Molecular Biomedicine in the Era of Teraflop Computing – Opportunities Ahead

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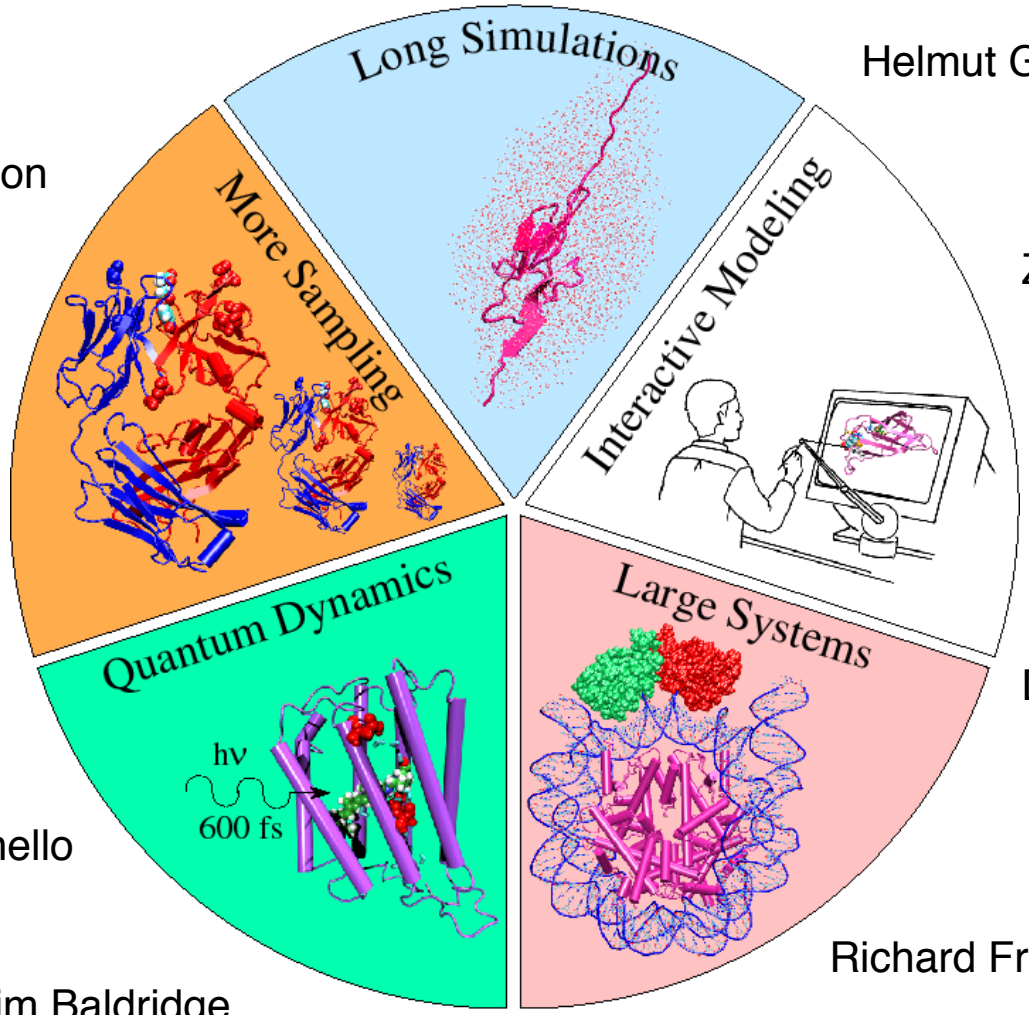

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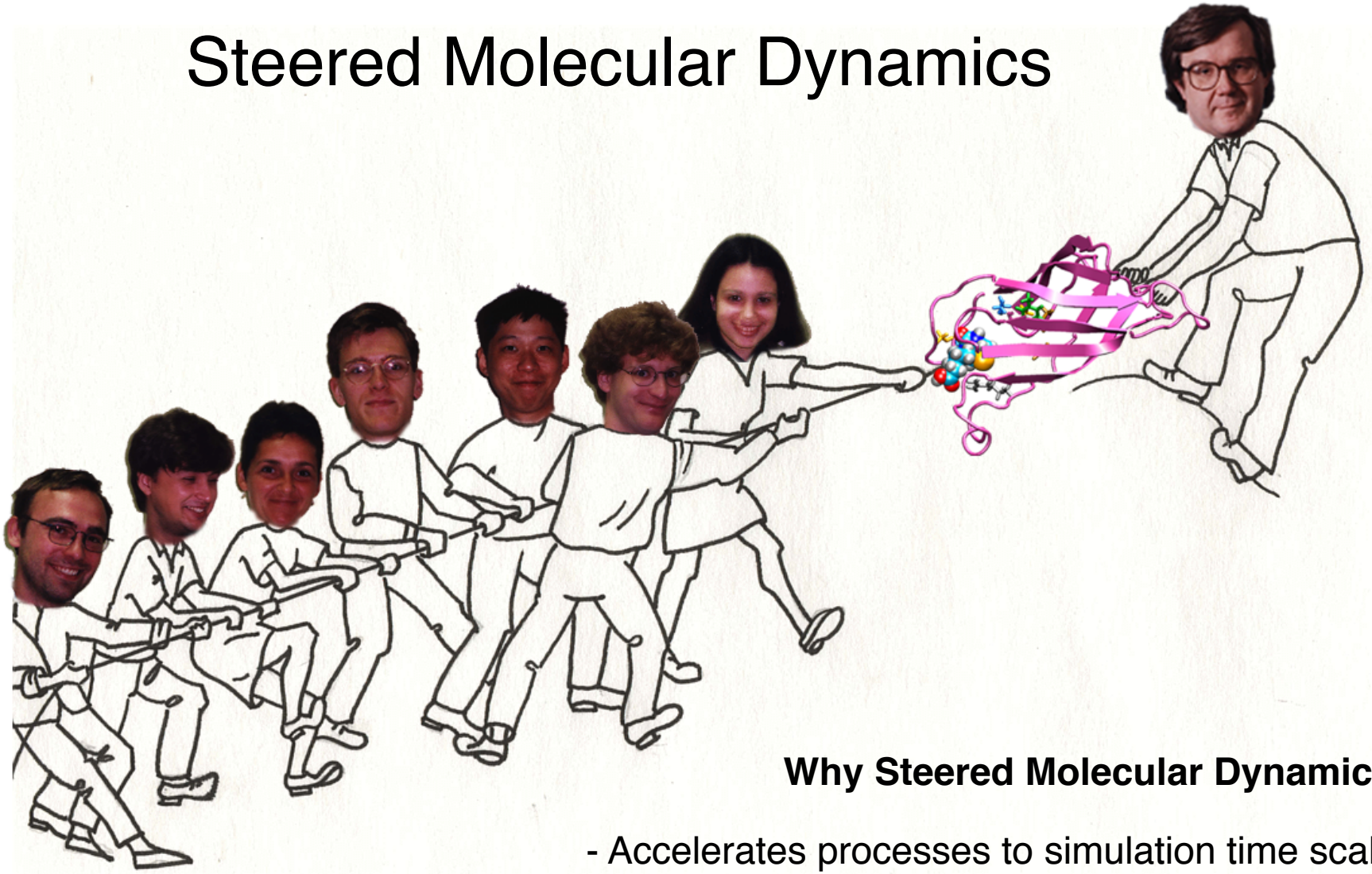
Steered Molecular Dynamics



Why Steered Molecular Dynamics?

- Accelerates processes to simulation time scales (ns
-Yields explanations of biopolymer mechanic
- Finds underlying unbinding potential

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Atomic Force Microscopy

in vivo,

in vitro,

in silico

Prof. Klaus Schulten

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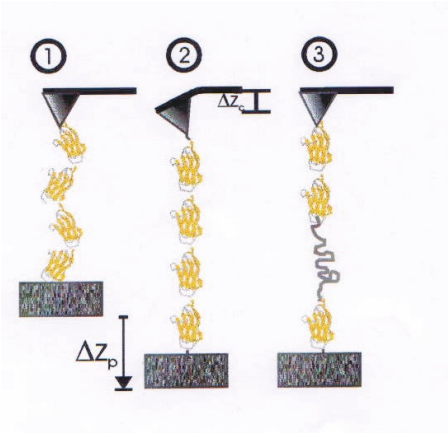
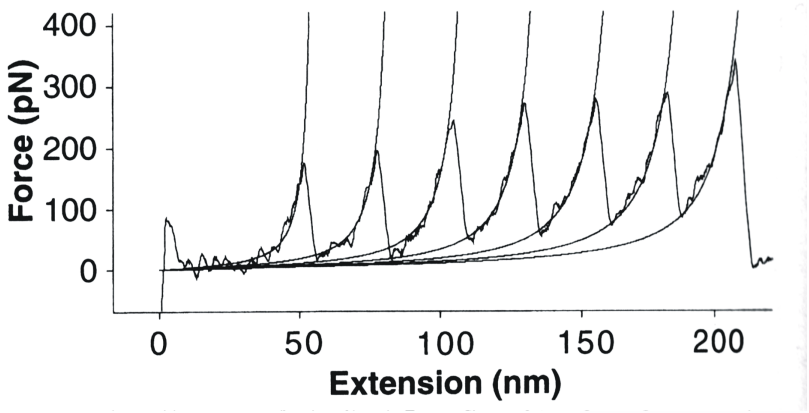
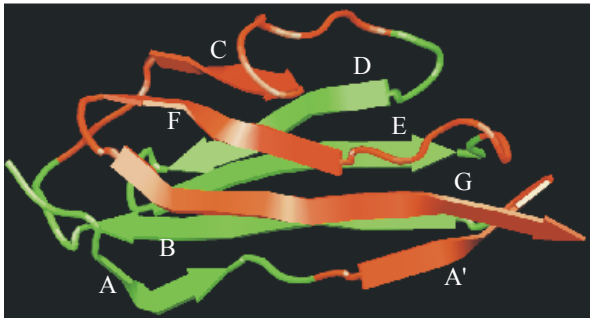
Titin Ig Domain Extension

