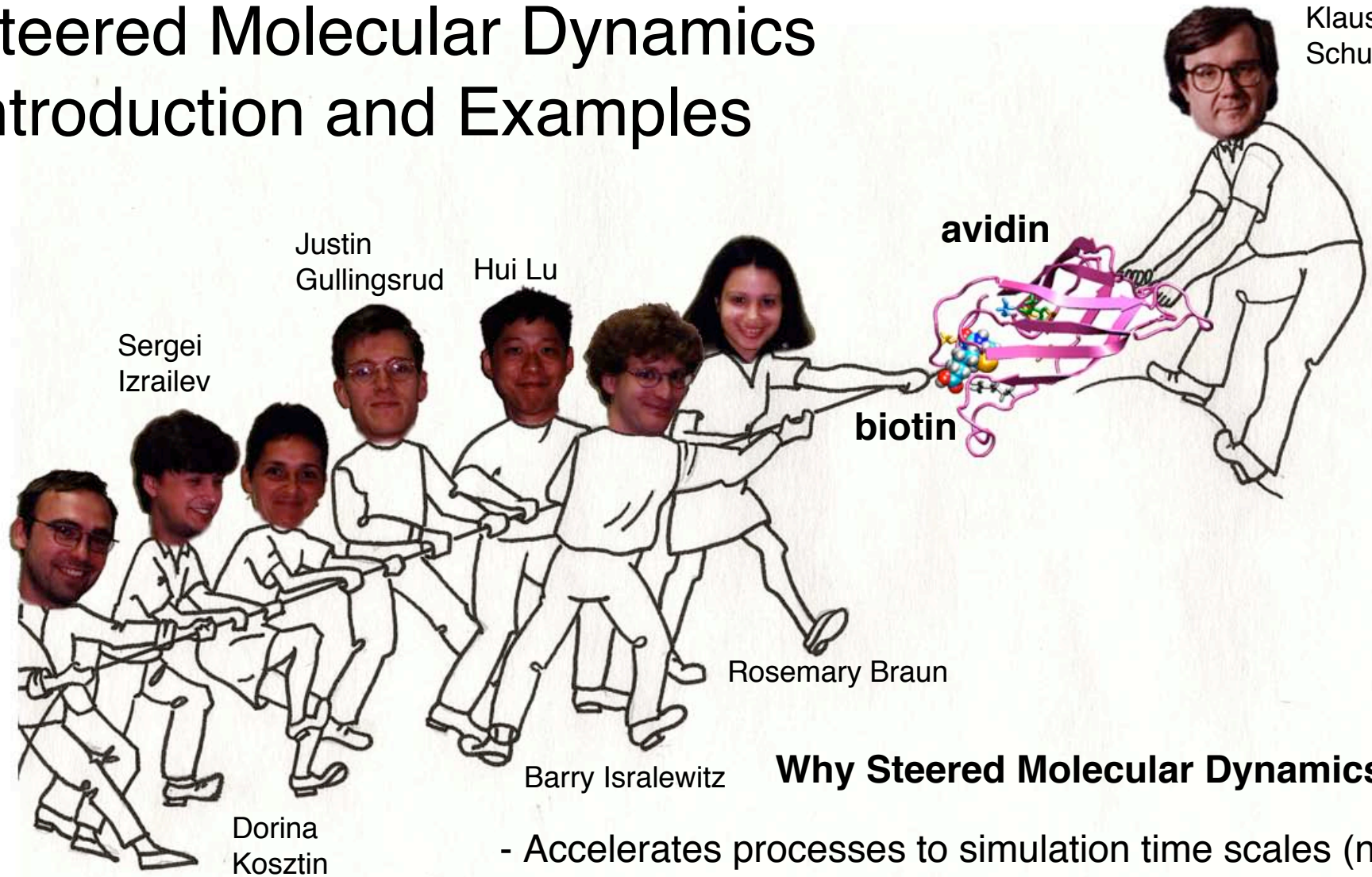
Steered Molecular Dynamics Introduction and Examples



Why Steered Molecular Dynamics?

- Accelerates processes to simulation time scales (ns)
- Yields explanations of biopolymer mechanics
- Complements Atomic Force Microscopy
- Finds underlying unbinding potentials
- Generates and tests Hypotheses

Acknowledgements:
Fernandez group, Mayo C.; Vogel group, U. Washington
NIH, NSF, Carver Trust

Mechanical Functions of Proteins

Forces

naturally arise in cells

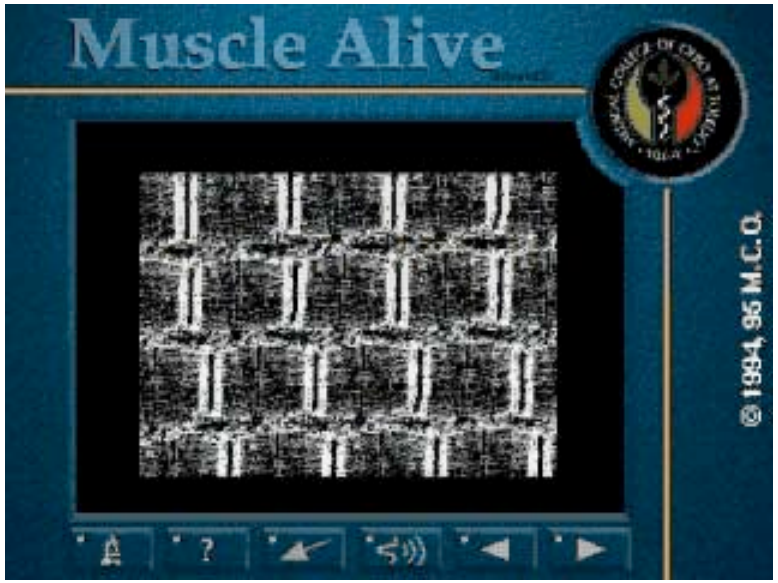
and can also be

substrates (ATPase)

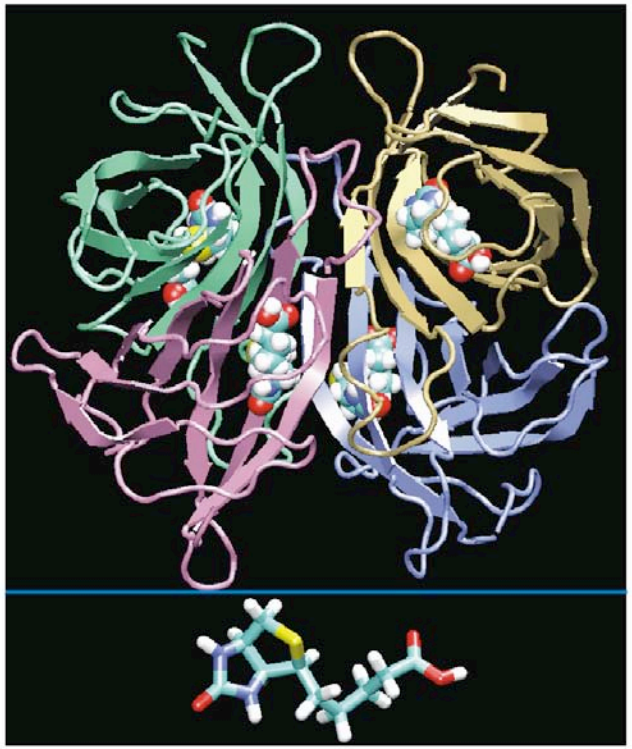
products (myosin)

signals (integrin)

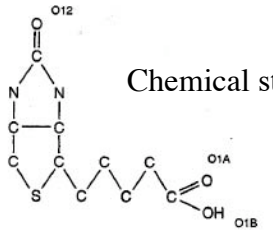
of cellular processes



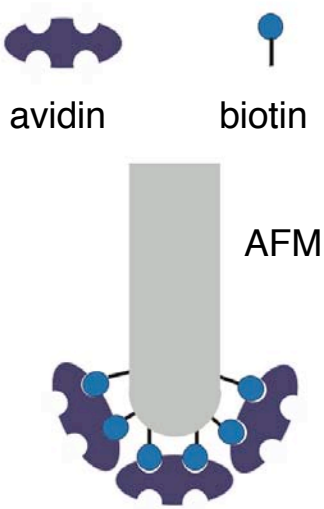
Atomic Force Microscopy Experiments of Ligand Unbinding

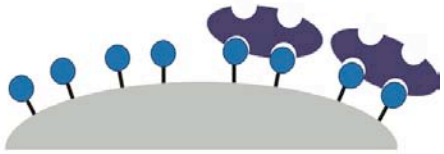


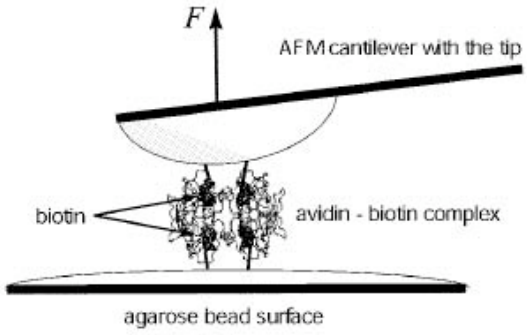
Biotin



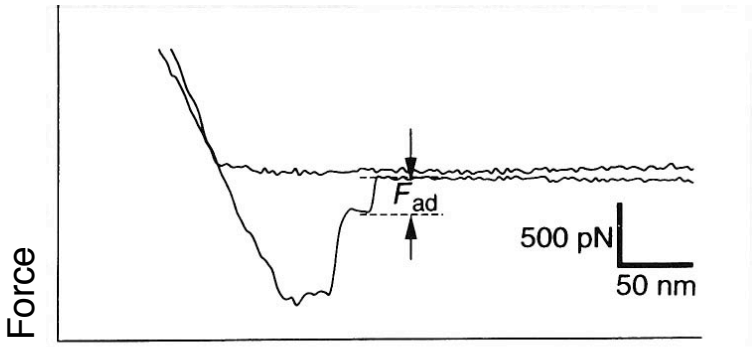
Chemical structure of biotin



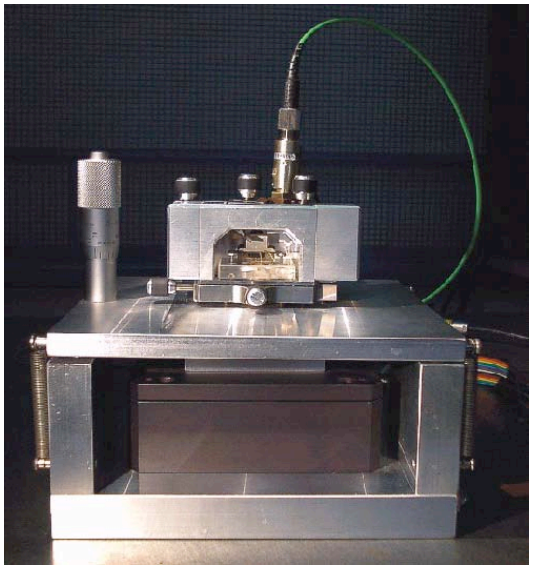




Florin et al., Science 264:415 (1994)



Displacement of AFM tip



Atomic Force Microscopy Experiments of Ligand Unbinding

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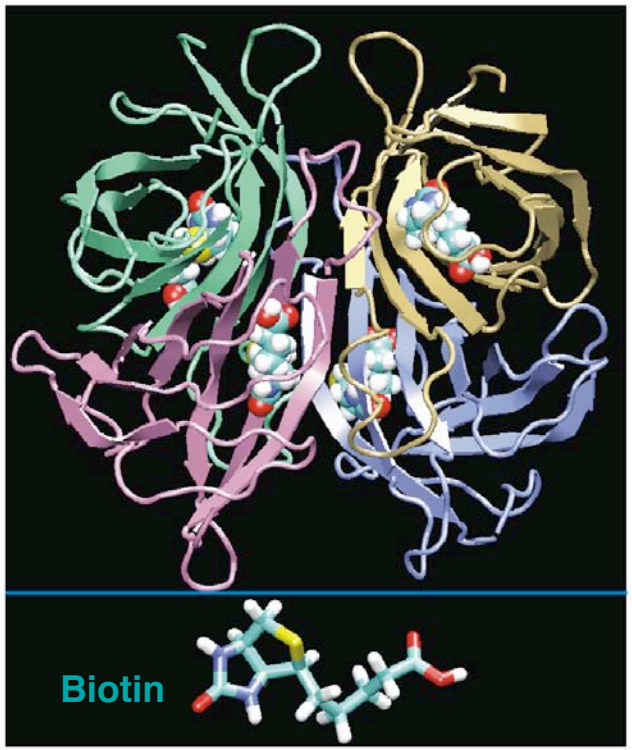

