Steered and Interactive Molecular Dynamics

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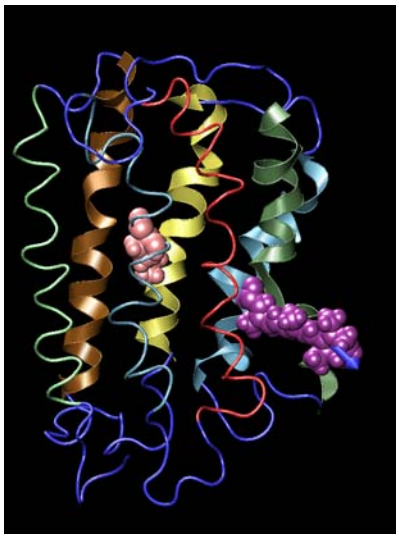
Steered Molecular Dynamics

- Steered Molecular Dynamics means the acceleration of conformational changes in biomolecular systems through the application of external forces.
- Using this technique, we can:
  - Explain single-molecule experiments;
  - Overcome slow natural time scales;
  - Explore putative conformational pathways.



SMD/IMD Publications

- "Steered molecular dynamics investigations of protein function." *J. Molec. Graphics & Modeling,* 2001.
- "Steered molecular dynamics and mechanical functions of proteins." *COSB,* 2001.
- "Mechanical unfolding intermediates in titin modules." *Nature*, 2000.
- "Simulated refolding of stretched titin immunoglobulin domains." *Biophys. J.,* 2001.
- "Comparison of the early stages of forced unfolding of fibronectin type III modules." *PNAS*, 2001.
- "Structural determinants of MscL gating studied by molecular dynamics simulations." *Biophys. J.,* 2001.
- "A system for interactive molecular dynamics simulation." *2001 ACM Symposium on Interactive 3D Graphics.*

SMD/IMD Methodology

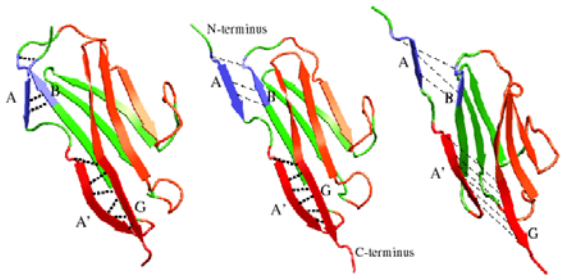
Investigations proceed in three stages:

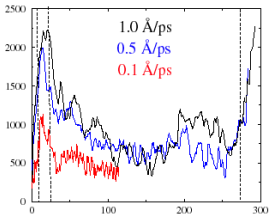
1. *Generate a hypothesis* for the conformational transition (reaction coordinate).
2. *Apply forces* that induce the hypothetical process during reasonable wall clock time.
3. *Analyze results* in terms of energetic barriers and specific unbinding events to evaluate the hypothesis.

Force Application in SMD

- Linear forces: a moving harmonic restraint or constant forces drag selected atoms in a given direction.
- Surface tension: nonequilibrium boundary conditions rescale atomic coordinates and momenta.
- Torque: Rotating restraints allow the simulation of rotating biomolecular assemblies.

Two-step Unfolding in Titin I27





Native structure; 0 A extension

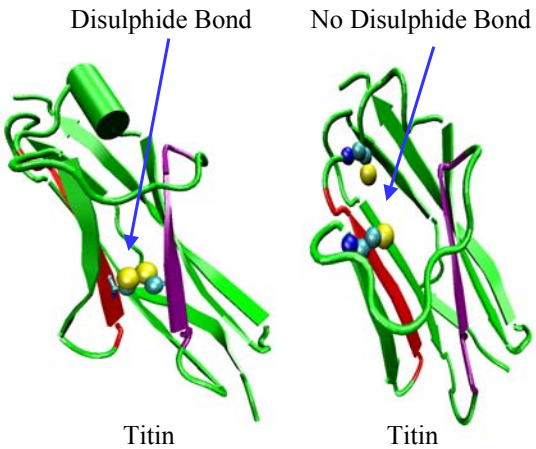
Mechanical unfolding intermediate; 10 A extension

Unfolded state; 25 A extension

Simultaneous H-bond breaking leads to large force peak.

The Role of Disulphide Bonds In Titin Modules

SMD simulations will examine how, and to what extent, the disulfide bond can protect the integrity of I1 domains during forced unfolding.

