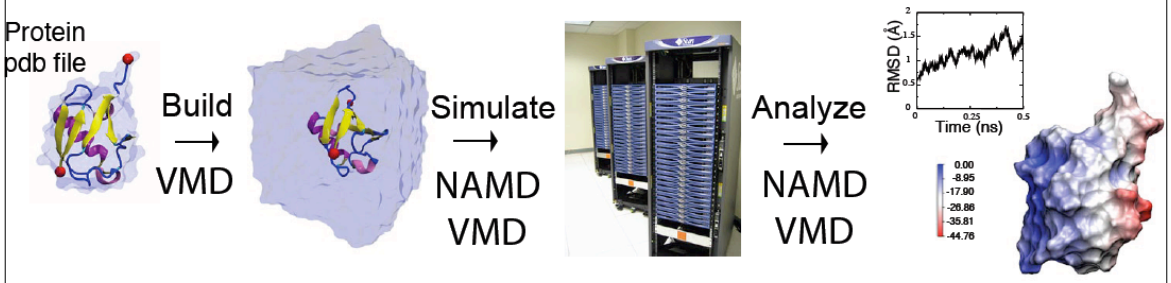
The Molecular Dynamics Simulation Process



For textbooks see:

M.P. Allen and D.J. Tildesley. ***Computer Simulation of Liquids.***Oxford University Press, New York, 1987.
D. Frenkel and B. Smit. ***Understanding Molecular Simulations. From Algorithms to Applications.*** Academic Press, San Diego, California, 1996.
A. R. Leach. ***Molecular Modelling. Principles and Applications.***Addison Wesley Longman, Essex, England, 1996.
More at http://www.biomath.nyu.edu/index/course/99/textbooks.html

Classical Dynamics

at 300K

Energy function: $U(\vec{r}_1, \vec{r}_2, \cdots \vec{r}_N) = U(\vec{R})$

used to determine the force on each atom:

$$m_i \frac{d^2\vec{r}_i}{dt^2} = \vec{F}_i = -\vec{\nabla} U(\vec{R})$$

yields a set of 3N coupled 2nd-order differential equations that can be propagated forward (or backward) in time.

Initial coordinates obtained from crystal structure, velocities taken at random from Boltzmann distribution.

Maintain appropriate temperature by adjusting velocities.

Classical Dynamics

discretization in time for computing

$$m_i \frac{d^2 \vec{r}_i}{dt^2} = \vec{F}_i = -\vec{\nabla} U(\vec{R})$$

Use positions and accelerations at time t and the positions from time t-δt to calculate new positions at time t+δt.

$$\mathbf{r}(t+\delta t) \approx \mathbf{r}(t) + \mathbf{v}(t)\delta t + \frac{1}{2}\mathbf{a}(t)\delta t^2$$

+

$$\mathbf{r}(t-\delta t) \approx \mathbf{r}(t) - \mathbf{v}(t)\delta t + \frac{1}{2}\mathbf{a}(t)\delta t^2$$

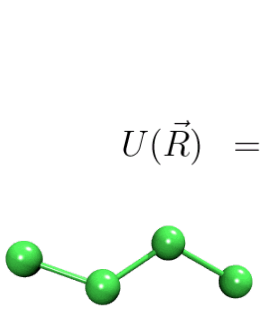
"Verlet algorithm"

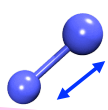
$-\vec{\nabla} U(\vec{R}) / m_i$

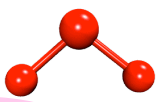
$$\boxed{\mathbf{r}(t+\delta t) \approx 2\mathbf{r}(t) - \mathbf{r}(t-\delta t) + \mathbf{a}(t)\delta t^2}$$

Potential Energy Function of Biopolymer

- Simple, fixed algebraic form for every type of interaction.
- Variable parameters depend on types of atoms involved.







heuristic

$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} +$$

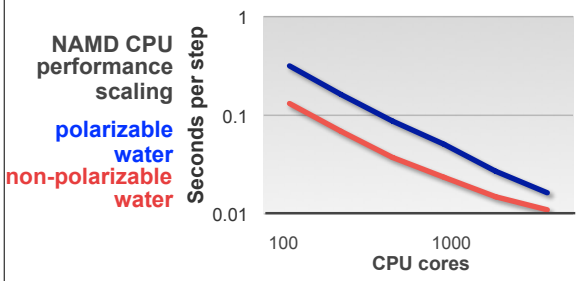
$$\underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} +$$

from physics

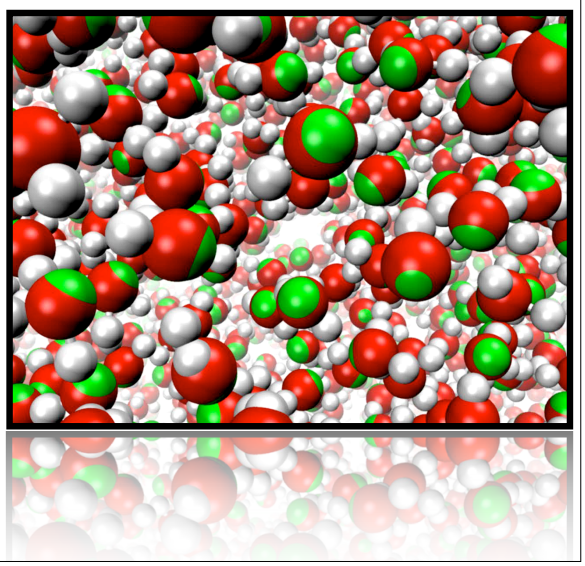
$$\underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}$$