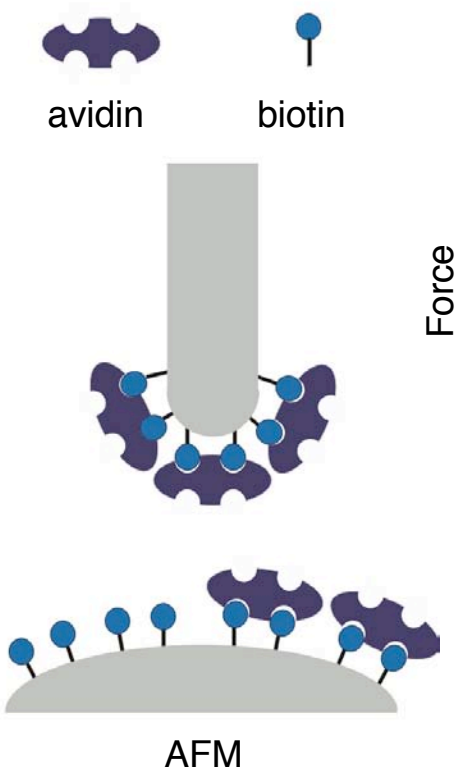

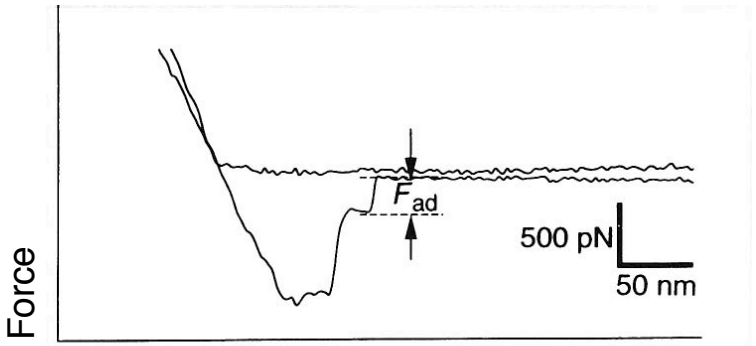

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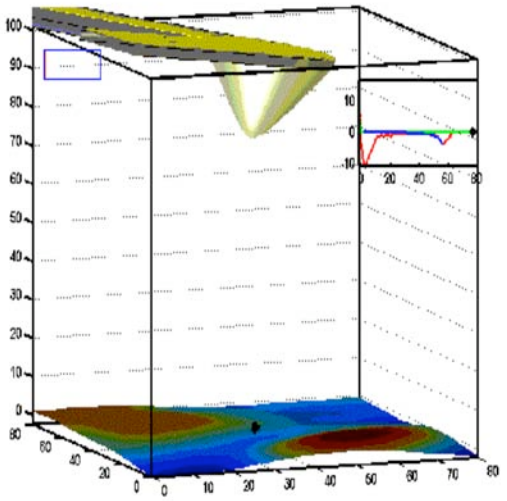
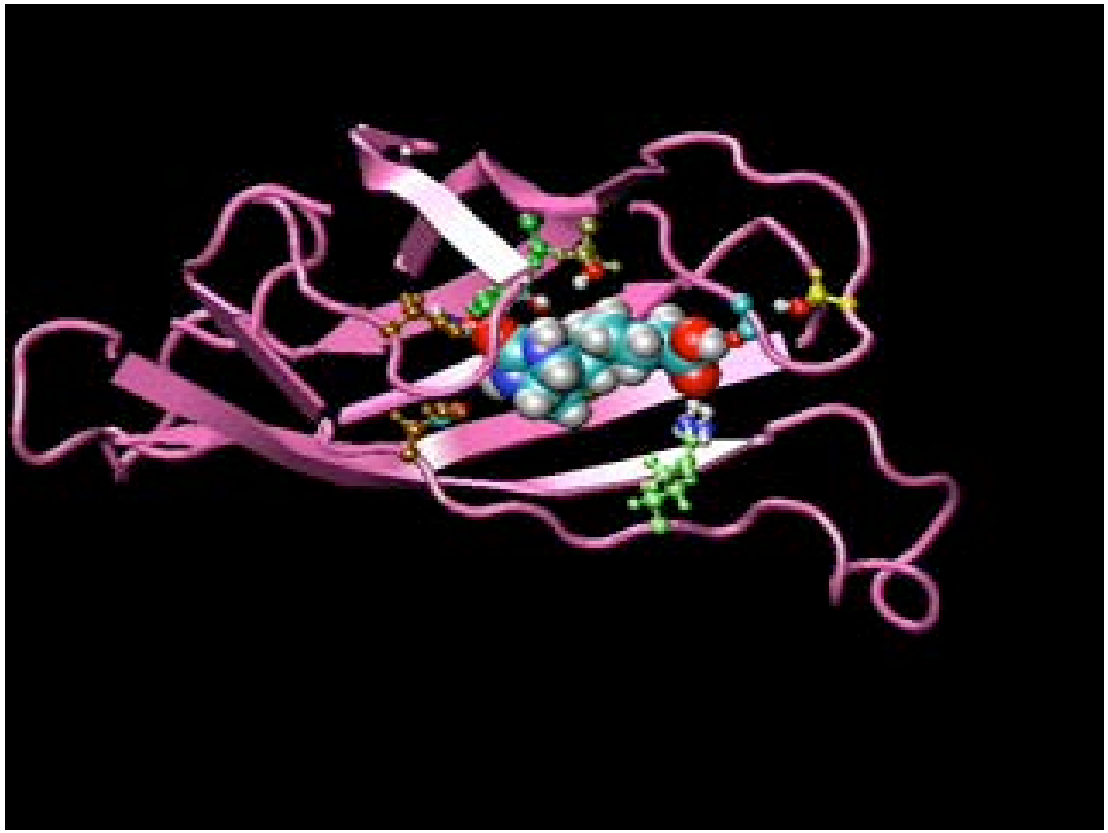


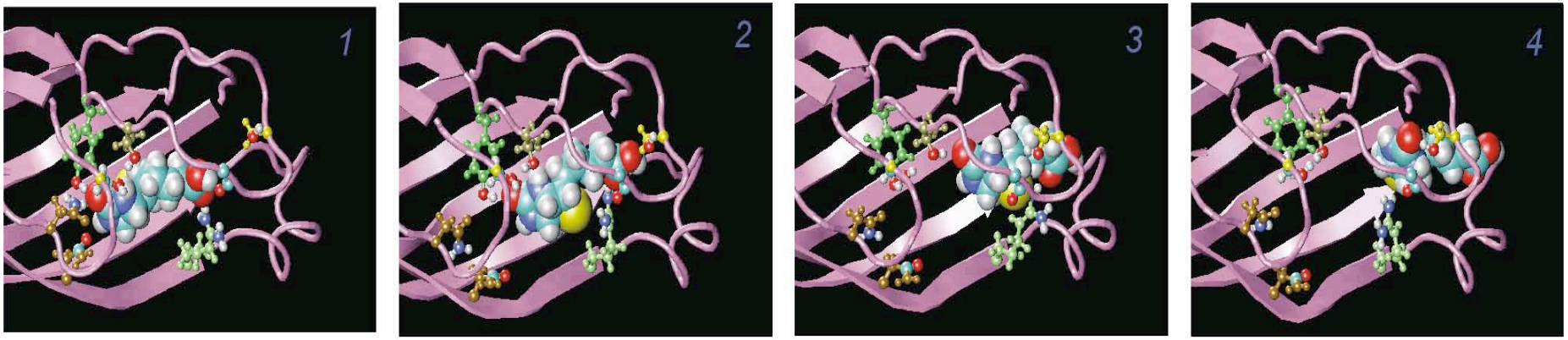
Pulling Biotin out of Avidin

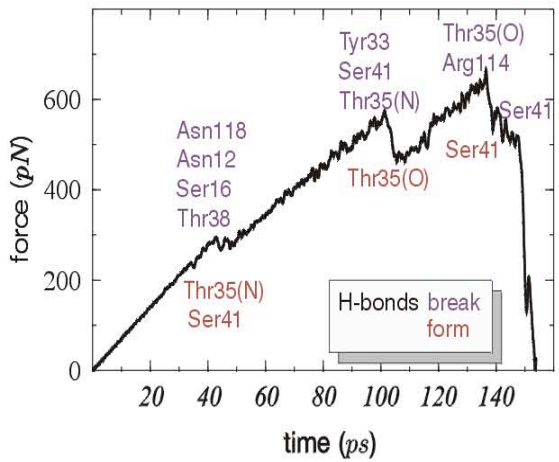


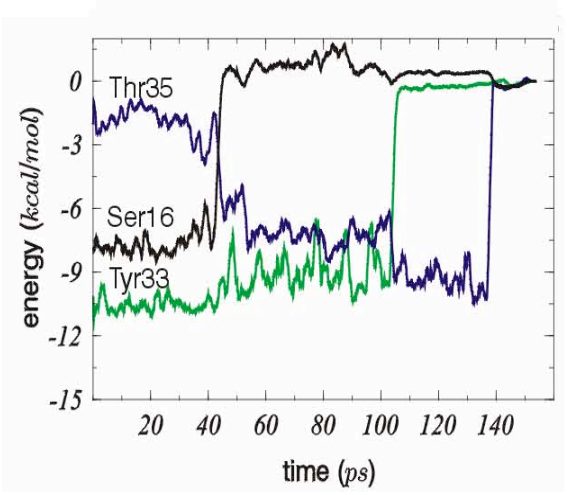
Molecular dynamics study of unbinding of the avidin-biotin complex. Sergei Izrailev, Sergey Stepaniants, Manel Balsera, Yoshi Oono, and Klaus Schulten. *Biophysical Journal*, 72:1568-1581, 1997.

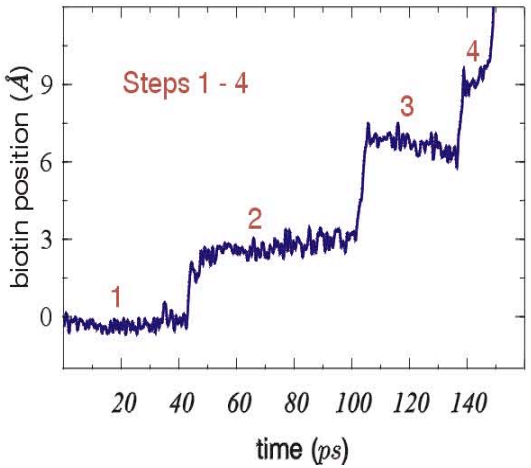
SMD of Biotin Unbinding: What We Learned

biotin slips out in steps, guided by amino acid side groups, water molecules act as lubricant, MD overestimates extrusion force









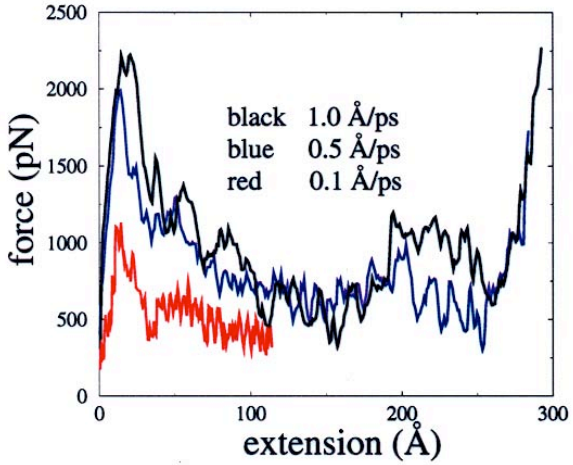
http://www.ks.uiuc.edu

Israilev *et al*., Biophys. J., **72**, 1568-1581 (1997)