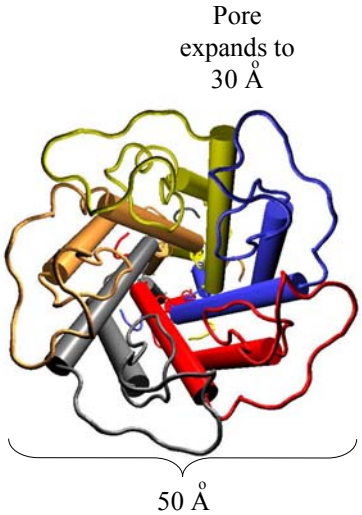


Titin Immunoglobulin 1

Titin Immunoglobulin 27

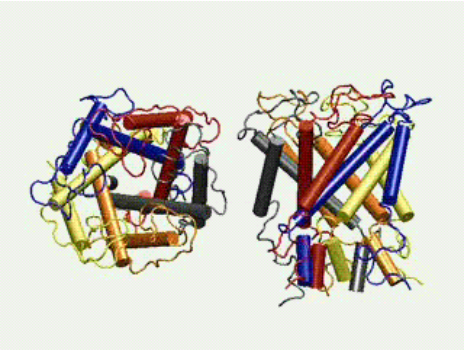
MscL: A Mechanosensitive ion channel

- MS channels are mechanical force trans-ducers, implicated in hearing, touch and balance in eukaryotes.
- In prokaryotes, MscL is an osmotic pressure safety valve.
- MscL gates through membrane tension alone, and undergoes large conformational changes!



MscL: Applied Surface Tension

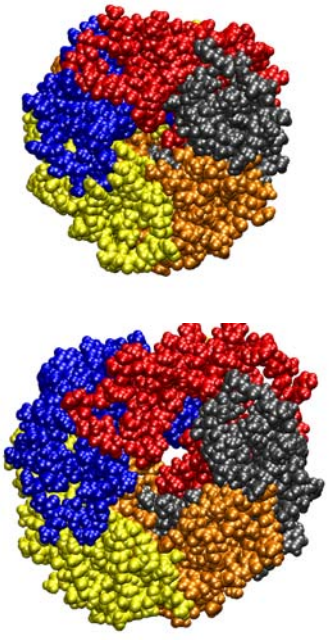
- 81,000 atom protein-membrane simulation.
- 2 ns equilibration followed by 2 ns of applied surface tension.
- Application of surface tension results in the controlled refolding of the protein to a more flattened, open state.



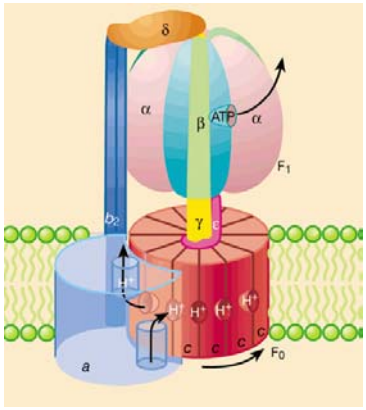
Final 1 ns of applied surface tension

MscL: surface tension results

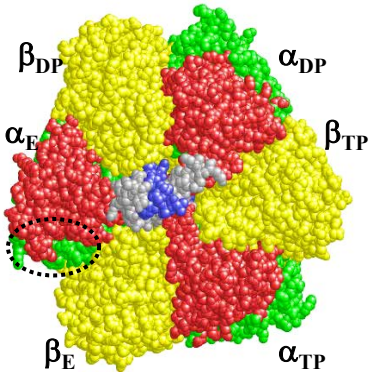
• 2 ns simulation at 200 dyn/cm
• Membrane thickness decreased from 40 A to 25 A.
• Transmembrane helices tilted to follow hydrophobic thickness of the membrane.
• Protein diameter increased from 50 to 60 A. The pore diameter also increased but has not fully gated.
• Protein expansion, followed later by pore opening, has been suggested by Sukharev et al. (J. Gen. Phys. 1999, Nature 2001)



Mechanism of ATP Synthase



How does central stalk transmit torque? What structural changes in α and β subunits does it induce?



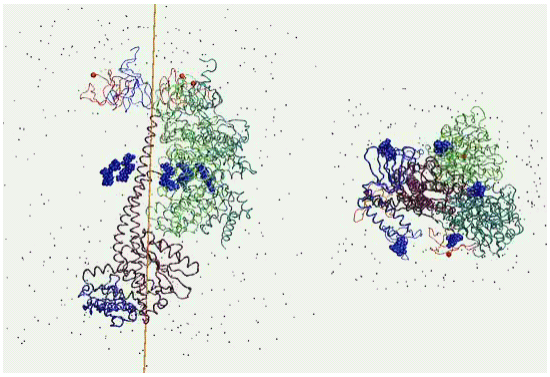
SMD can help to provide an answer…

Torque-Induced Rotation

Test steered MD simulations:
fast (30 rev/ns) forced stalk rotation

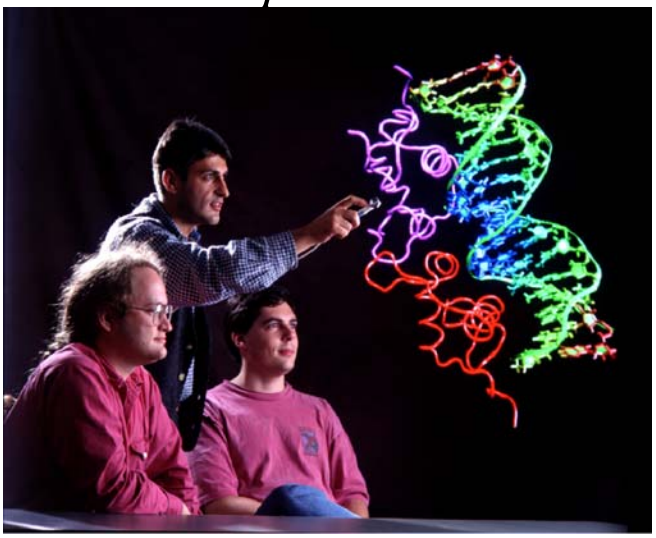
System size**:** ~327,000 atoms

side view



top view

"If I could just get my hands on that protein!"