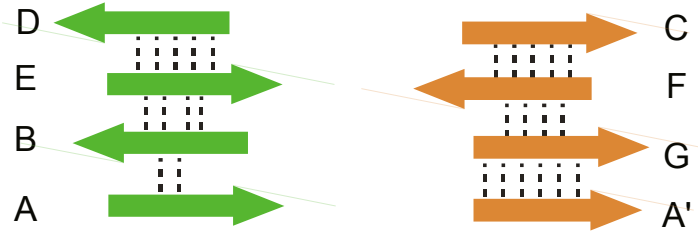


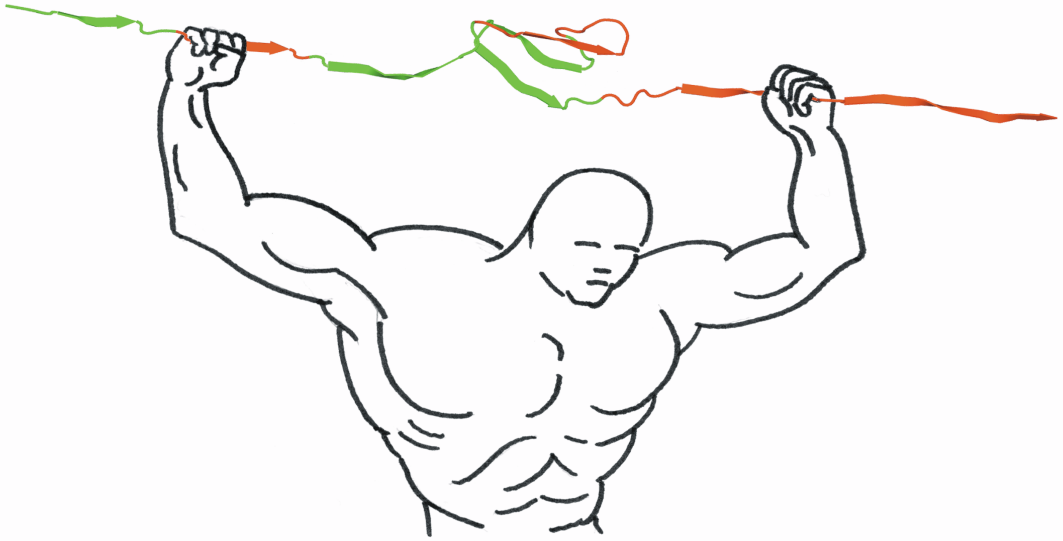


AFM extension of titin Ig multimers, Reif *et al.*, Science **276**, 1109 (1997)

Titin I27 topology







SMD is performed on titin Ig domains using constant velocity and constant force protocols.

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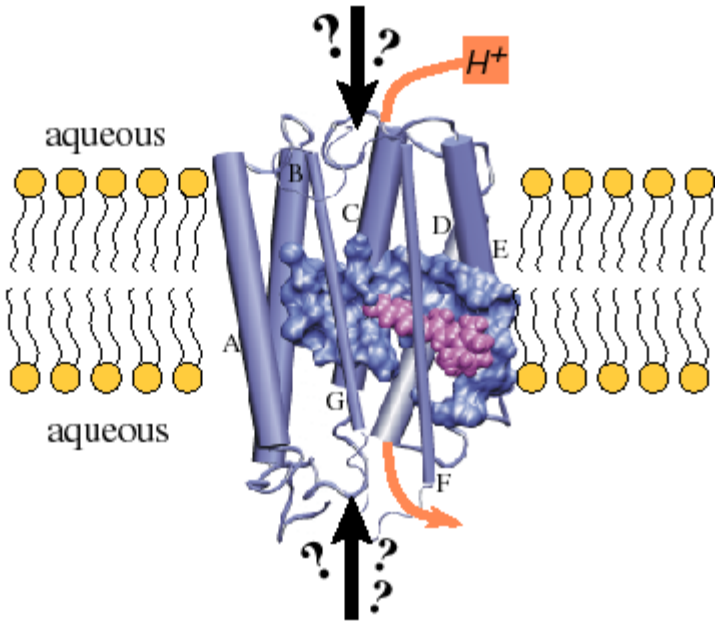
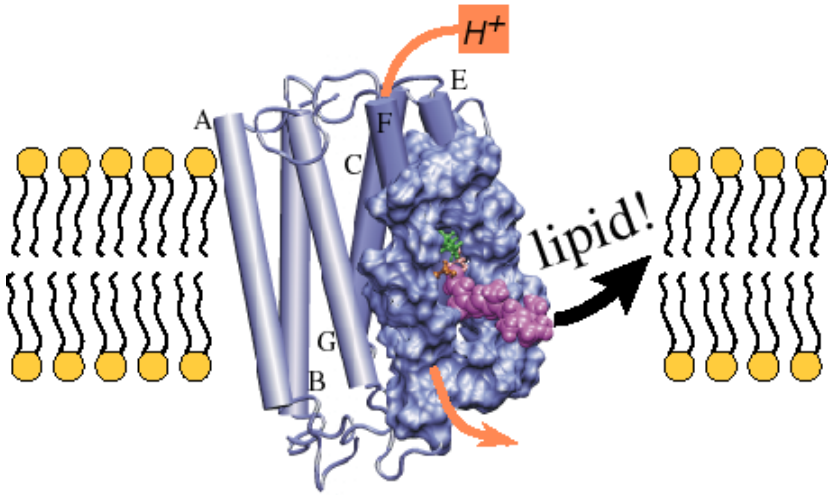
Interactive Modeling

Binding path of retinal to bacterio-opsin (1)



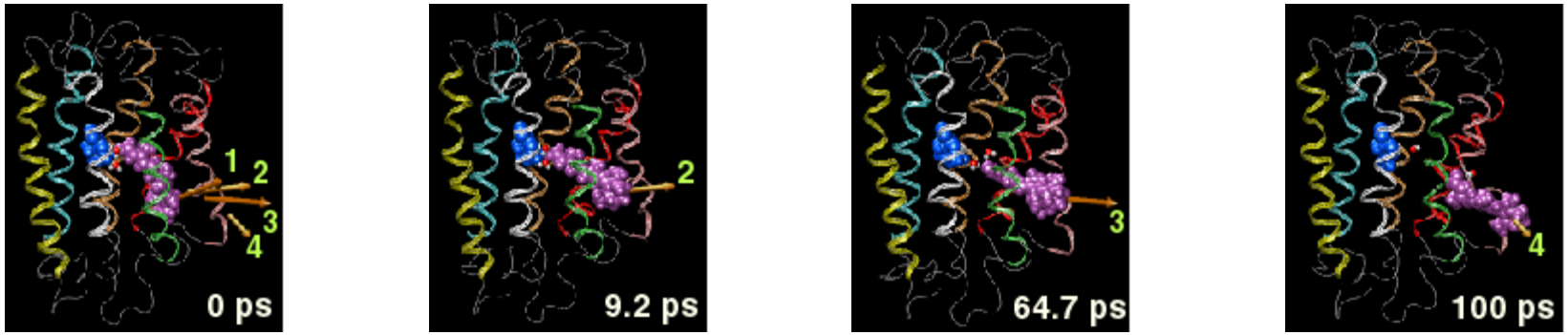
- Retinal deep in bacterio-opsin binding cleft
- How does it get in?
- Use batch mode interactive steered molecular dynamics to pull retinal out of cleft, find possible binding path