Quantitative Comparison

Bridging the gap between SMD and AFM experiments

Force-extension curve



Schematic potentials

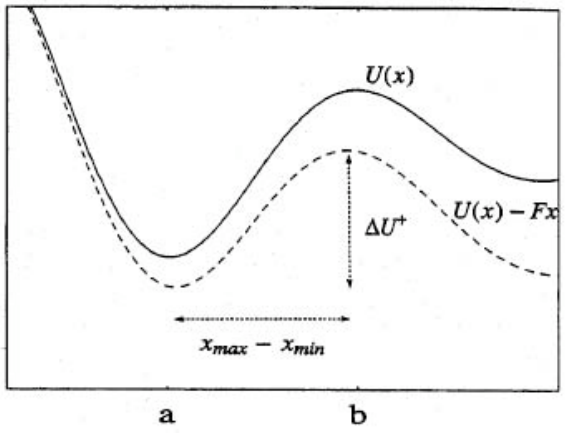
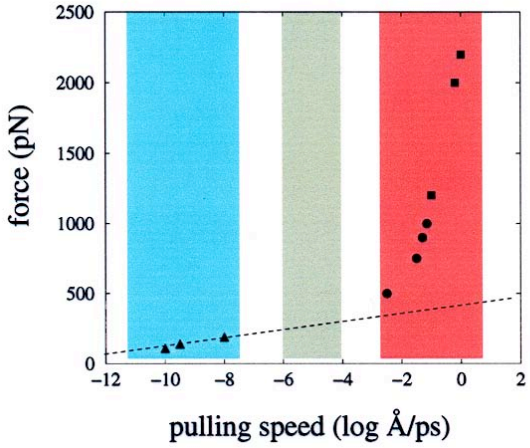


FIGURE 9 Schematic potentials $U(x)$, and $U(x) - Fx$.

$$\delta(F) = \beta\,[\Delta U - F(b\text{-}a)]$$

Force-pulling velocity relationship



AFM range

Current SMD range

Target simulation range

■ ● SMD data

▲ AFM data

------ Extrapolation of AFM data

AFM regime

$$e^{\delta(F)} >> 1$$

$$\tau_{AFM} \sim 2\tau_D \delta^{-2}(F) e^{\delta(F)}$$

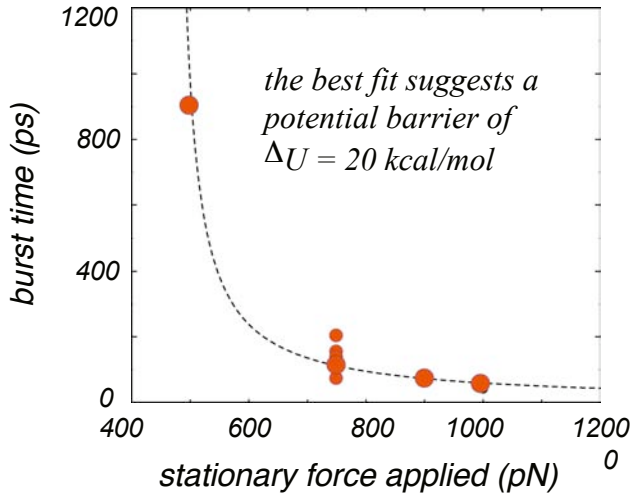
SMD regime

$$e^{\delta(F)} << 1$$

$$\tau_{SMD} \sim 2\tau_D |\delta(F)|^{-1}$$

Rupture/Unfolding Force F_0 and its Distribution

determination of barrier height based on mean first passage time



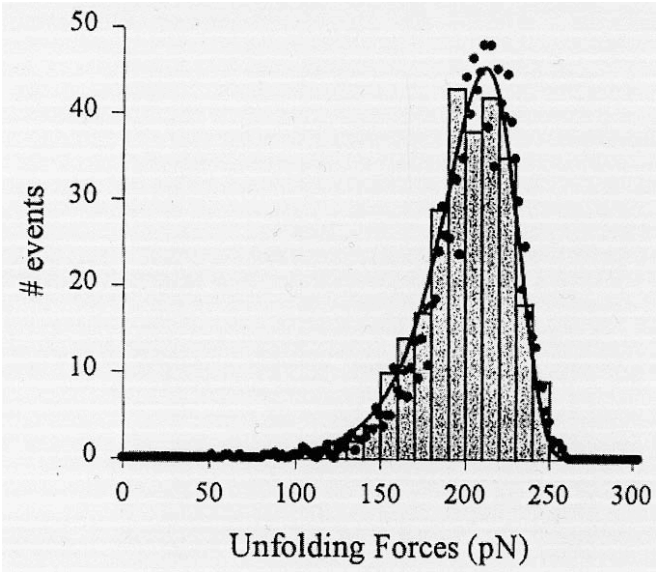
$\tau(F_0)$ = 1 ms time of measurement

=> F_0 rupture/unfolding force

Distribution of rupture/unfolding force

$$p(F_0) = \kappa \exp[\beta F_0(b-a) - \beta\Delta U - \frac{\kappa k_B T}{b-a} e^{-\beta\Delta U}\left(e^{\beta F_0 (b-a)} - 1\right)]$$

$$\kappa = \delta^2(F)/2\tau_D kv$$

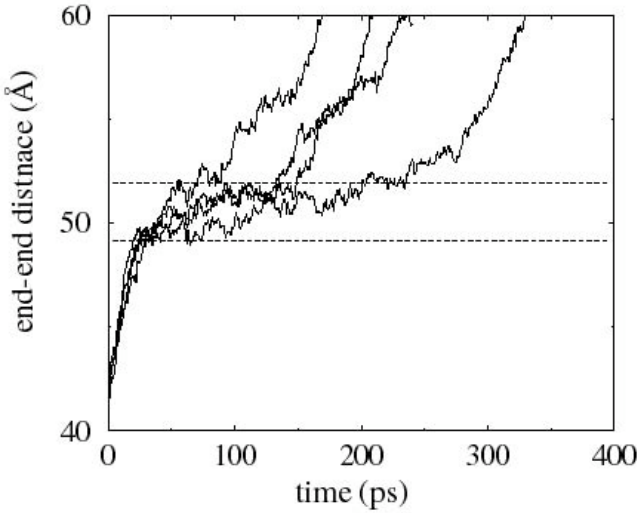


Israilev *et al.,* Biophys. J., **72**, 1568-1581 (1997)

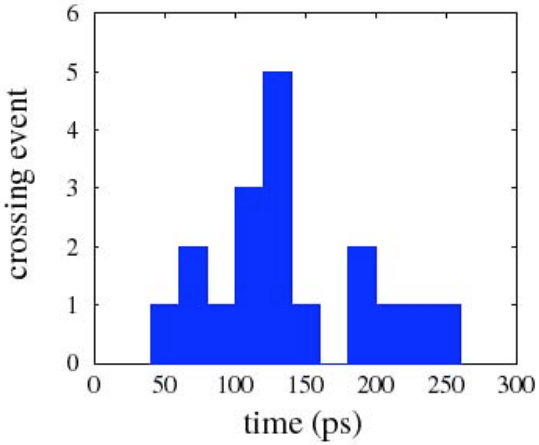
Balsera *et al*., Biophys. J., **73**, 1281-1287 (1997)

Distribution of the Barrier Crossing Time

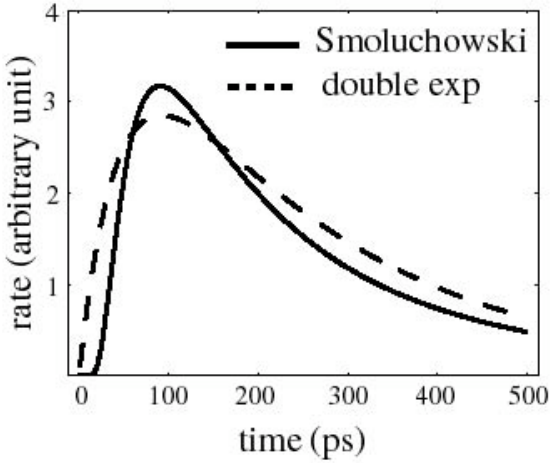
Multiple runs with same force of 750 pN



Barrier crossing times of 18 SMD simulations



Theoretical prediction of the barrier crossing times



The fraction N(t) that has not crossed the barrier can be expressed through solving the Smoluchowski diffusion equation (linear model potential):

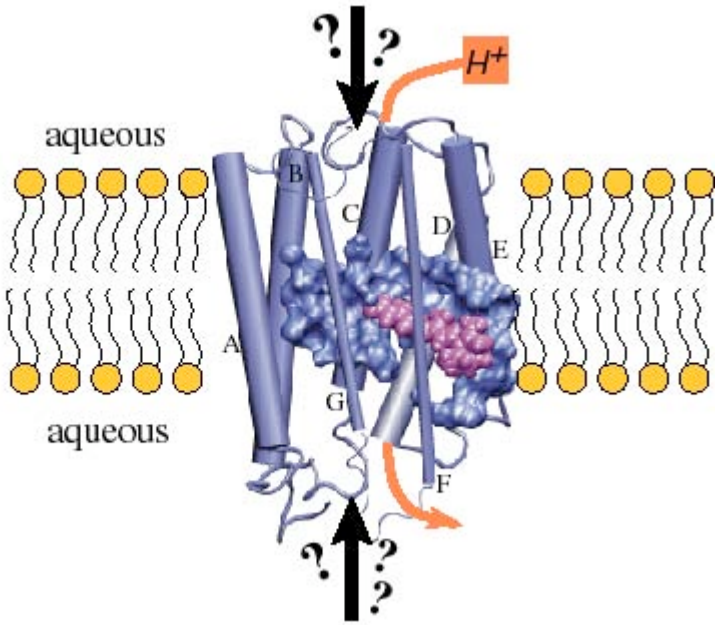
$$N(t) = \frac{1}{2} erfc\left[\frac{-a + \delta(F) D t/(b-a)}{\sqrt{4Dt}}\right] - \frac{1}{2} exp\left[\frac{\delta(F) a}{b-a}\right] erfc\left[\frac{-a + \delta(F) D t/(b-a)}{\sqrt{4Dt}}\right]$$

Or approximated by double exponential (general potential):

$N(t) = [t_1 \exp(-t/t_1) - t_2 \exp(-t/t_2)]/(t_1-t_2)$, Nadler & Schulten, JCP., **82**, 151-160 (1985)

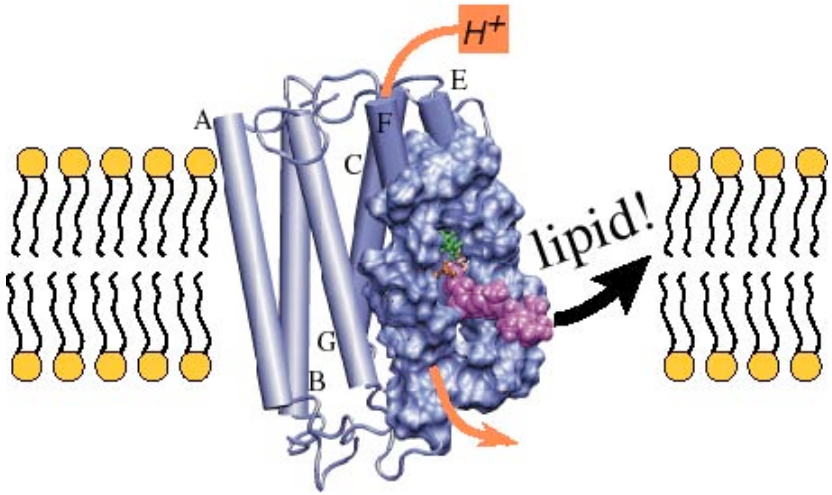
Interactive Modeling

Binding path of retinal to bacterio-opsin (1)



- Retinal deep in bacterio-opsin binding cleft
- How does it get in?
- Use batch mode interactive steered molecular dynamics to pull retinal out of cleft, find possible binding path

- 10 path segments, 3 attempts each
- Choose best attempt at 9 points during pull
- Found path through membrane, and electrostatically attractive entrance window



Interactive Modeling

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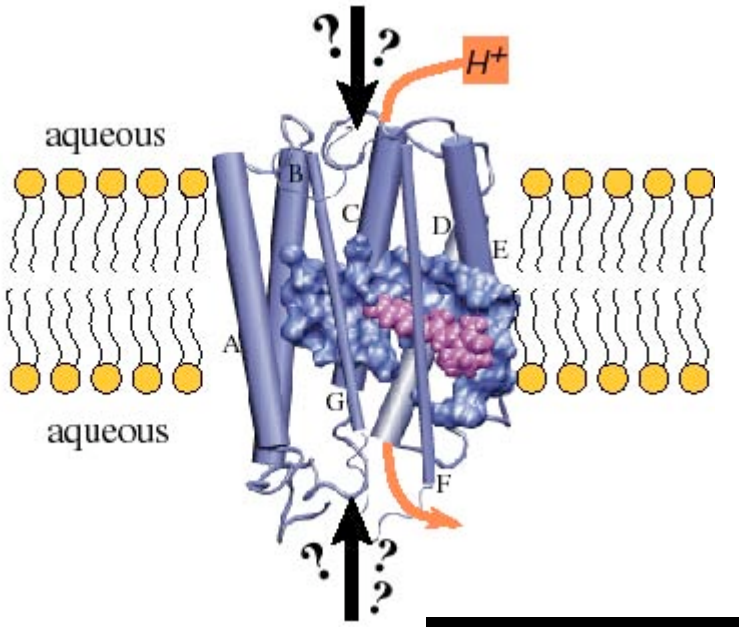

