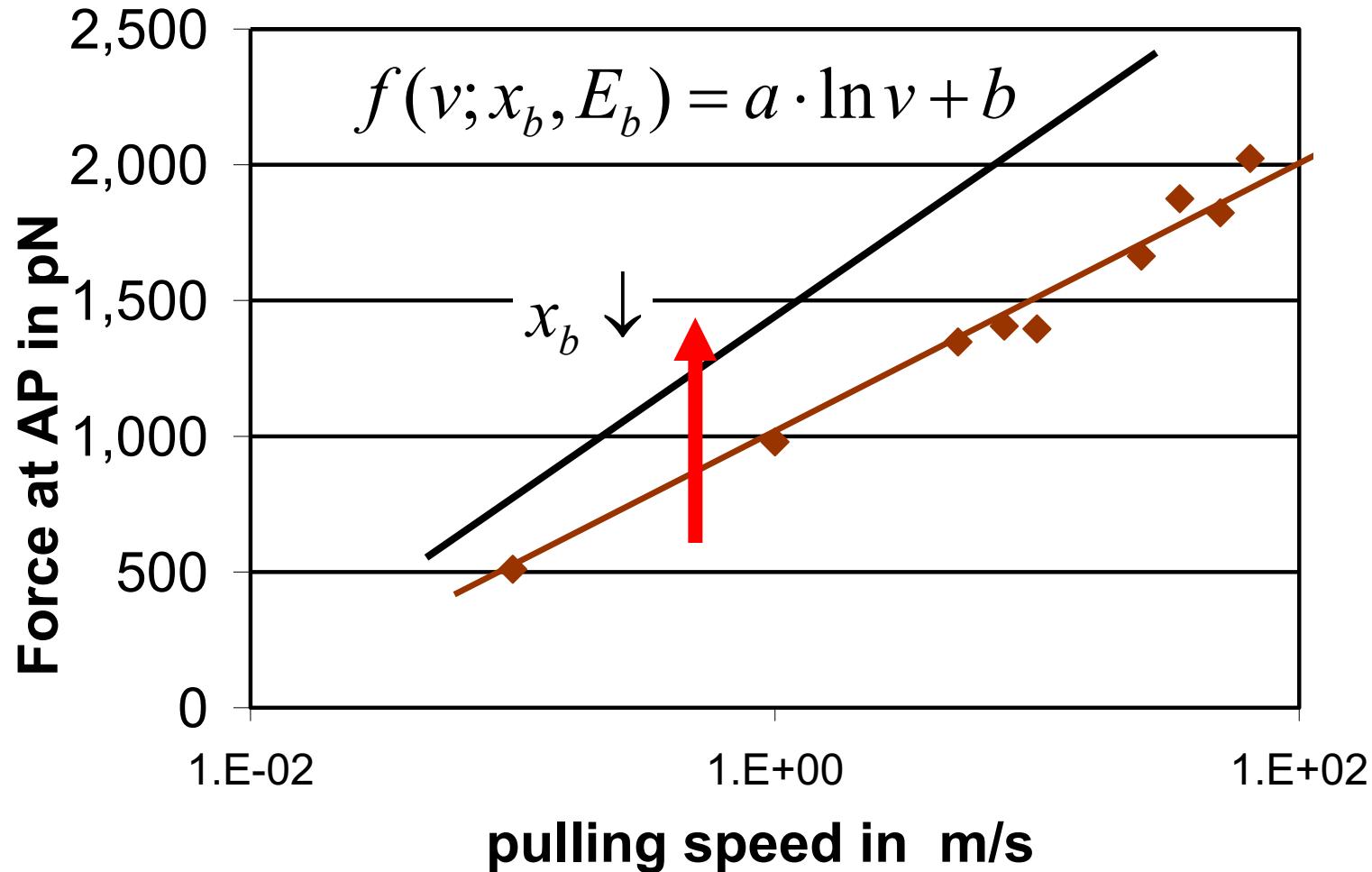


$$a = \frac{k_B \cdot T}{x_b}$$

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

$$\nu_0 = \omega_0 \cdot x_b \cdot \exp\left(-\frac{E_b}{k_b^{85} \cdot T}\right)$$