- 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

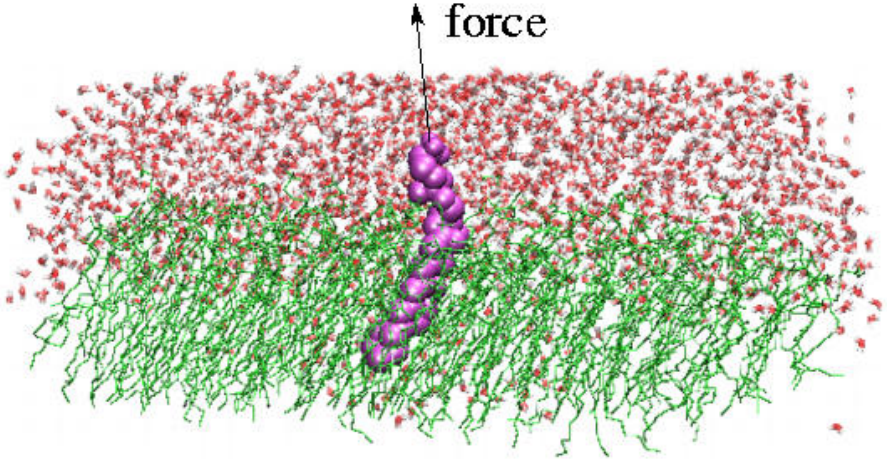
Binding path of retinal to bacterio-opsin (2)

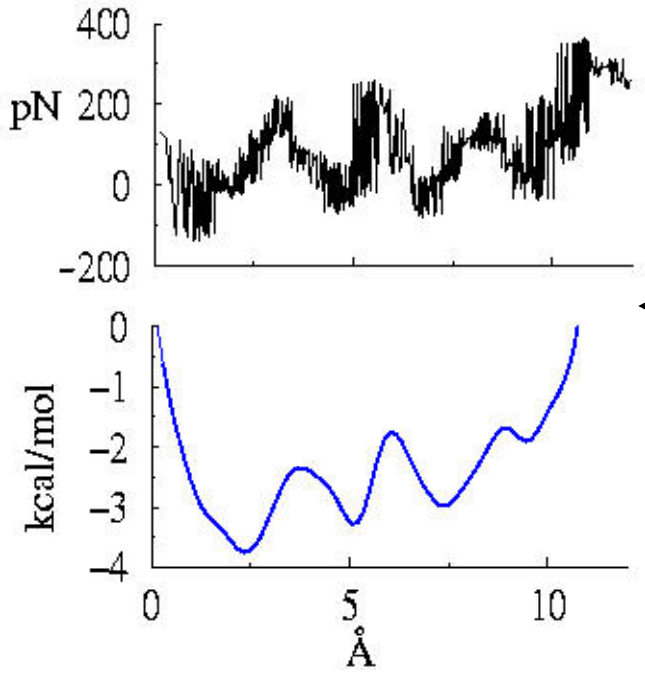


B. Isralewitz, S. Izrailev and K. Schulten, *Biophys. J.*, **73**, 2972-2979 (1997)

Other systems studied: avidin-biotin: Izrailev *et al.*, Biophys. J., **72**, 1568-1581 (1997); lipid-membrane: Stepaniants *et al.*, J. Molec. Modeling, **3**, 473-475 (1997); retinoic acid receptor: Kosztin *et al.*, Biophys. J., **76**, 188-197 (1999); actin phosphate release: Wriggers *et al.*, Proteins, **35**, 262-273 (1999); titin: Lu *et al.*, Biophys. J., **75**, 662-671 (1998); Lu and Schulten, Proteins, **35**, 453-463 (1999), Chem. Phys., **247**, 141-153 (1999); fibronectin: Krammer *et al.*, PNAS, **96**, 1351-1356 (1999); bc1 complex: Izrailev *et al*, Biophys. J., **77**, 1753-1768 (1999)

Quantitative Analysis of SMD





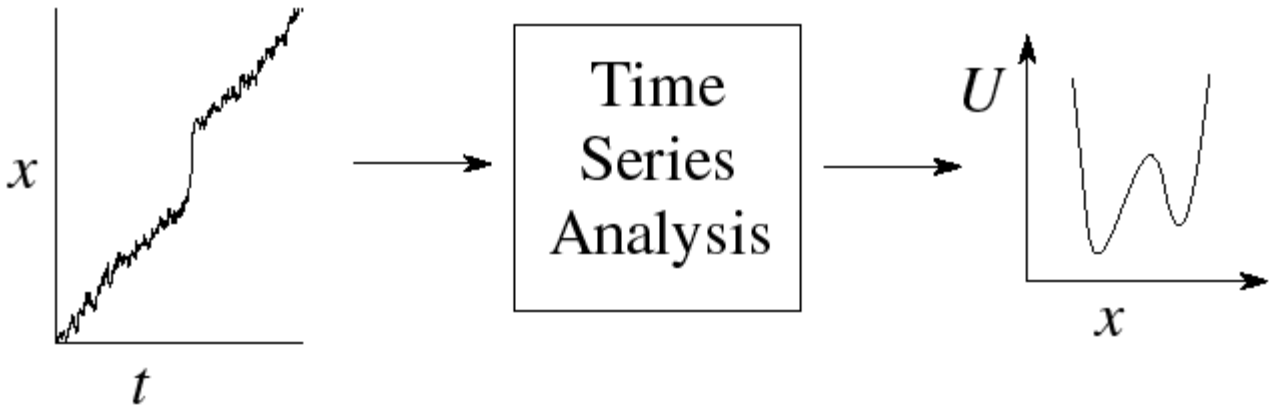
- The potential of mean force (PMF) is reconstructed from time series of applied force and displacement

- Non-equilibrium analysis based on the Langevin equation:

  $\gamma \dot{x} = F(x,t) - dU/dx + x(t)$

- Multiple trajectories can be combined to yield statistically significant results

Reconstruction Methods Investigated



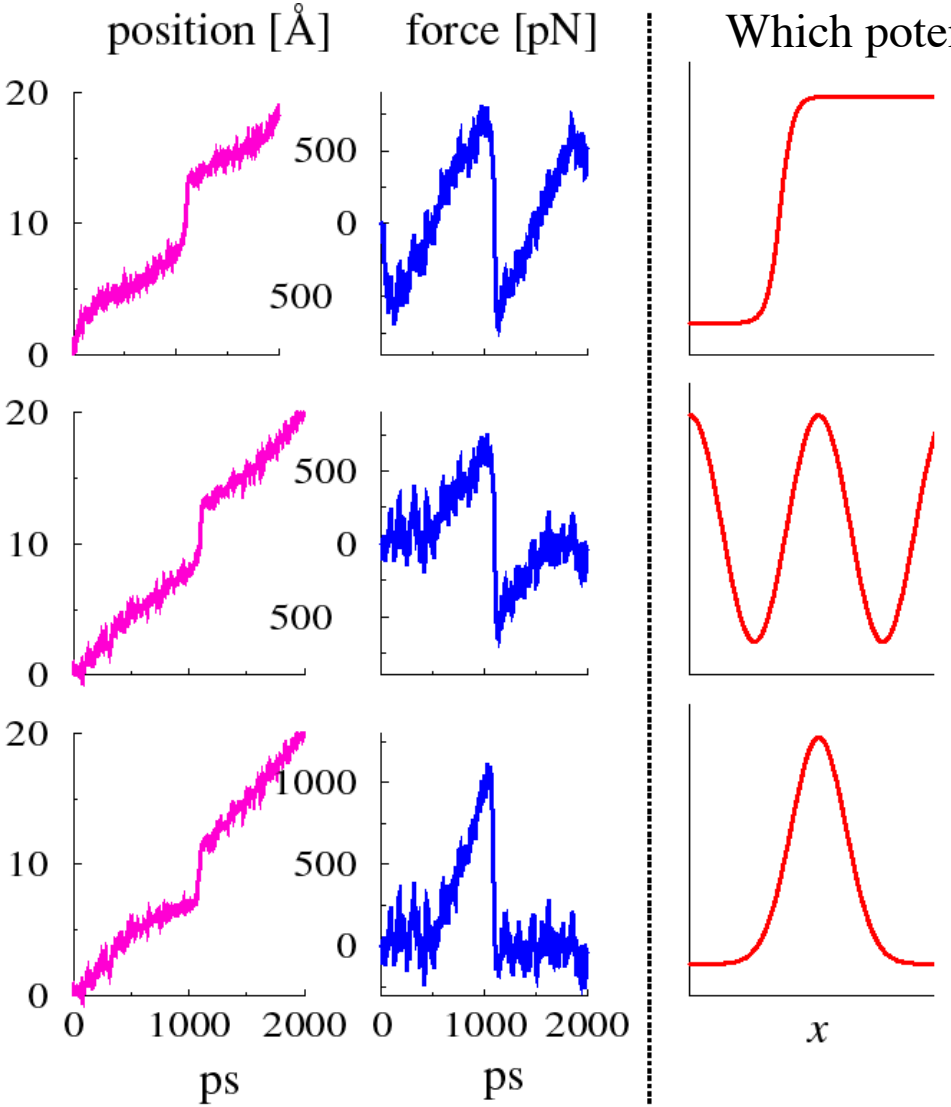
• WHAM: generate probability data from the time series *x(t)* and reconstruct the potential assuming quasi-equilibrium

• Gaussian Drift Method: measure the velocity *x(t)* and the size of the fluctuations