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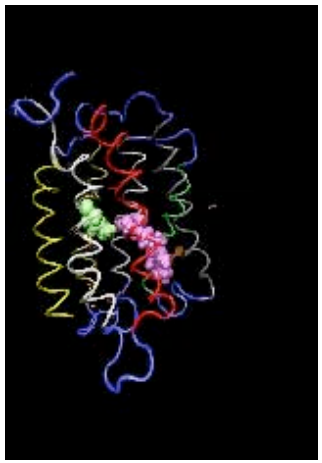
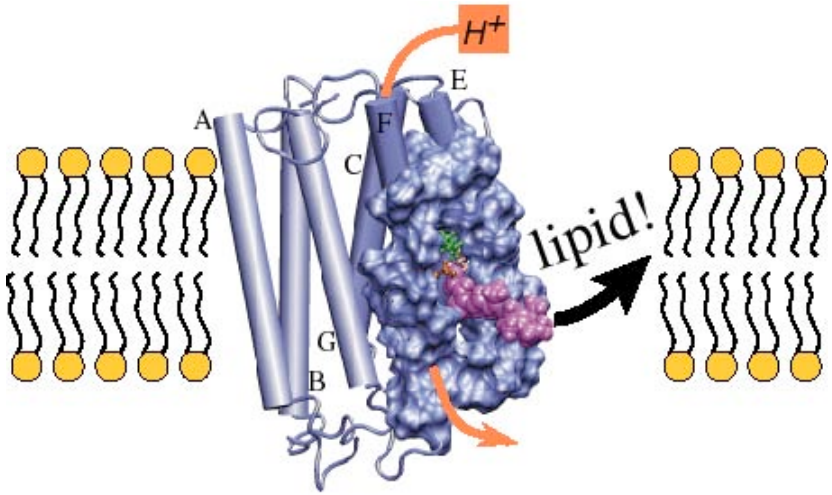
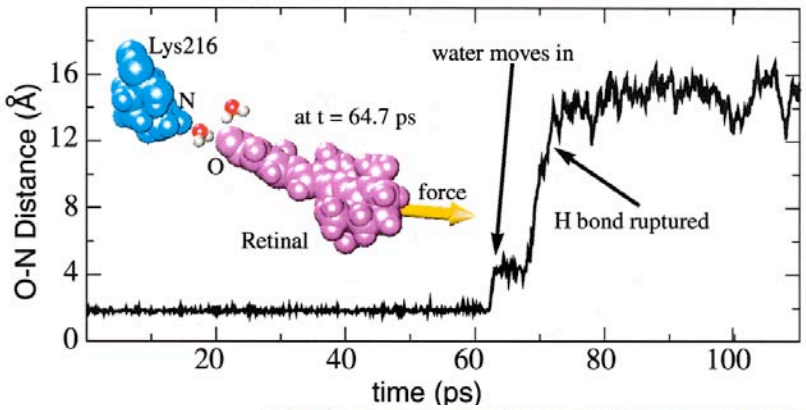


Binding pathway of retinal to bacterio-opsin: A prediction by molecular dynamics simulations. Barry Isralewitz, Sergei Izrailev, and Klaus Schulten. *Biophysical Journal* , 73:2972-2979, 1997.

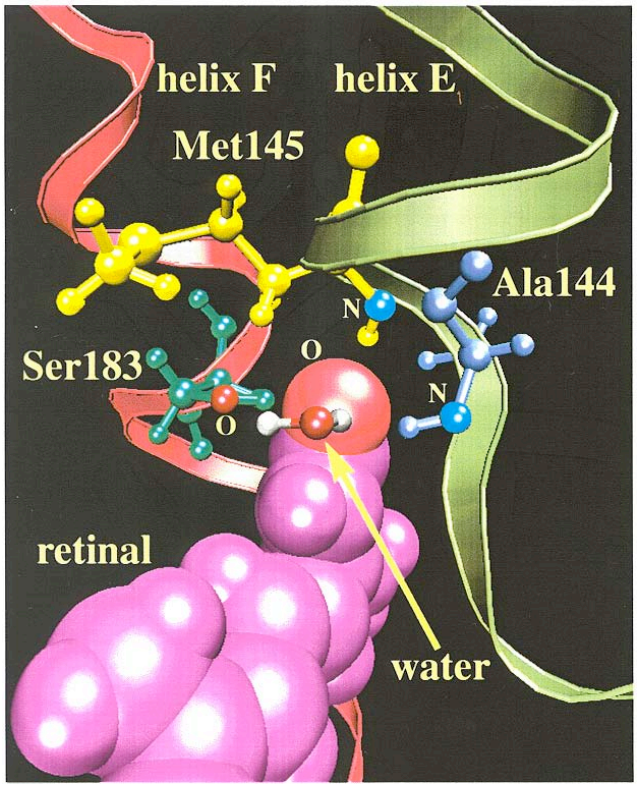


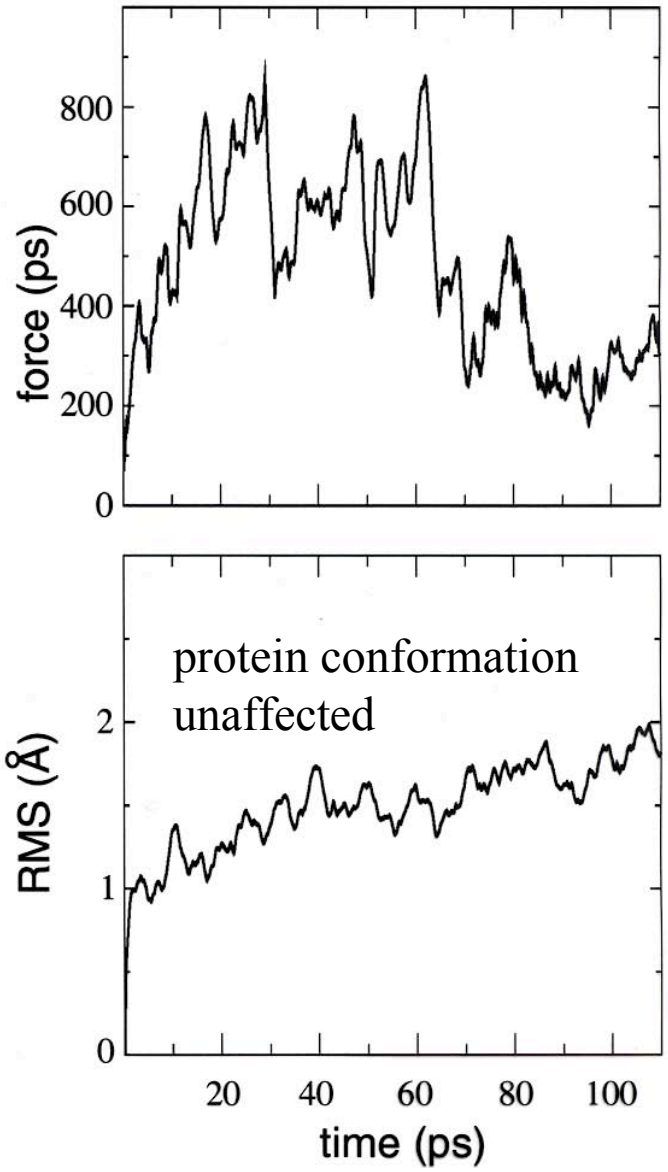
Stepwise Unbinding of Retinal from bR



water needed to shield lys – retinal interact.

Retinal's exit and entrance "door" attracts its aldehyde group





Israelewitz *et al.*, Biophys. J., **73**, 2972-2979 (1997)

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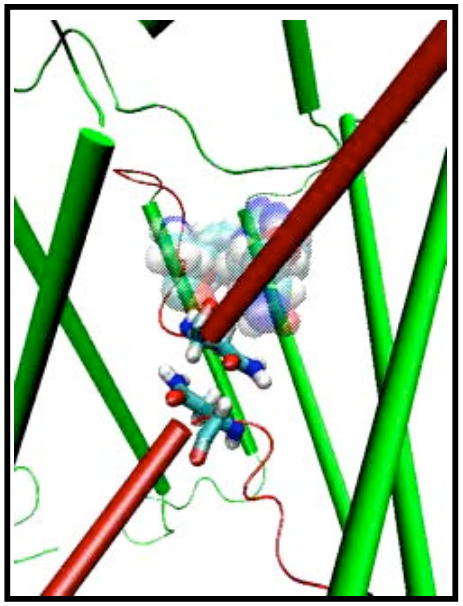
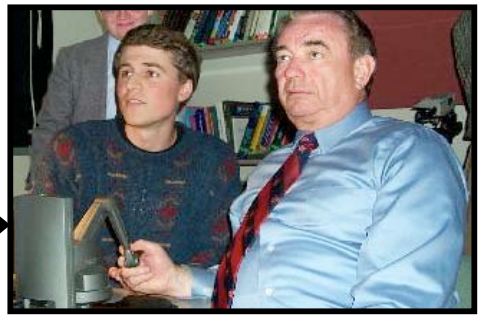
NIH Resource for Macromolecular Modeling and Bioinformatics
Theoretical Biophysics Group, Beckman Institute, UIUC

Interactive Molecular Dynamics

NAMD

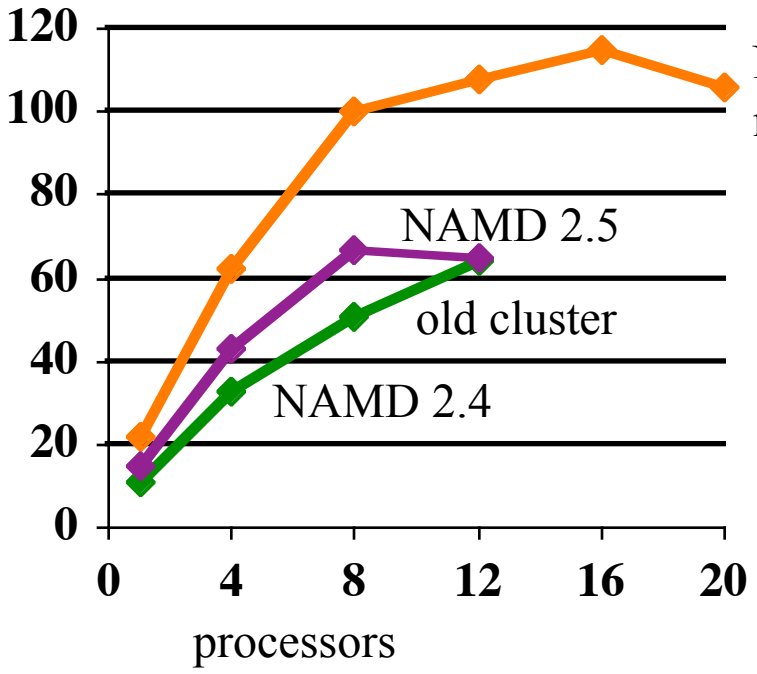


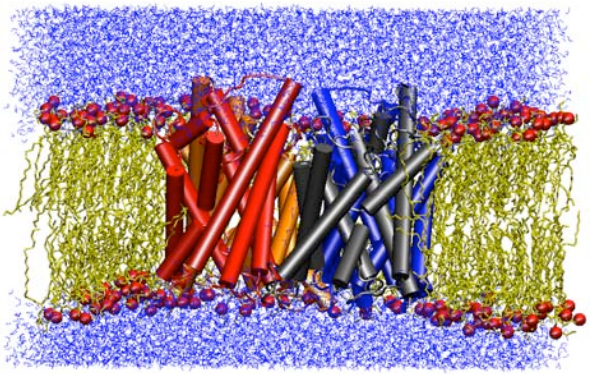
User



(HHS Secretary Thompson)

steps per second (more is better)