Scaling with x_b : changes slope

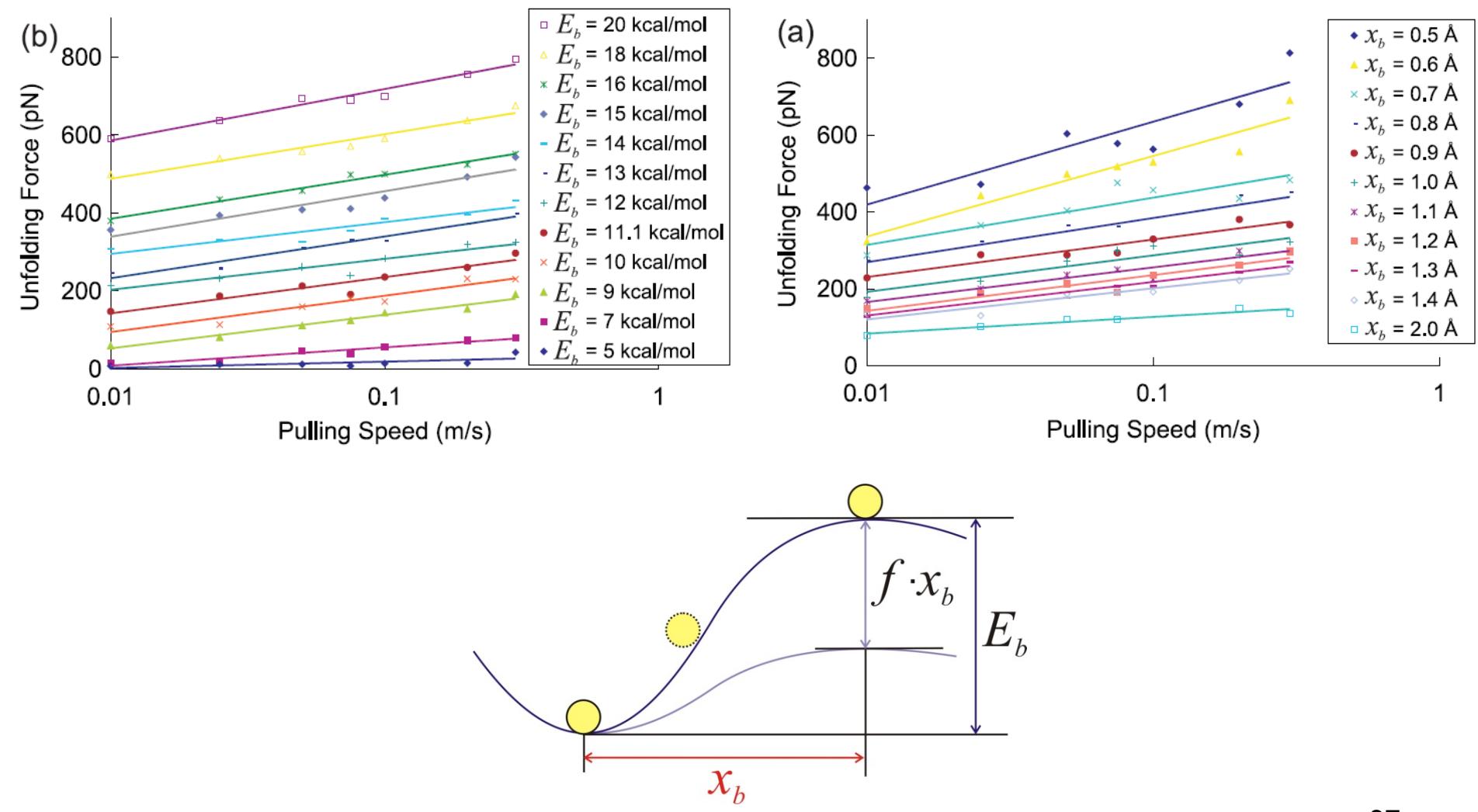


$$a = \frac{k_B \cdot T}{x_b}$$

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

$$\nu_0 = \omega_0 \cdot x_b \cdot \exp\left(-\frac{E_b}{k_b^{86} \cdot T}\right)$$