• Least Square Method: the most probable PMF minimizes the Onsager-Machlup action, given *x(t)* and *F(t)*

J. Gullingsrud, R. Braun and K. Schulten, J. Comp. Phys, **151**, 190-211 (1999)
Earlier study: M. Balsera et al., Biophys. J., **73**, 1281-1287 (1997)

Reconstructing Potentials from Time Series Data



Data from Langevin model

$$\gamma\dot{x} = -dU/dx + k(vt-x) + \sigma\xi(t)$$

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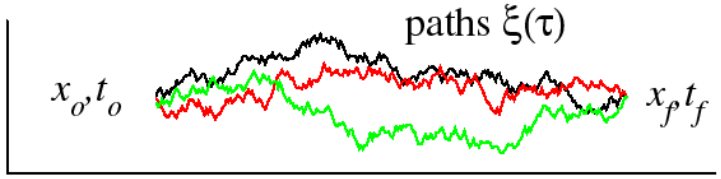
Least Squares Method



• For path $\xi(\tau)$, probability $p[\xi(\tau)] \propto \exp\{-S[\xi(\tau)]\}$, where

$$S[\xi(\tau)] \propto \frac{1}{2}\int d\tau \left\{\left[\gamma\dot{\xi} - F(\xi,\tau) + dU/d\xi\right]^2 - k_B T\frac{d^2U}{d\xi^2}\right\}$$

(Onsager-Machlup action)

• ***Conversely, the most likely potential for a given x(t) can be determined by minimizing S with respect to the choice of potential.***

• Expand *-dU/dx* in terms of basis functions $f_n(x)$,

$$-\frac{dU}{dx} = \sum_{n=1}^{n_{max}} c_n f_n(x)$$

• Minimize *S* with respect to $c=(c_1,c_2,\ldots,c_{nmax})^T$.

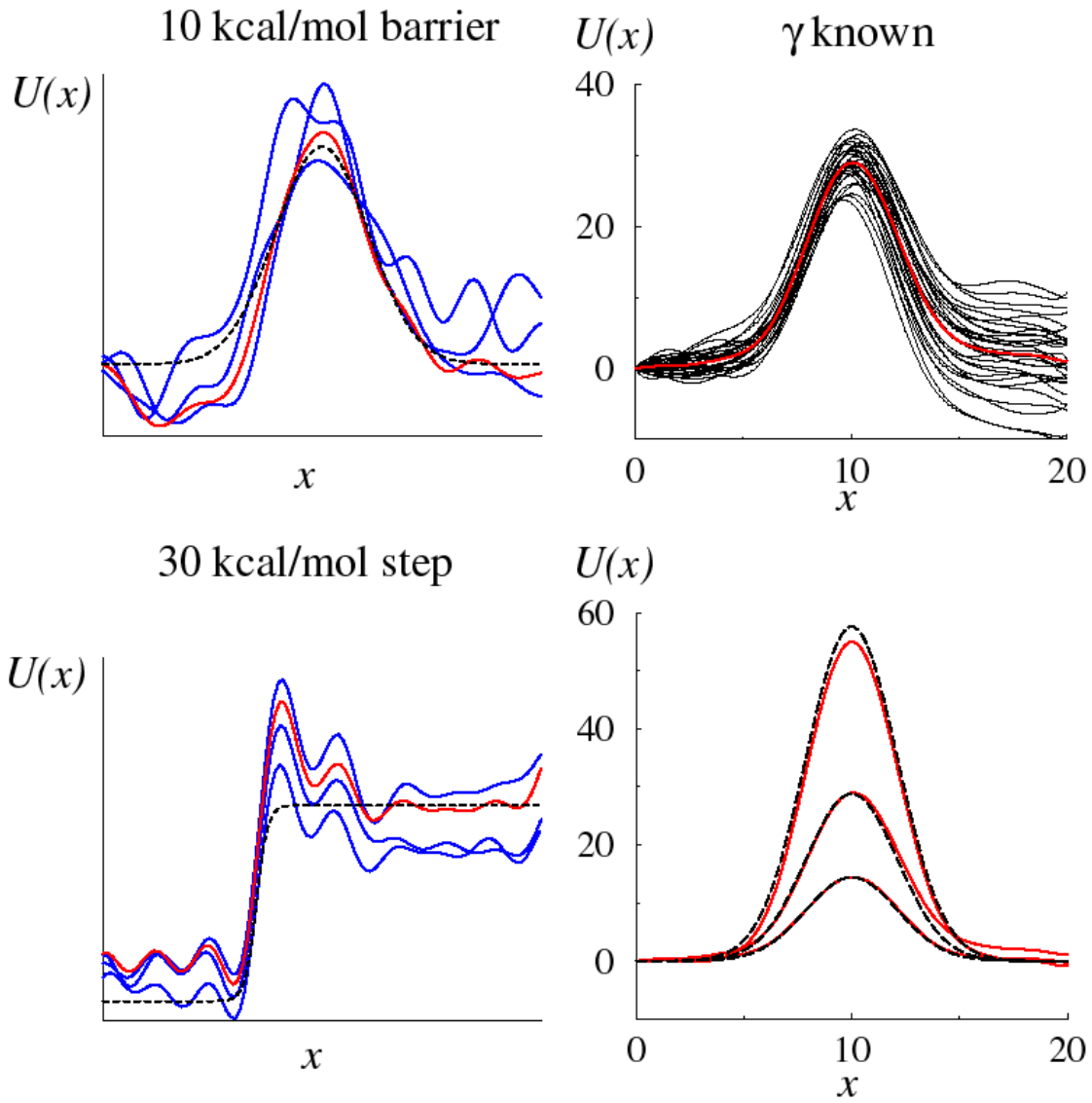
• Numerically integrating each basis function gives a linear least squares problem.

• Choice of basis functions: $f_n(x)=\cos(nx/L)$, $\sin(nx/L)$.

• $x(t)/L$ scaled to $[-\pi,\pi]$: $U(x_f)$ clamped to zero.

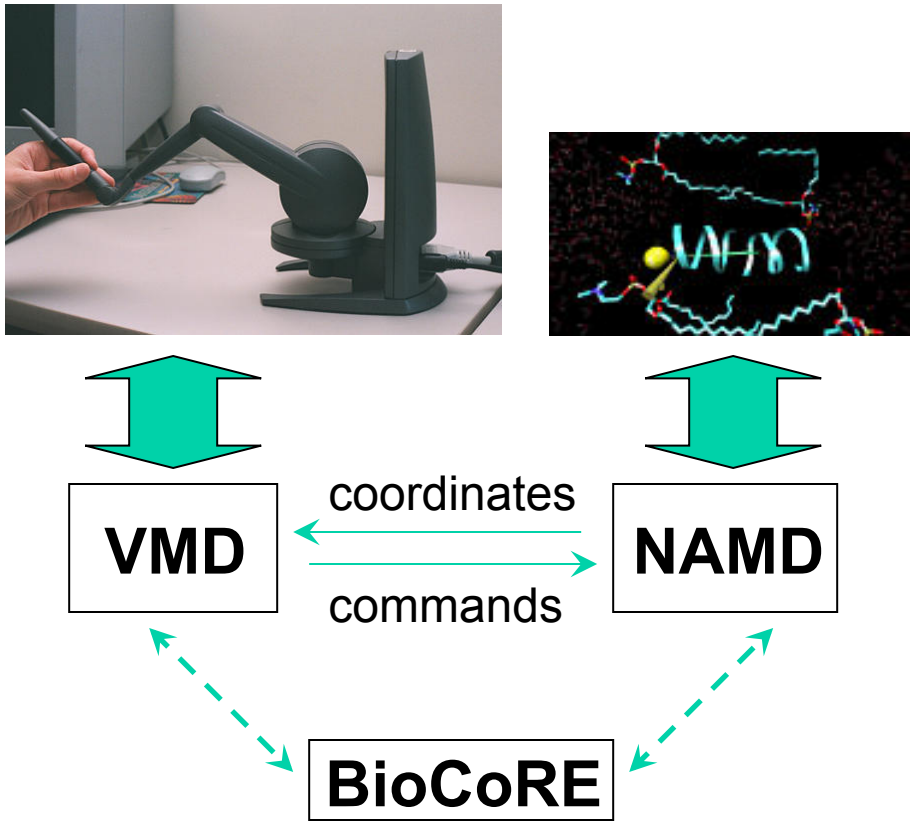
• $x(t)/L$ scaled to $[0,\pi]$: $U(x_f)$ unclamped.

Reconstructing Potentials Using Full Onsager-Machlup Action and Multiple Trajectories



Interactive Molecular Dynamics

Design



Goals

- Speed up slow events in molecular dynamics simulations.
- Assist in the discovery of new motions and pathways in biomolecules.
- Supply immediate feedback to researchers about the physical system.