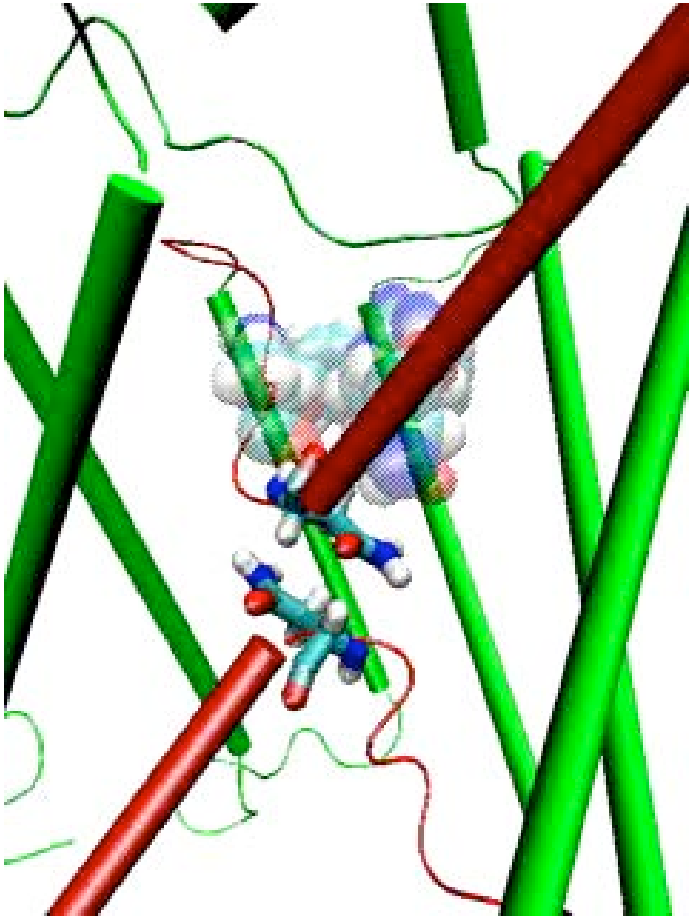
GlpF IMD Benchmark:

- 4210 atoms
- 3295 fixed atoms
- 10A cutoff, no PME
- Limited by network latency

Interactive Molecular Dynamics

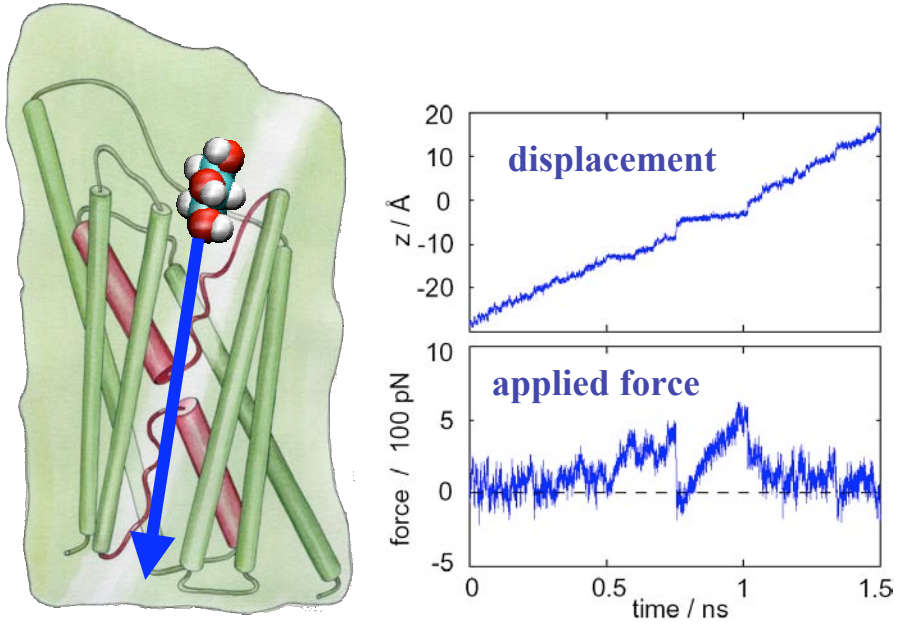
VMD ◄·····► **NAMD**

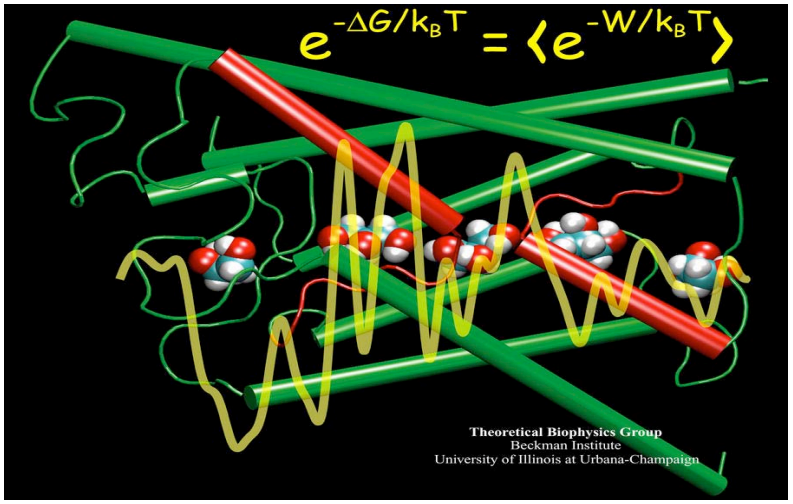
- Any PC/Workstation
- Supports 3D force-feedback devices for interaction



J. Stone, J. Gullingsrud, K. Schulten, and P. Grayson.
A System for Interactive Molecular Dynamics Simulation.
2001 ACM Symposium on Interactive 3D Graphics, pp.191-194, ACM SIGGRAPH
P. Grayson, E. Tajkhorshid, and K. Schulten.
Biophysical J, **83**: 36 (2003)

Quantitative Analysis of Substrate Permeation





Jensen et al, *PNAS* **99:** 6731-6736 (2002)

Calculation of the free energy profile of sugar transport from SMD simulations by Jarzynski's identity

Thermodynamics: $\Delta G \leq \langle W \rangle$

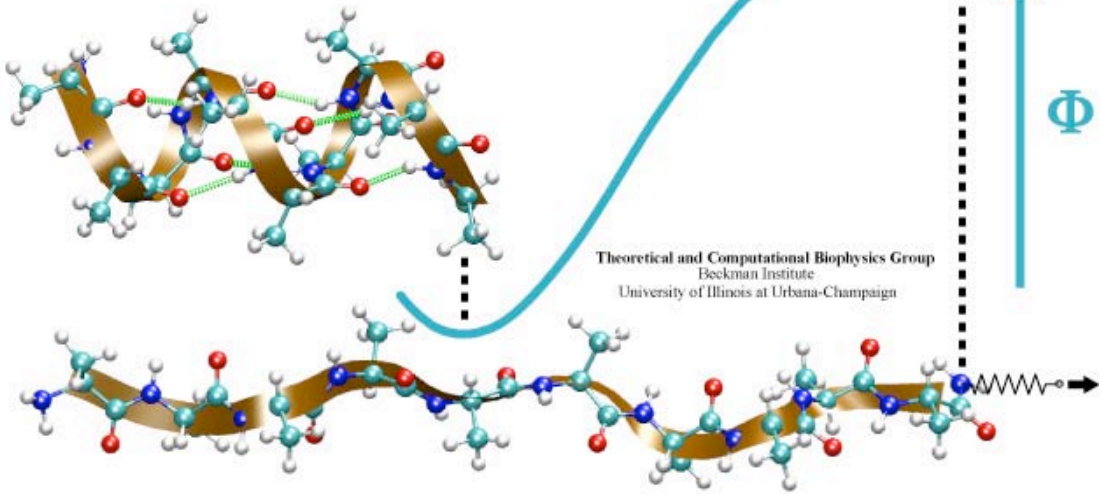
Is there any chance to discount the irreversible work? Yes!

Free Energy of Stretched Alpha-Helix

Thermodynamics: $\Delta G \leq \langle W \rangle$

Jarzynski (1997): $e^{-\Delta G / k_B T} = \left\langle e^{-W / k_B T} \right\rangle$

$$\Phi = \langle W \rangle - \frac{\beta}{2}\left(\langle W^2 \rangle - \langle W \rangle^2\right)$$

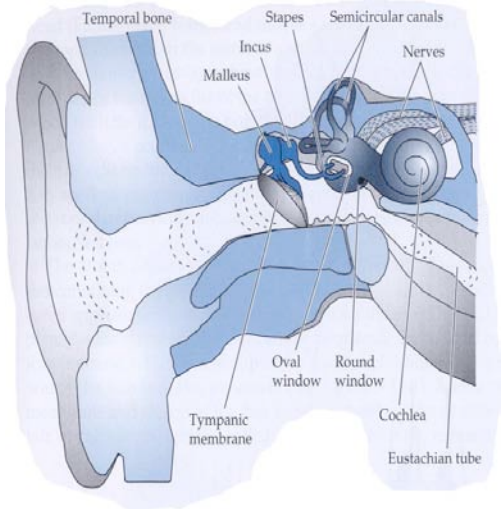


Free energy calculation from steered molecular dynamics simulations using Jarzynski's equality. S. Park, F. Khalili-Araghi, E. Tajkhorshid, and K. Schulten. *Journal of Chemical Physics* , 119:3559-3566, 2003

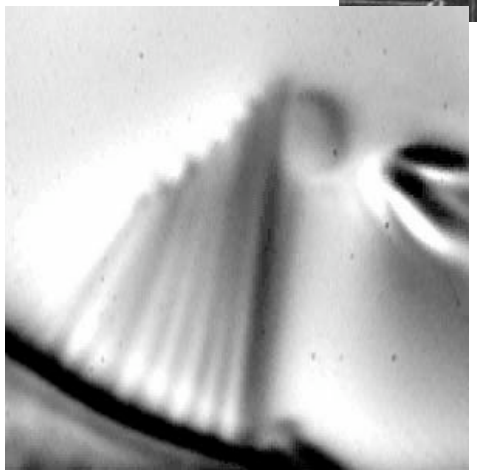
Calculating potentials of mean force from steered molcular dynamics simulations. S. Park and K. Schulten. *Journal of Chemical Physics* , 120: 5946-5961, 2004

Ankyrin Repeats: Springs in the Inner Ear

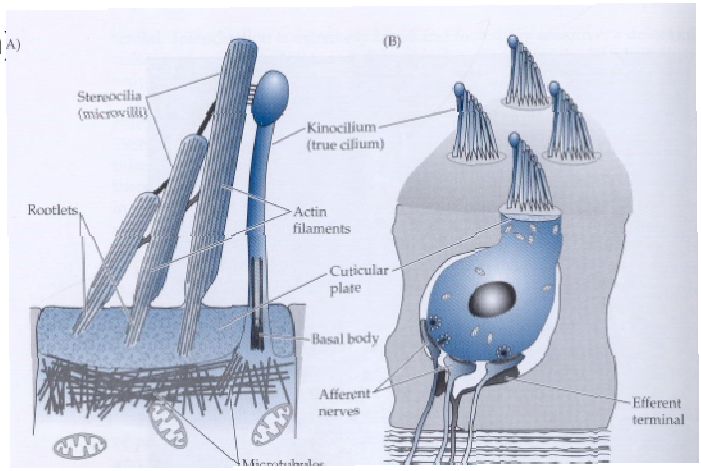
Marcos Sotomayor



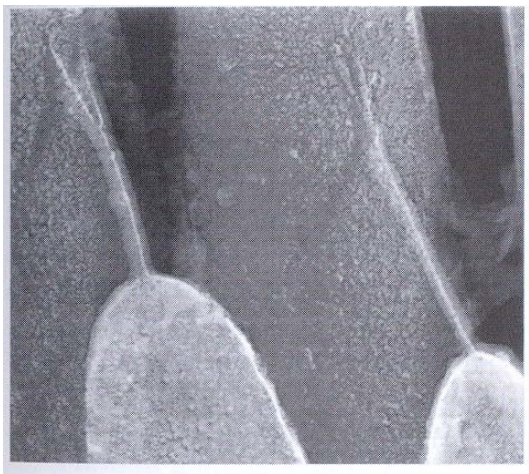
Mammalian Inner Ear (from Sensory Transduction, G. L. Fain)



Hair bundle (D.P. Corey)

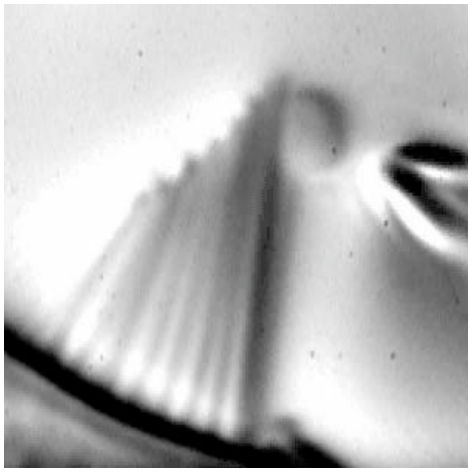


Cuticular plate, stereocilia and kinocilium in hair cells (from Sensory Transduction, G. L. Fain)



