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

Avidin

Biotin

AFM

Displacement of AFM tip

Force

500 pN
50 nm

AFM cantilever with the tip

Agarose bead surface

Avidin - biotin complex
Atomic Force Microscopy Experiments of Ligand Unbinding

Pulling Biotin out of Avidin

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

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

http://www.ks.uiuc.edu

NIH Resource for Macromolecular Modeling and Bioinformatics
Theoretical Biophysics Group, Beckman Institute, UIUC
Quantitative Comparison
Bridging the gap between SMD and AFM experiments

\[ \delta(F) = \beta [\Delta U - F(b-a)] \]

**AFM regime**

\[ e^{\delta(F)} \gg 1 \]

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

**SMD regime**

\[ e^{\delta(F)} \ll 1 \]

\[ \tau_{SMD} \sim 2\tau_D |\delta(F)|^{-1} \]
Rupture/Unfolding Force $F_0$ and its Distribution

$\tau(F_0) = 1 \text{ ms}$ \hspace{0.5cm} \text{time of measurement}

$\Rightarrow F_0$ \hspace{0.5cm} \text{rupture/unfolding force}

Distribution of rupture/unfolding force

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

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

Israilev et al., Biophys. J., 72, 1568-1581 (1997)
Balsera et al., Biophys. J., 73, 1281-1287 (1997)
Distribution of the Barrier Crossing Time

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

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

Or approximated by double exponential (general potential):

\[
N(t) = [t_1 \exp(-t/t_1) - t_2 \exp(-t/t_2)]/(t_1-t_2), \quad \text{Nadler & Schulten, JCP., 82, 151-160 (1985)}
\]
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

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Interactive Modeling

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Retinal’s exit and entrance “door” attracts its aldehyde group. Water needed to shield lys – retinal interact.

Isralewitz et al., Biophys. J., 73, 2972-2979 (1997)
Interactive Molecular Dynamics

NAMD

User

(HHS Secretary Thompson)

GlpF IMD Benchmark:
- 4210 atoms
- 3295 fixed atoms
- 10A cutoff, no PME
- Limited by network latency

steps per second (more is better)

processors
Interactive Molecular Dynamics

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


Quantitative Analysis of Substrate Permeation

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 (Deca-alanin)

Thermodynamics: \[ \Delta G \leq \langle W \rangle \]

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

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


Ankyrin Repeats: Springs in the Inner Ear

Marcos Sotomayor

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

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

Hair bundle (D.P. Corey)

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.

NAMD: 128 processors NCSA teragrid

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

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

Inner Ear Mechanism
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

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

NAMD: 128 processors NCSA teragrid

Non-entropic, nearly indistructable molecular spring

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

Inner Ear Mechanism
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

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

First peak when the first beta strand is stretched out
Ubiquitin Unfolding II

Time (ps)

Extension (Å)

K48 fixed

0 Å, 1 ps

9 Å, 60 ps

17 Å, 320 ps

19 Å, 340 ps

Mu Gao
Pulling Dimer

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