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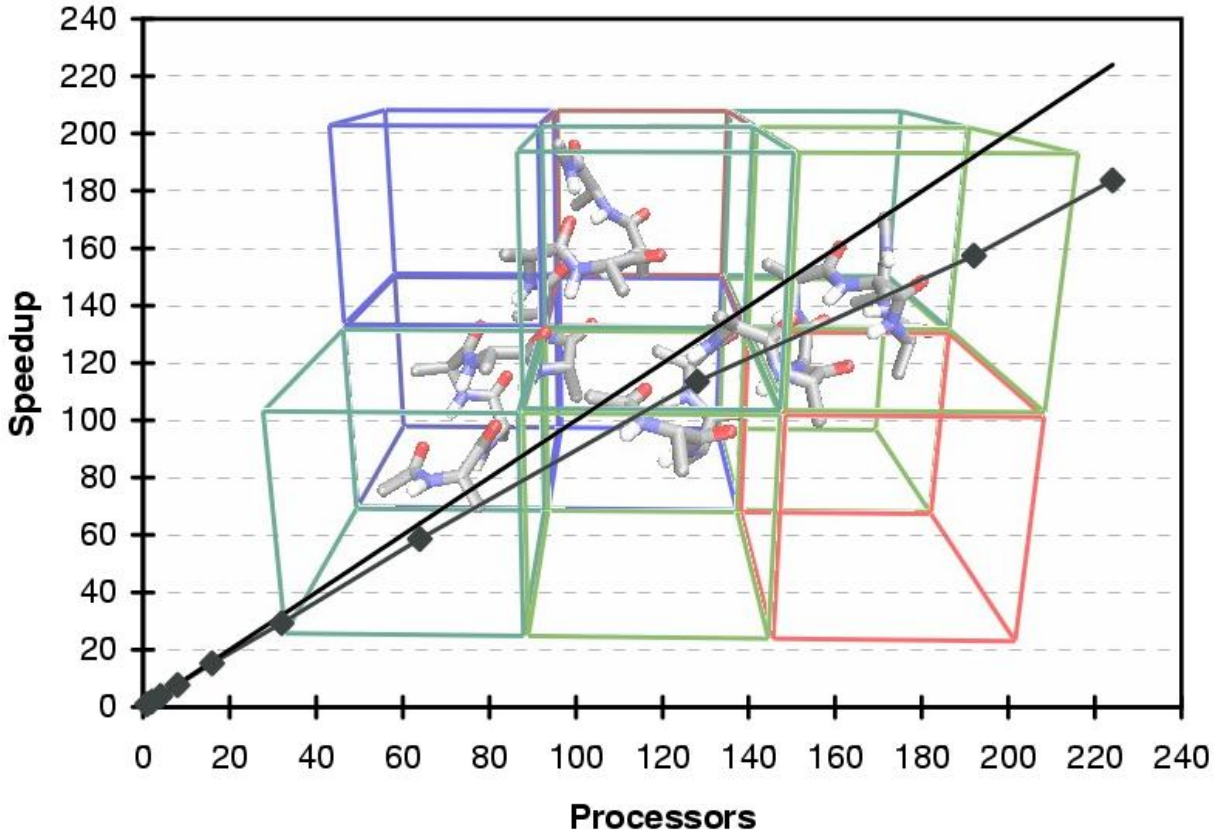
NAMD: Scalable Molecular Dynamics



Parallel simulation of biomolecular systems

Spatial decomposition for distributed memory

Message driven for latency tolerance

Object-oriented and implemented in C++

http://www.ks.uiuc.edu/Research/namd

Kalé *et al.*, J. Comp. Phys., 151, 283 (1999)

NAMD
Scalable Molecular Dynamics

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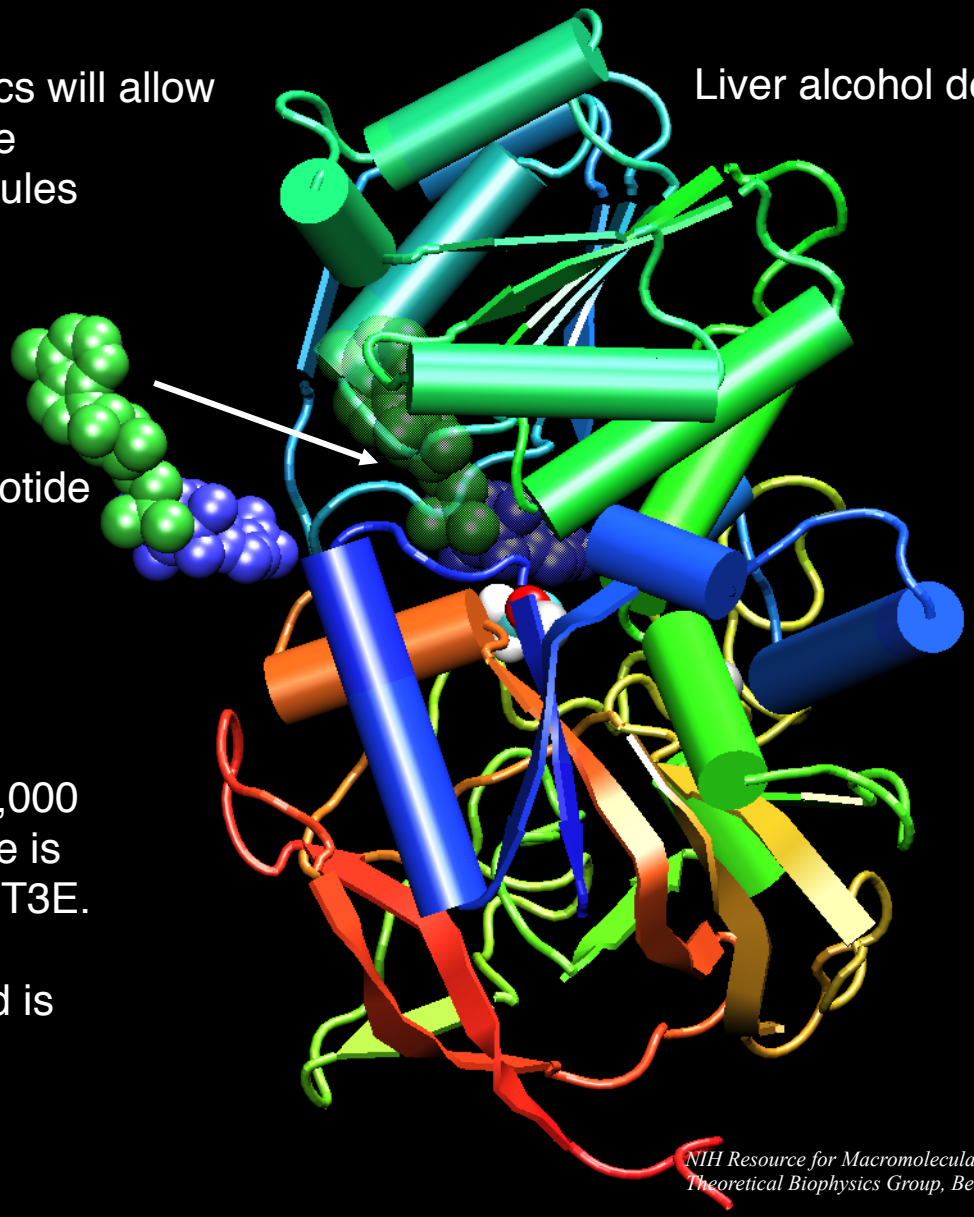
Interactive Modeling
Structure based drug design

Interactive molecular dynamics will allow docking studies to incorporate the realistic motions of molecules

Liver alcohol dehydrogenase

Inhibitor SAD (selenazole-4-carboxamide adenide dinucleotide



For a system of this size (~15,000 atoms solvated), 0.5 ps/minute is possible on 64 nodes of Cray T3E.

Factor of 50 increase in speed is desirable.