Tip Links (Kachar et al., 2000)

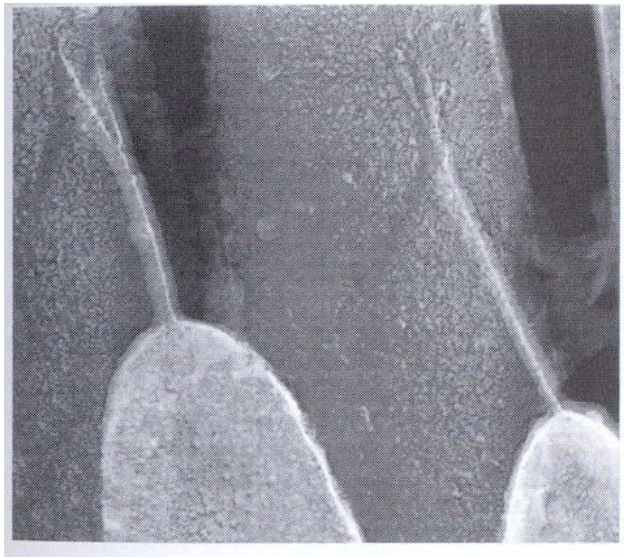
340,000 atom simulation of 24 repeat ankyrin



- 340,000 atoms including explicit water molecules
- CHARMM27 force-field
- Periodic boundary conditions
- Steered MD (25-75 pN)
- PME for full electrostatic calculation
- Teragrid benchmark: 0.7 day/ns on 128 Itanium 1.5GHz processors.

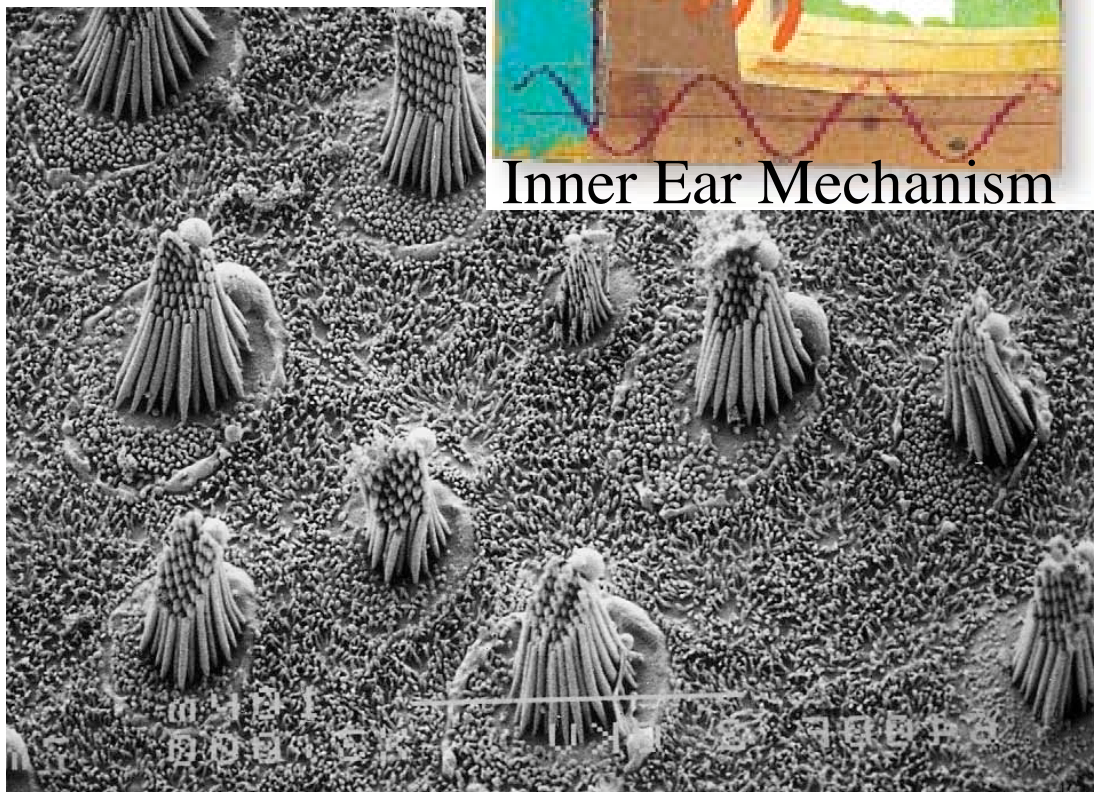
Inner Ear Mechanism

NAMD: 128 processors NCSA teragrid

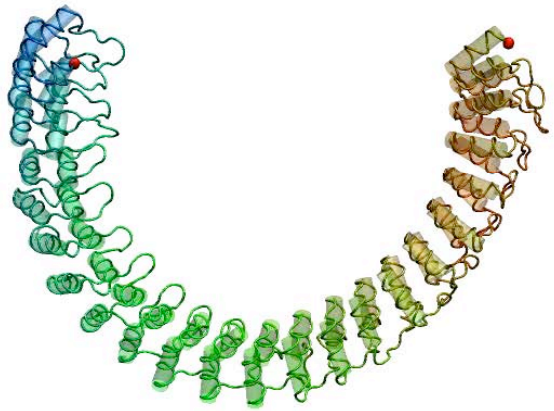


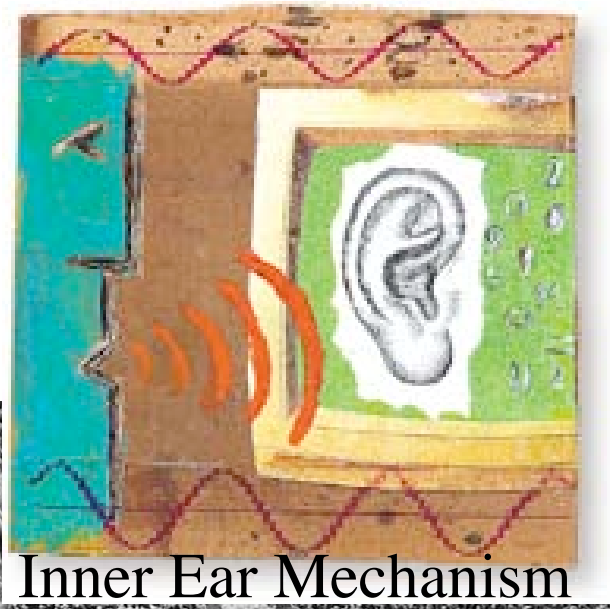
Tip Links (Kachar et al., 2000; Corey Lab)

Hair bundle (Assad and Corey, from Sensory Transduction, G. L. Fain).

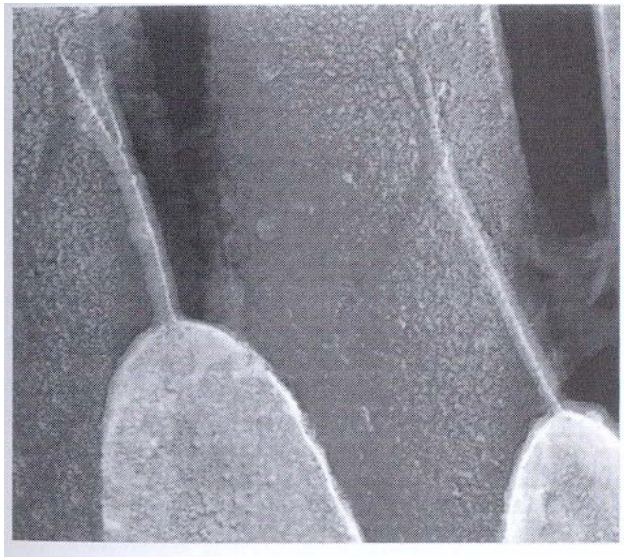


340,000 atom simulation of 24 repeat ankyrin

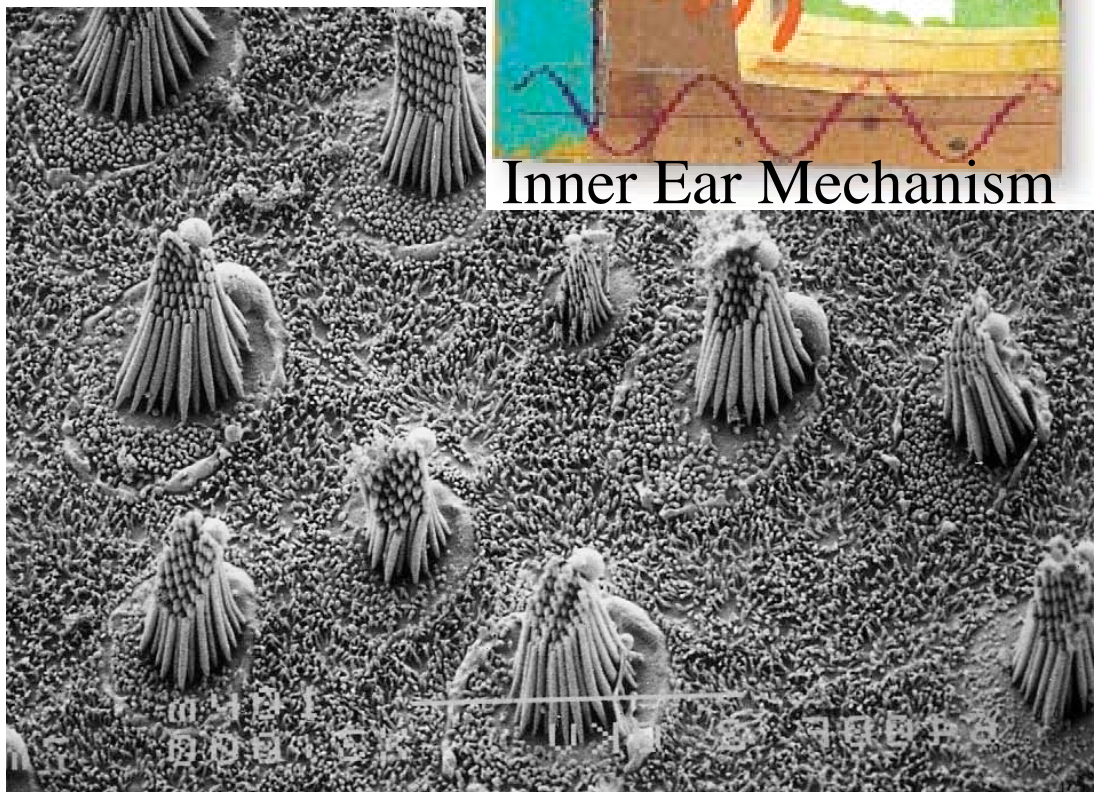




NAMD: 128 processors NCSA teragrid

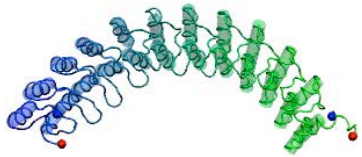


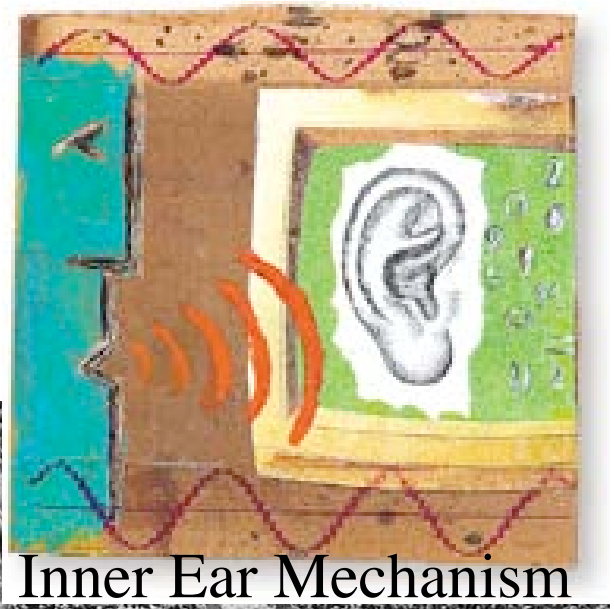
Tip Links (Kachar et al., 2000; Corey Lab)



Hair bundle (Assad and Corey, from Sensory Transduction, G. L. Fain).