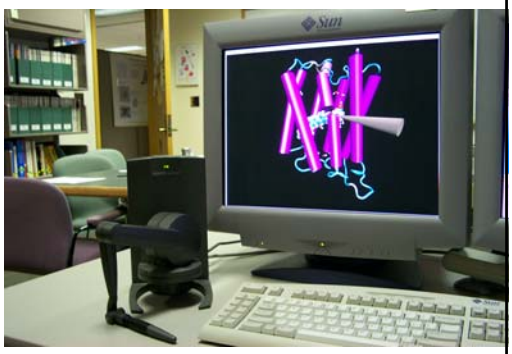


Interactive Molecular Dynamics

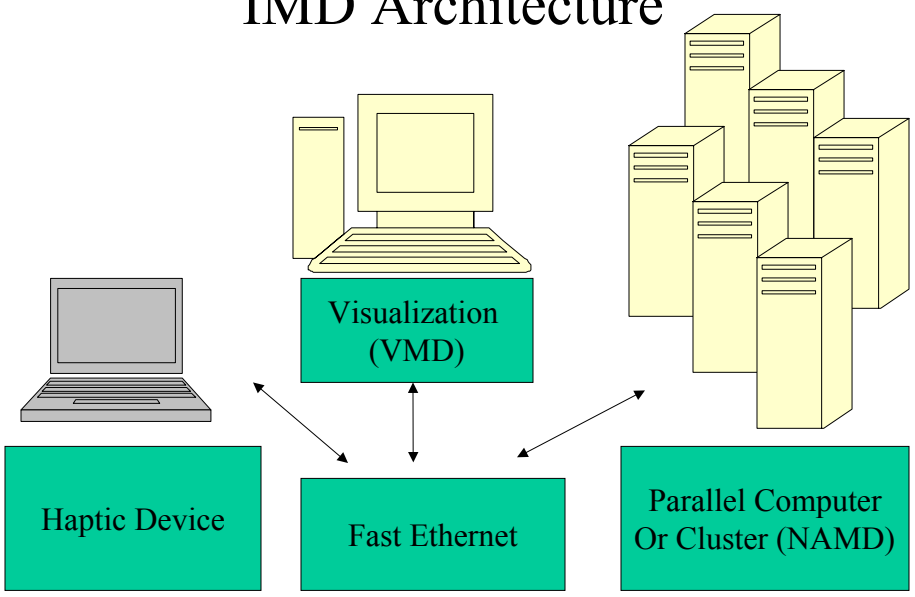
- Replaces pre-determined constraint point and spring with interactive user input and run-time configurable spring parameters;
- Provides user with real-time force feedback through the use of a haptic device;
- Allows user to direct simulation and gain insight by interactive exploration of structure and mechanical properties of molecular system.

A Haptic Interface

- Haptic devices allow multidimensional manipulation and force feedback.
- Pathways for steered molecular dynamics simulations can be identified interactively.



IMD Architecture



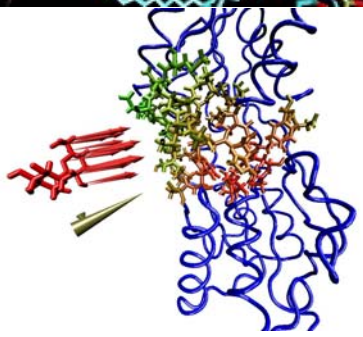
Force Feedback Model

- The response of the IMD system to user input is ultimately determined by *:
  - Speed of the simulation;
  - Strength of applied forces;
  - Scaling of atomic coordinates.
- The sensitivity of the haptic interface to atomic interactions goes as the *square* of the speed of the simulation.
- Responsiveness can be improved by increasing the simulation force, but at the cost of sensitivity.

* Stone, Gullingsrud & Schulten, 2001.

IMD Test Applications

- Gramicidin A system: ion channel system with 4400 atoms.
- Dynamics were calculated at 79 timesteps/sec using 32 PC's - fast enough to feel collisions.
- Lac repressor: docking simulation with 4500 atoms.
- Able to guide ligand into binding pocket.



Future Work

- Improve interactivity through faster dynamics integrators and more efficient haptic update schemes.
- Torque feedback or multiple haptic devices for interactive docking.
- Apply to more interesting biological systems.