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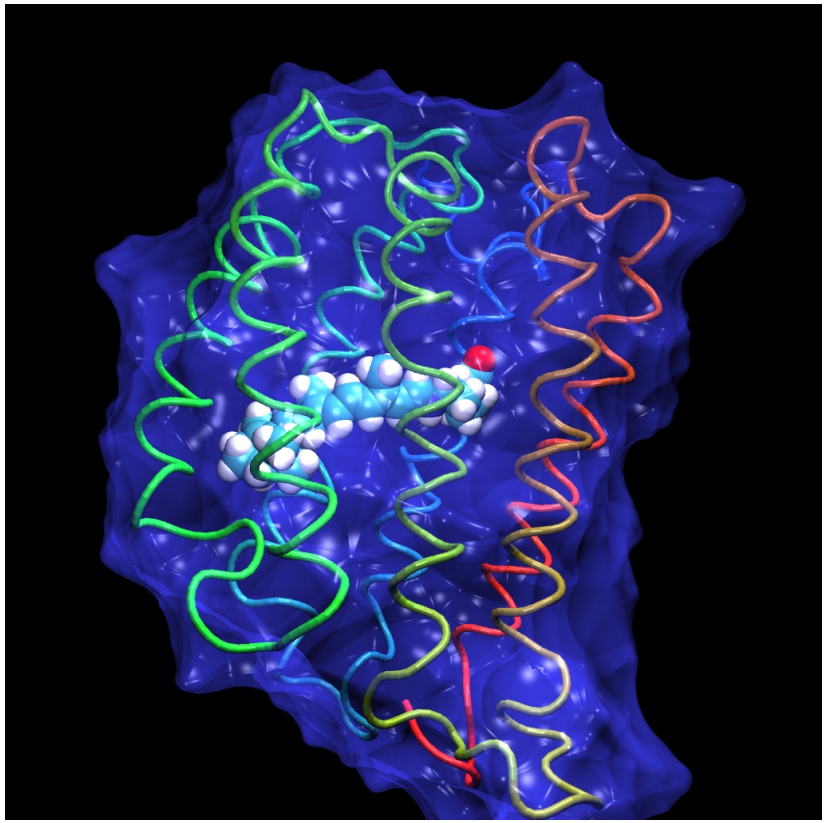
VMD: Visual Molecular Dynamics



Key Features:

Display and animation of macromolecules

Real-time interaction with molecular dynamics simulations

Supports Windows 95/98/NT, and a wide variety of Unix platforms

Hardware accelerated 3D rendering and stereoscopic display

http://www.ks.uiuc.edu/Research/vmd/

Humphrey *et al.*, J. Molec. Graphics, 14.1, 33 (1996)

VMD
Visual Molecular Dynamics

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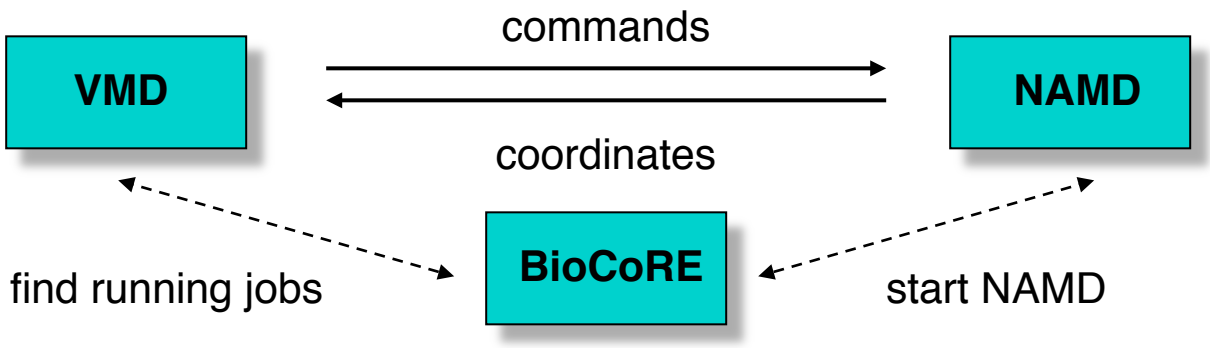
How the connection works

• The visualization program (VMD) and the simulation engine (NAMD) exchange commands and coordinates so that the user can interactively steer the simulation.

• A collaboratory environment (BioCoRE) comlements IMD with the ability to start and monitor several jobs at once.



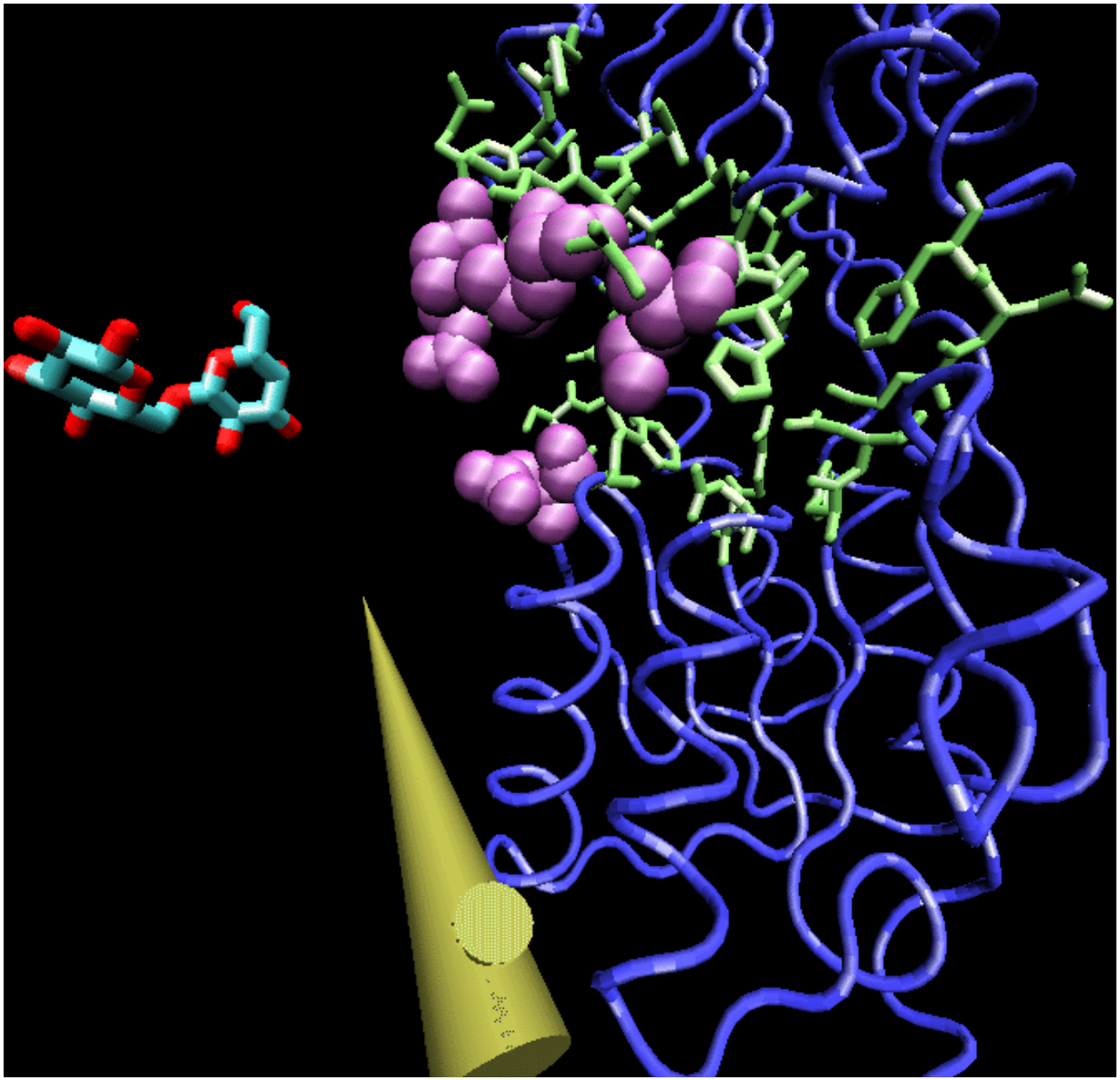
A Haptic Device for IMD

A haptic device is the most natural tool with which to interact with a running simulation.

The haptic device can function in a number of different modes in VMD, to fully utilize the device's 6 DOF capability.

- **Grab Tool**: translate and rotate a molecule simultaneously
- **Tug Tool**: steer a running simulation and receive interactive force feedback
- **SMD Tool**: Apply a force along a chosen direction and record force vs. displacement