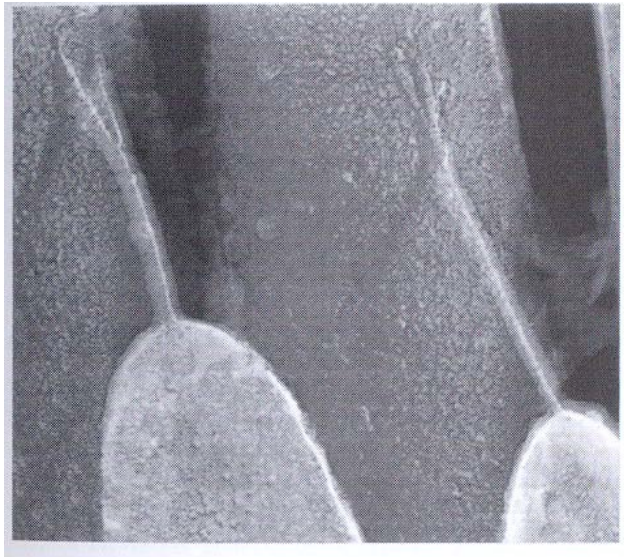
340,000 atom simulation of 24 repeat ankyrin





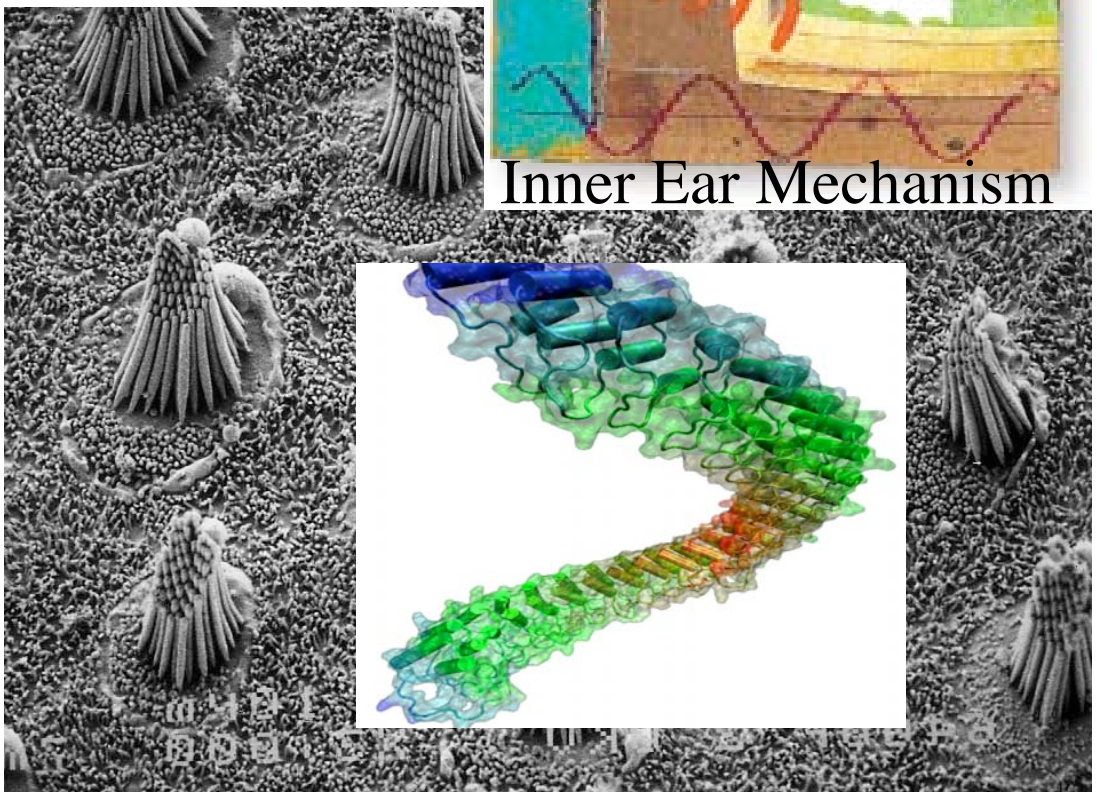
Non-entropic, nearly indistructable molecular spring

NAMD: 128 processors NCSA teragrid

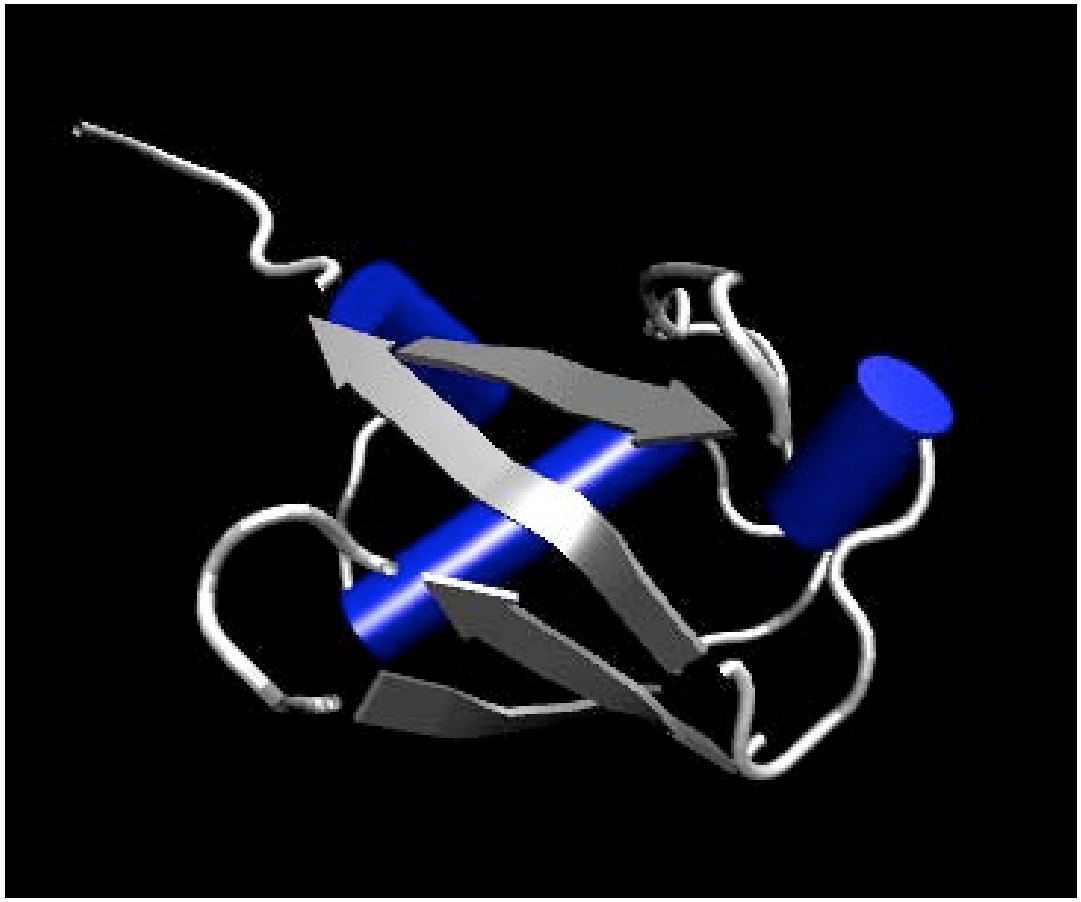


Tip Links (Kachar et al., 2000; Corey Lab)

Hair bundle (Assad and Corey, from Sensory Transduction, G. L. Fain).

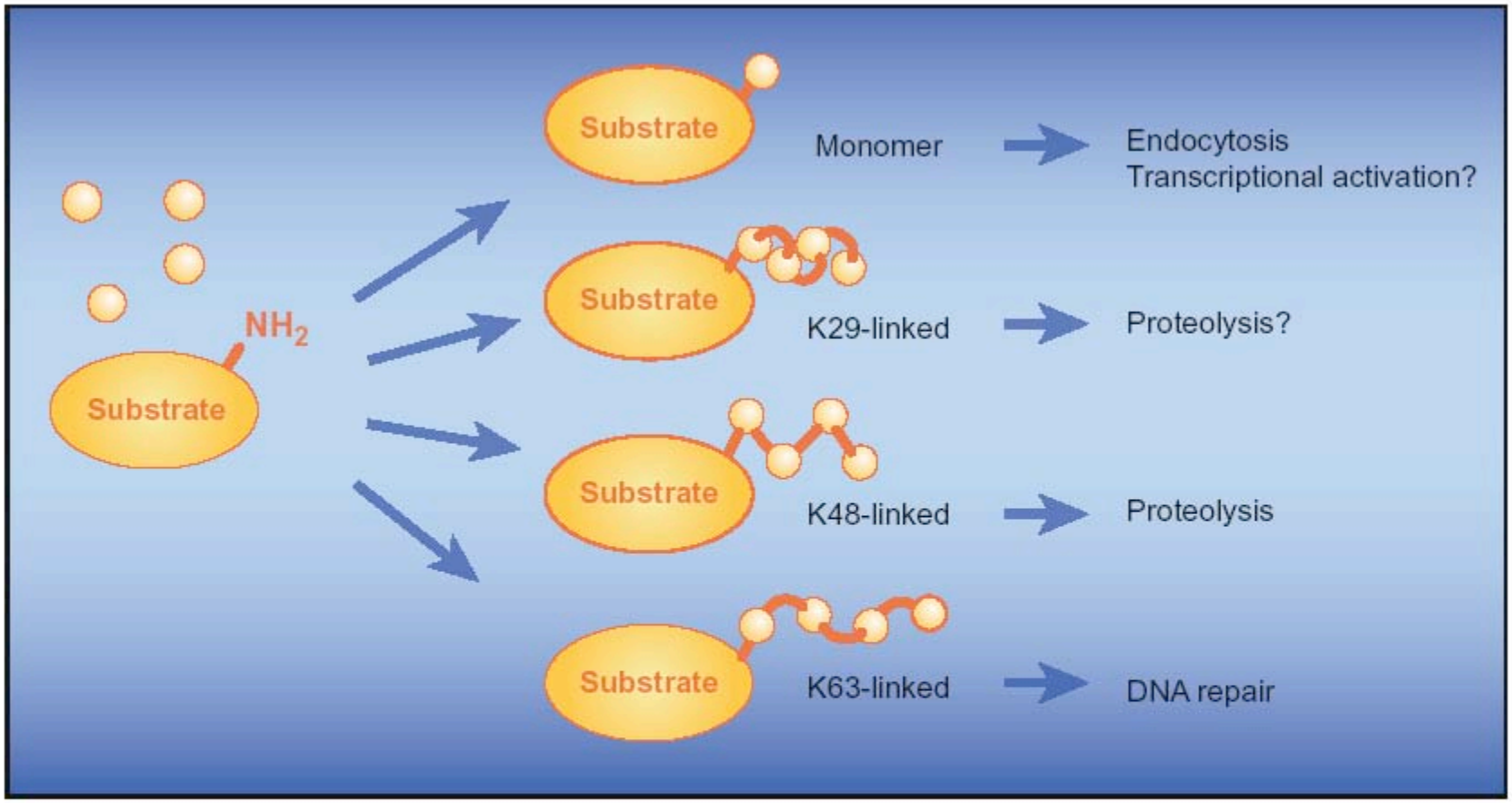


Ubiquitin



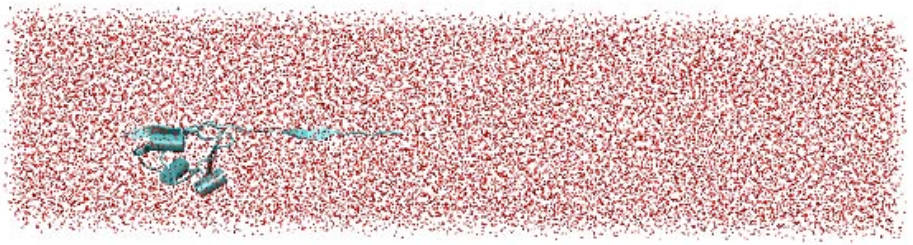
Fatemeh Araghi, Timothy Isgro, Marcos Sotomayor

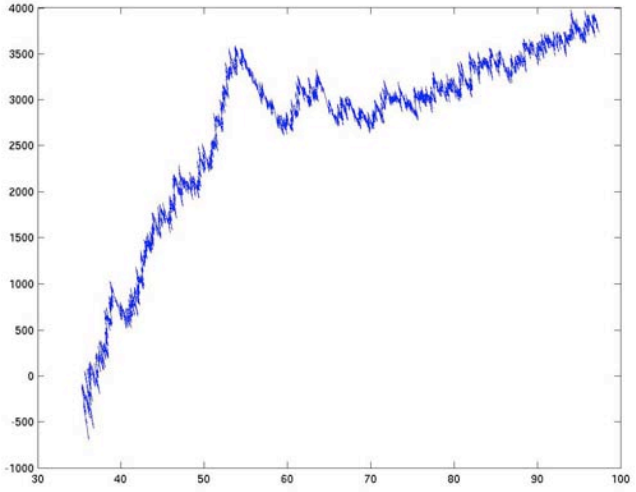
Monoubiquitylation versus multi-ubiquitylation



Multifaceted. Ubiquitin can attach to its various substrate proteins, either singly or in chains, and that in turn might determine what effect the ubiquitination has. (K29, K48, and K63 refer to the particular lysine amino acid used to link the ubiquitins to each other.)