Simulation results



Mechanisms associated with protein fracture

Change in fracture mechanism



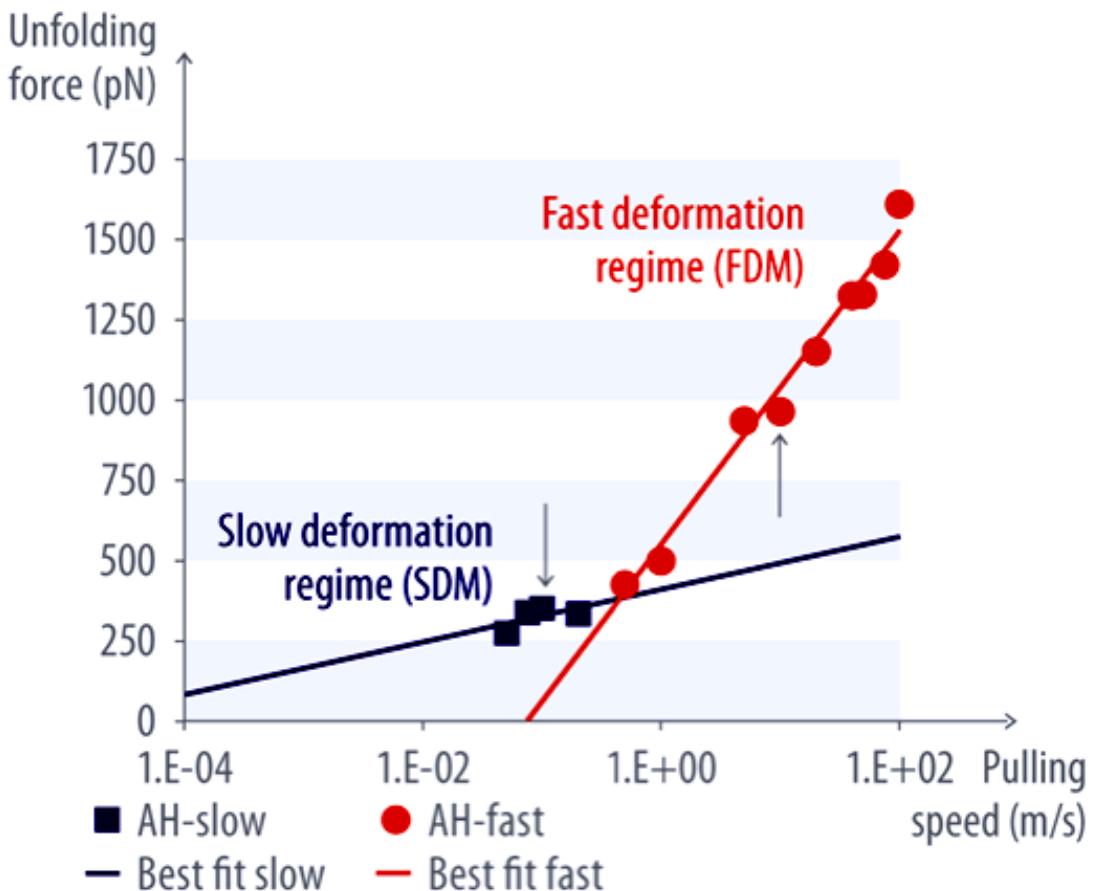
Single AH structure

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

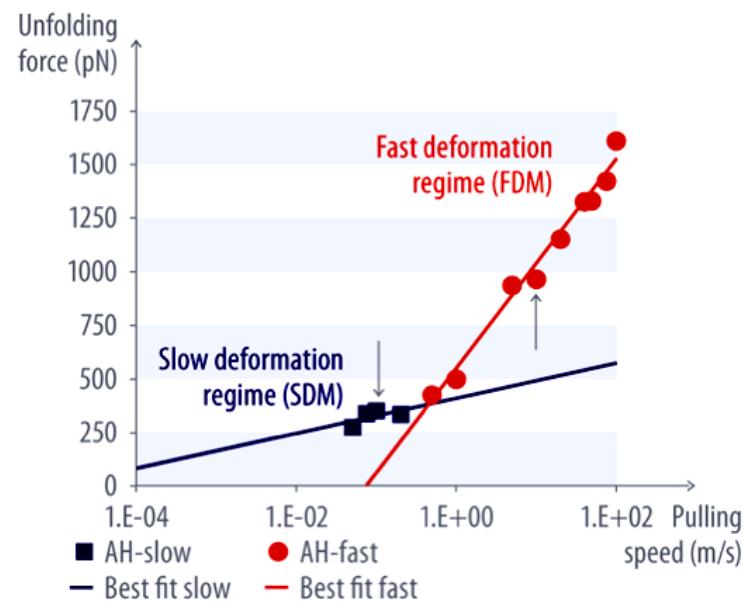
Table 1. Summary of the differences between the SDM and FDM, for AH1, AH2, and BS