Interactive Docking of Lactose *lac* Repressor



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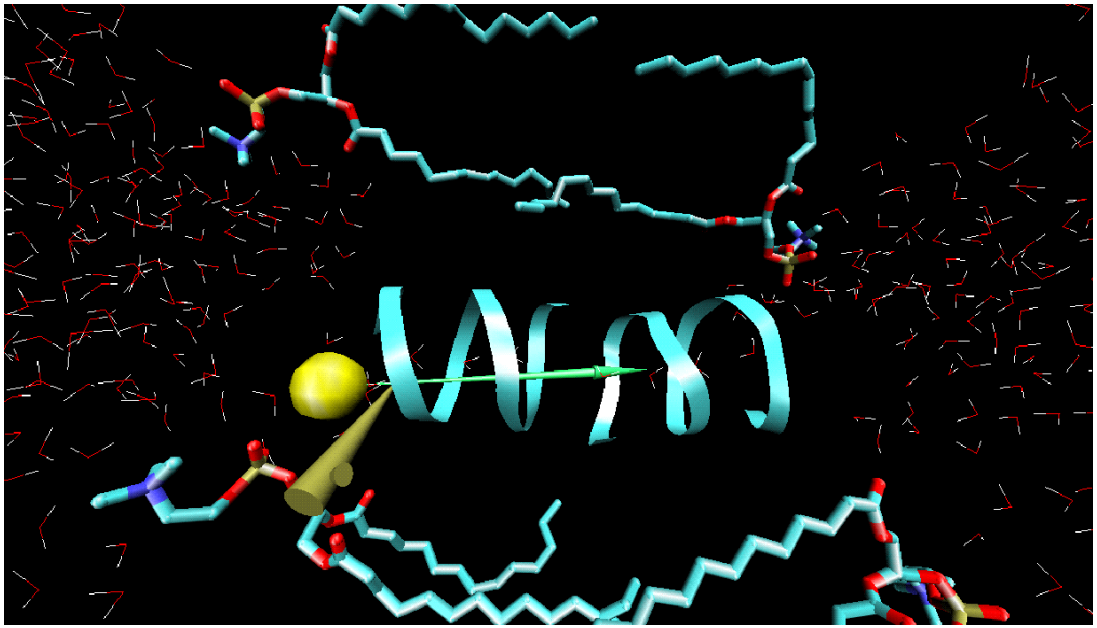
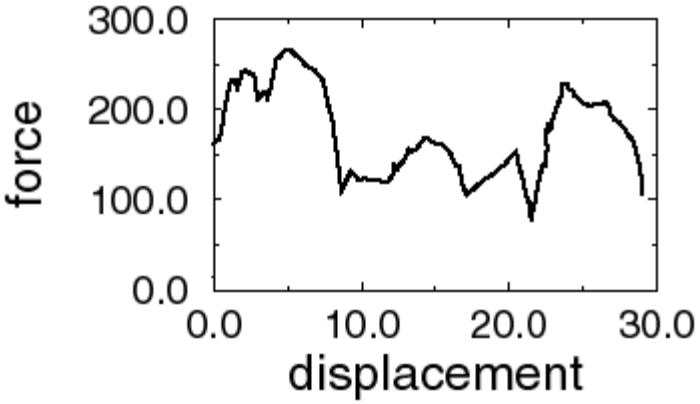
Application to Gramicidin A System





The SMD tool can be used to interactively steer the ion through the channel.

The applied force vs. displacement is recorded for later use.

Interactive Molecular Dynamics (IMD)

Interactive Molecular dynamics (IMD) provides a direct network connection for efficient exchange of steering commands and simulation coordinates. It is a tool that can:

- speed up slow events in molecular dynamics simulations
- assist in the discovery of new motions and pathways in biomolecules
- supply immediate feedback to researchers about the physical system

IMD can easily be performed with the simulation engine running on remote supercomputers, e.g. NCSA, SDSC, PSC, etc, and the visualization done locally.

Planned Work

Support developing haptic technology, including torque response as well as relatively inexpensive force-feedback joysticks.

Application to large macromolecular systems will take advantage of NAMD's excellent scaling on multiprocessor and distributed machines.

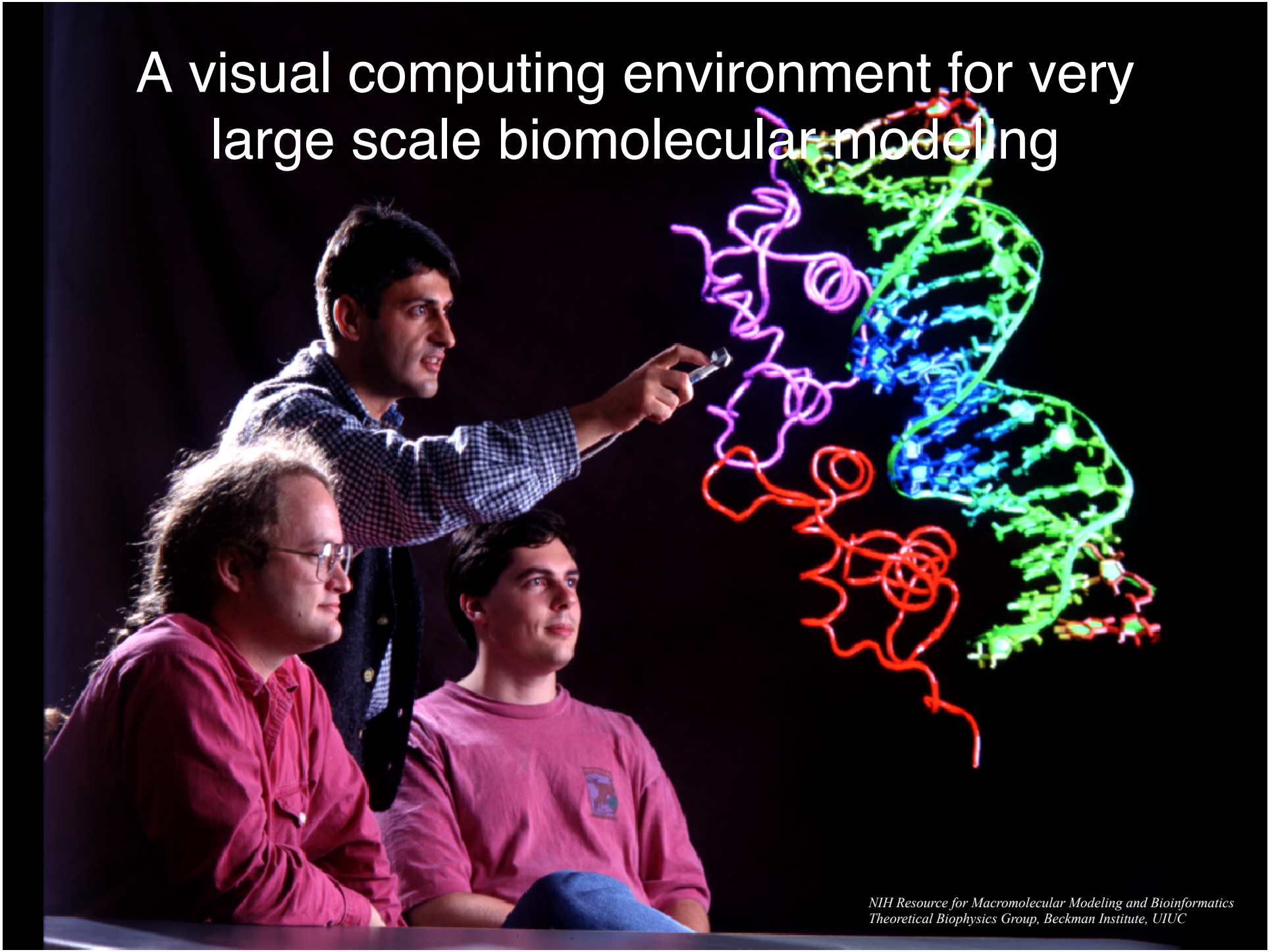
Quantitative analysis:

1. Apply PMF analysis to force-displacement time series gathered during interactive sessions. (Gullingsrud et al., J. Comp. Phys., 151, 190-211, 1999)

2. On the fly analysis of RMSD, correlation functions, etc.

Development of visual computing environment for "hands-free" input.

A visual computing environment for very large scale biomolecular modeling



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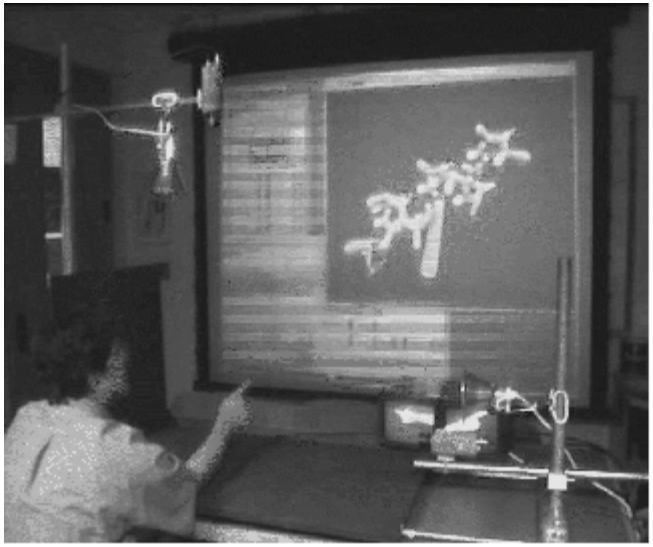
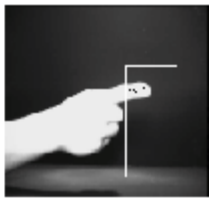
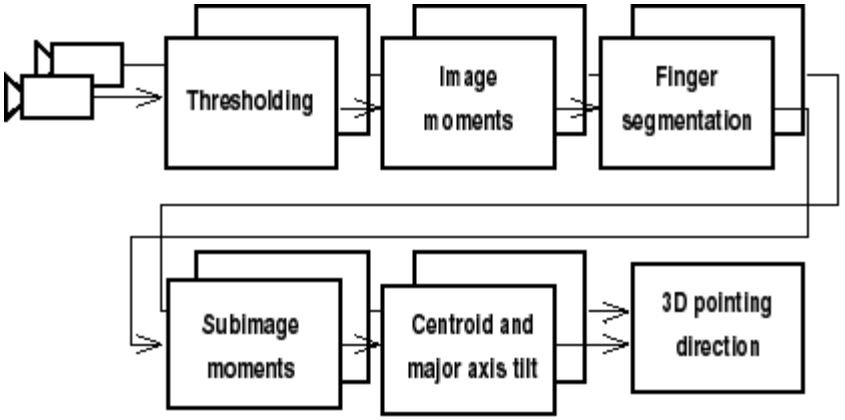
Gesture Recognition Setup