First SMD Simulation

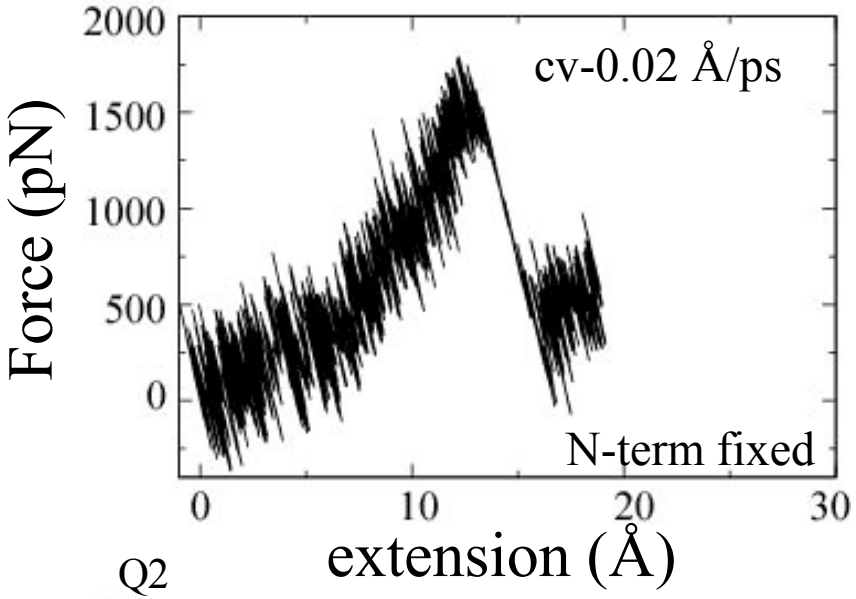


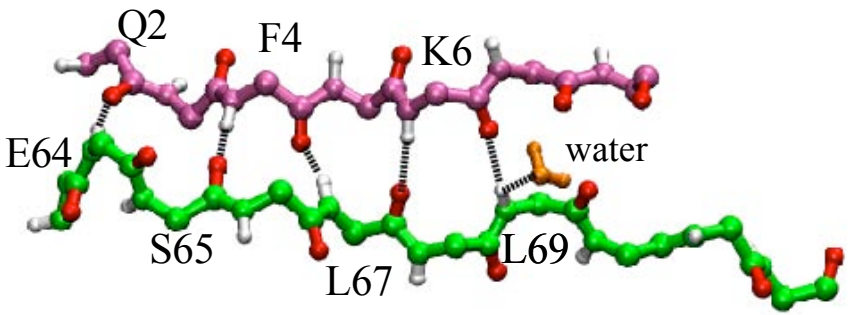


First peak when the first beta strand is stretched out

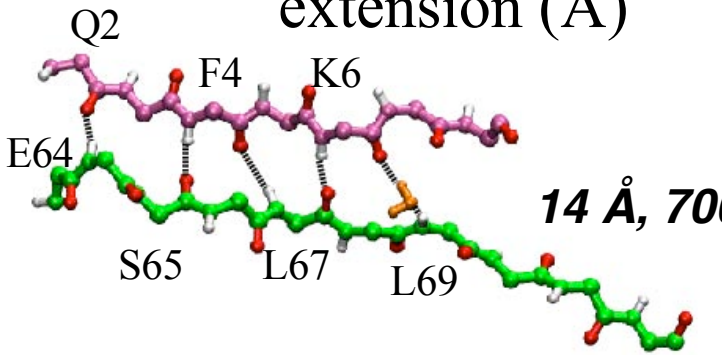
- SMD simulation, with constant velocity
- Box of water 70x240x70 A ~81K atoms
- smd velocity 0.4 A/ps
- smd spring constant 7 kcal/mol A^2

Ubiquitin Unfolding I

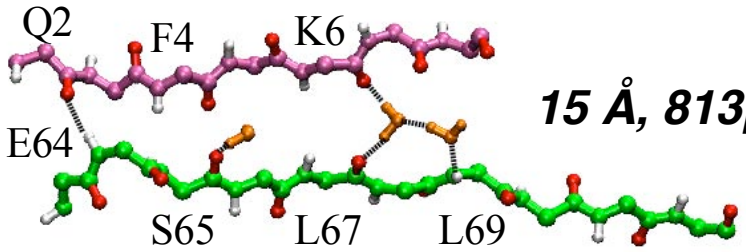




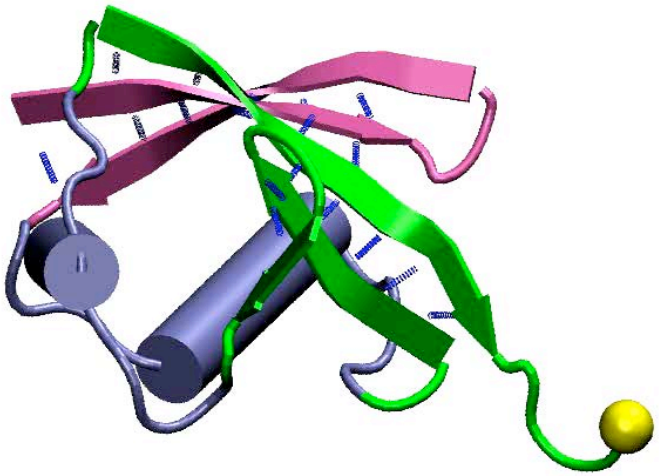
0 Å, 1 ps



14 Å, 700ps

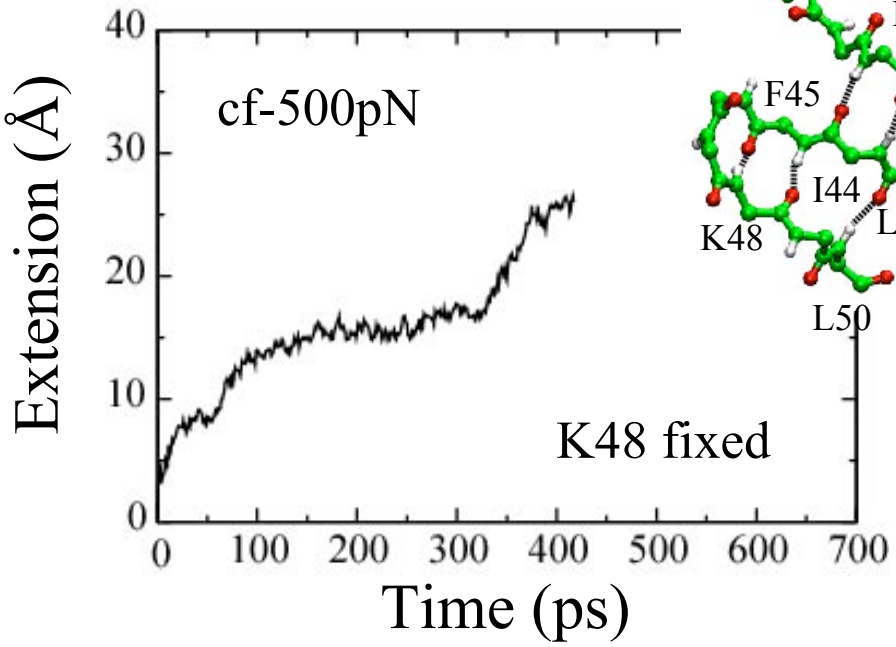


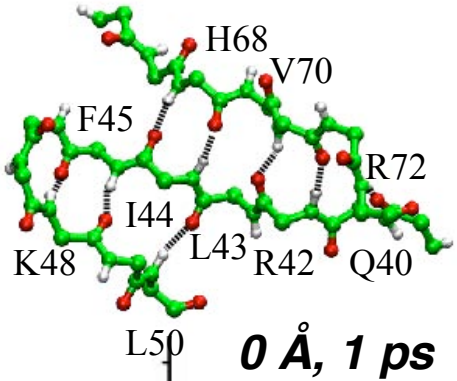
15 Å, 813ps



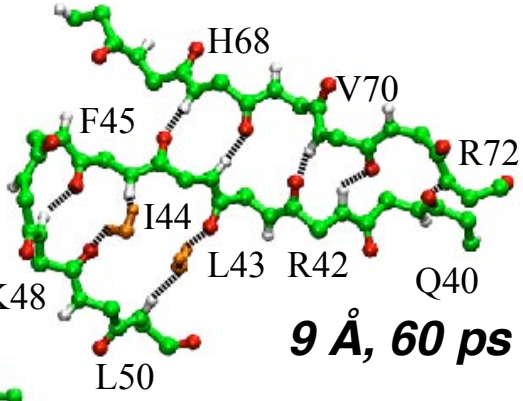
Mu Gao

Ubiquitin Unfolding II

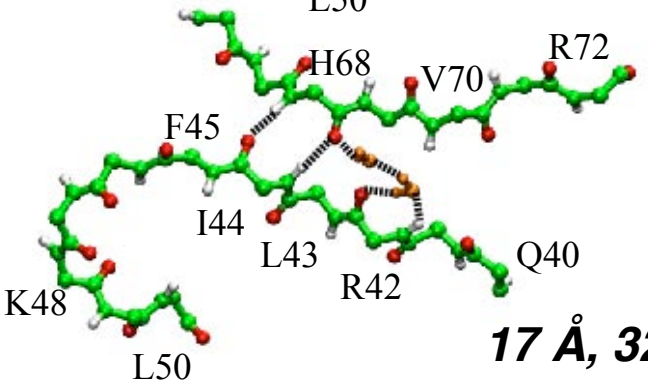




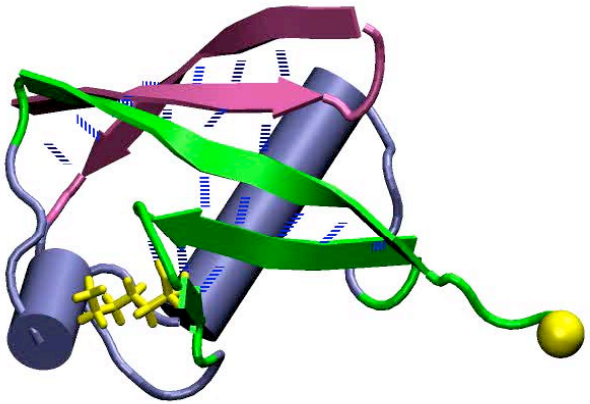
0 Å, 1 ps



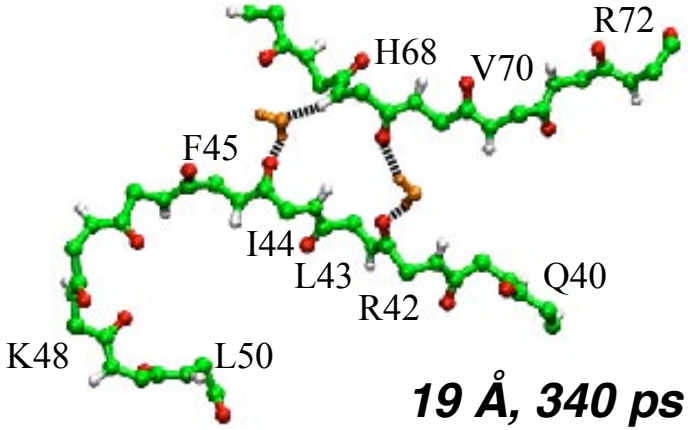
9 Å, 60 ps



17 Å, 320 ps



Mu Gao



19 Å, 340 ps

Pulling Dimer

- SMD (v=0.4 A/ps k=7 kcal/mol A^2) constant P
- Two monomers separate.