Parameter	AH1 (AH2) domain		BS domain	
	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

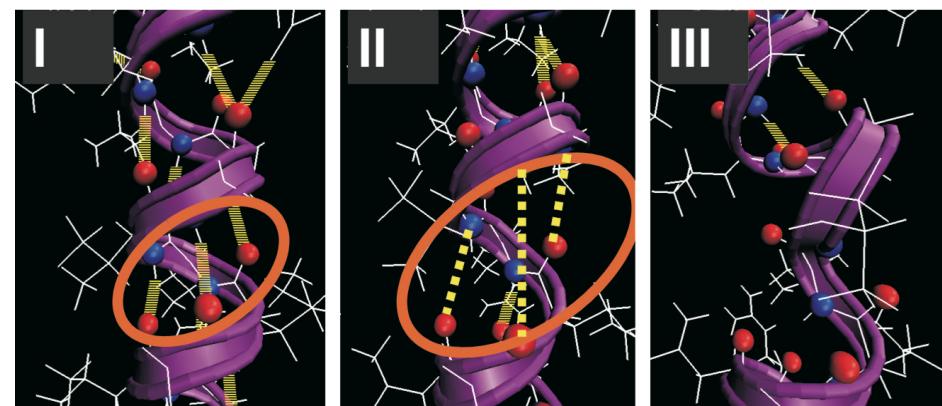
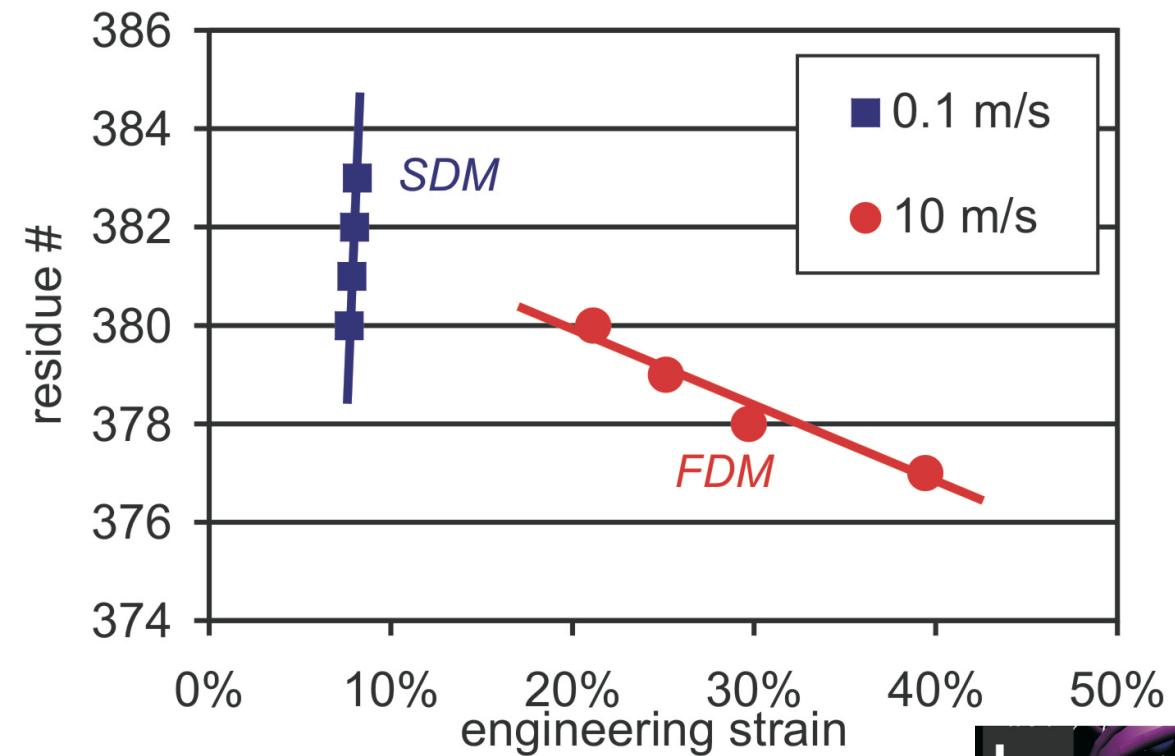
The values in parentheses in the AH columns represent the results for AH2.