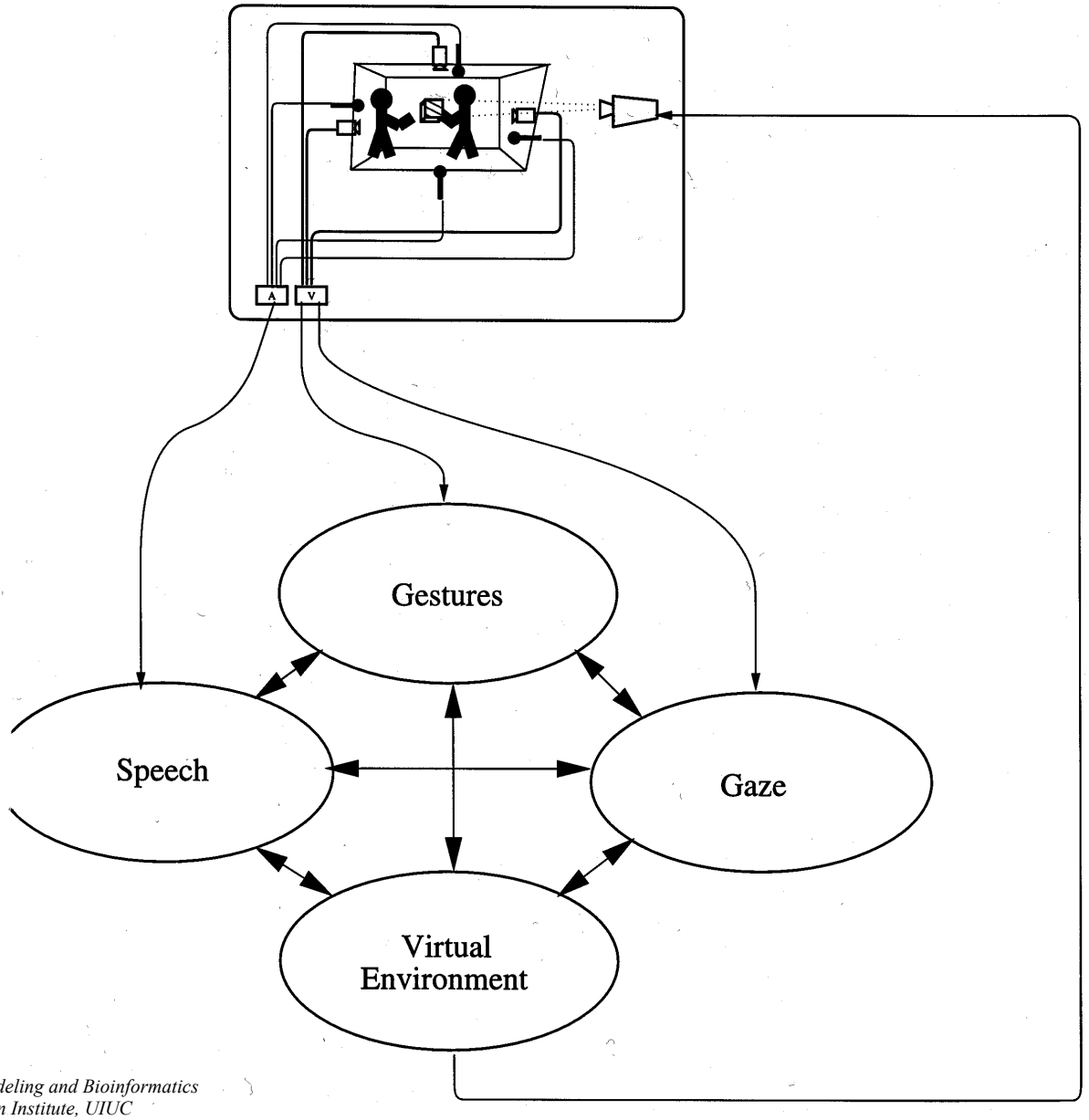
Top Camera



Side Camera

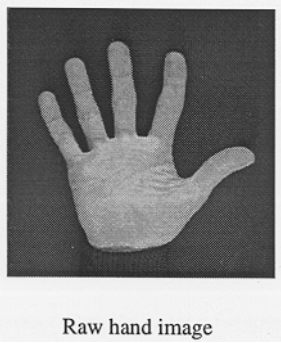


Multimodal CESB



Gesture Recognition in CESB

Role of hand model gesture analysis



Raw hand image

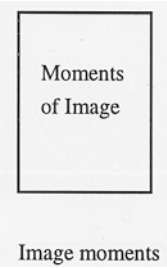
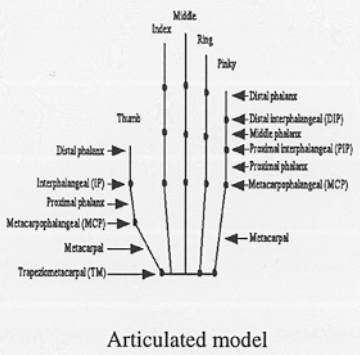
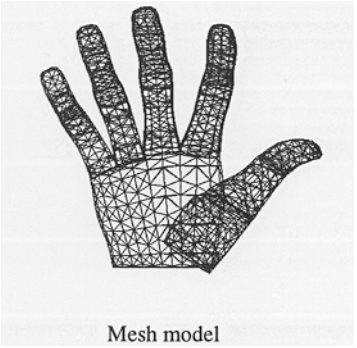


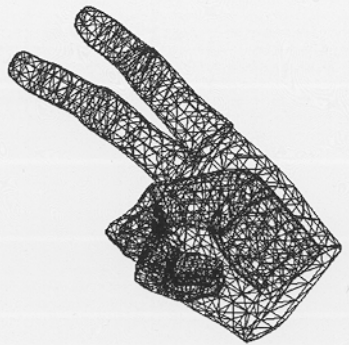
Image moments

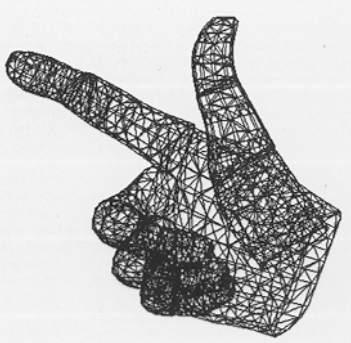


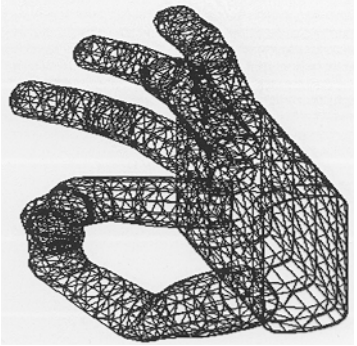
Articulated model



Mesh model







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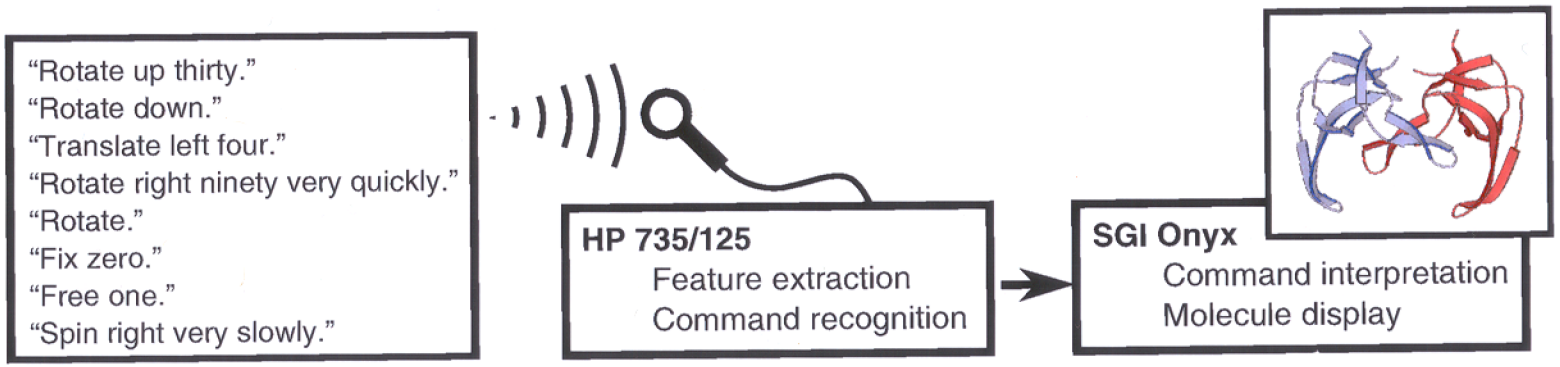
Speech recognition setup



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