Energy single H-bond: $\approx 3\text{-}4$ kcal/mol

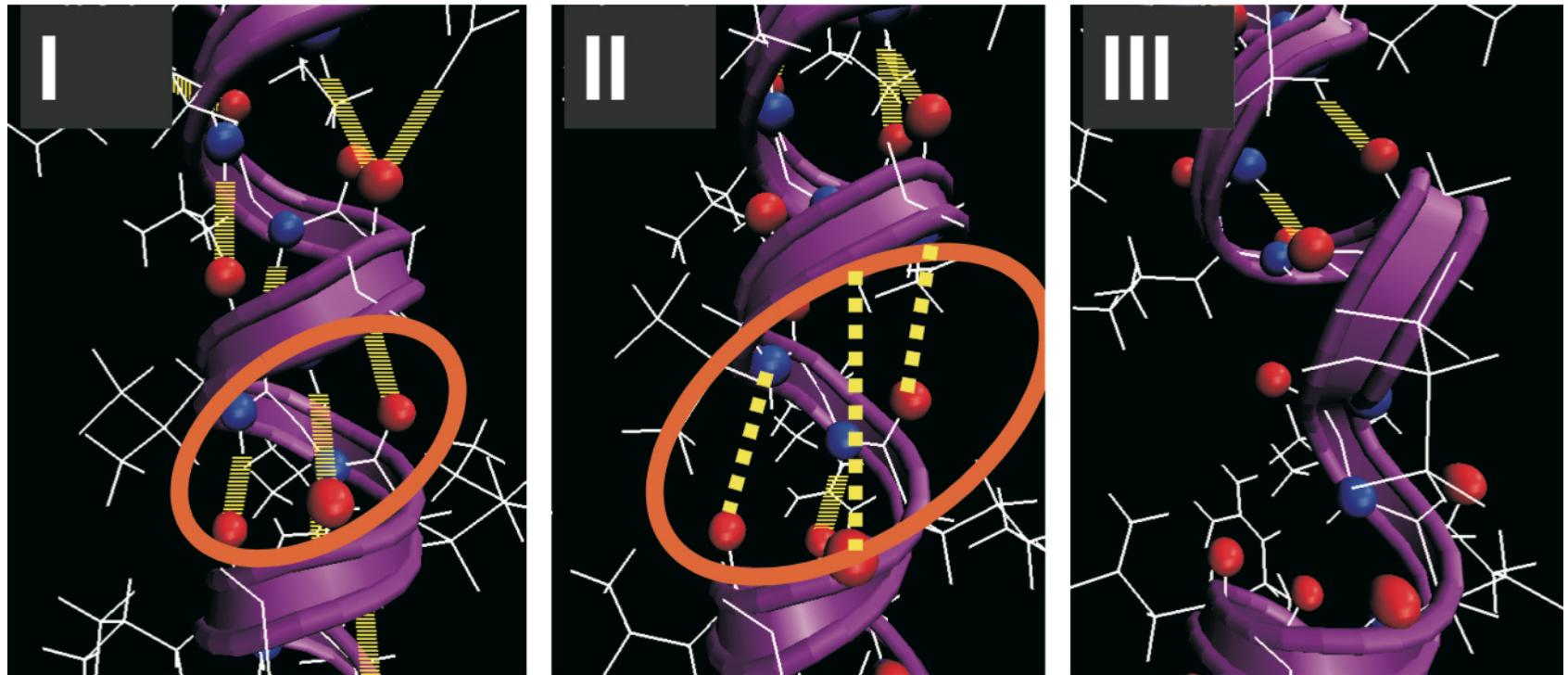
What does this mean???



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...