Improving the Force Field

- Atomic polarizability increases computation by 2x…
- …but, the additional computations are perfectly suited to the GPU!
- For now, NAMD calculates atomic polarizability on CPUs only...soon we will also use GPUs



Atomic polarizability of water, highly accurately simulated through additional particles (shown in green)



Molecular Dynamics Ensembles

Constant energy, constant number of particles (NE)

Constant energy, constant volume (NVE)

Constant temperature, constant volume (NVT)

Constant temperature, constant pressure (NPT)

Choose the ensemble that best fits your system and start the simulations, but use NE to check on accuracy of the simulation.

Langevin Dynamics

for temperature control

Langevin dynamics deals with each atom separately, balancing a small friction term with Gaussian noise to control temperature:

$$m\,\ddot{\vec{r}} \;=\; \vec{F}(\vec{r}) \;-\; \gamma\, m\,\dot{\vec{r}} \;+\; \vec{R}(t)$$

$$\left\langle \vec{R}(t)\cdot\vec{R}(t')\right\rangle \;=\; 6k_BT\gamma\,\delta(t\;-\;t')$$

Langevin Dynamics

for pressure control

Underlying Langevin-Hoover barostat equation for all atoms: Equations solved numerically in NAMD

$$\frac{d^2V(t)}{dt^2} \;=\; \frac{1}{W_{bs}}\,[P(t)\;-\;P_{\rm target}] \;-\; \frac{1}{\tau_{\rm bs}}\frac{dV(t)}{dt} \;+\; R_{\rm bs}(t)$$

$$P = \rho k_B T + \frac{1}{Vd}\sum_{i<j}\langle r_{ij}\frac{dU_{tot}(r_{ij})}{dr_{ij}}\rangle \qquad d \;=\; \text{dimension}$$

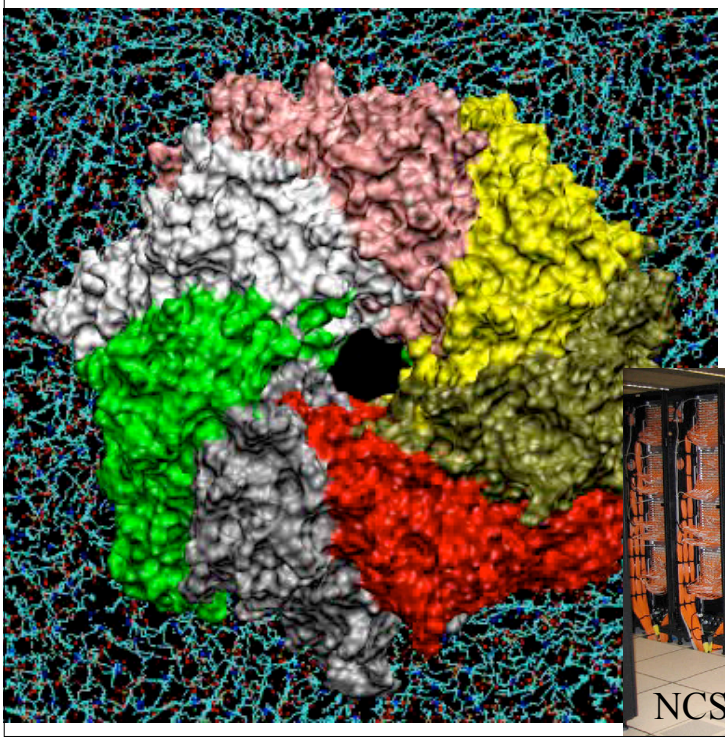
$$\langle R_{\rm bs}(t)\,R_{\rm bs}(t')\rangle \;=\; \frac{2\,k_{\rm B}\,T_{\rm target}\;\delta(t\;-\;t')}{W_{\rm bs}\,\tau_{\rm bs}} \qquad W_{\rm bs} \;=\; d\,N_{\rm atoms}\,k_{\rm B}T_{\rm target}\,\tau^2_{period}$$

$$\dot{\mathbf{r}}_i = \mathbf{v}_i + s\mathbf{r}_i \qquad\qquad \dot{\mathbf{v}}_i = \mathbf{F}_i\,/\,m_i - s\mathbf{v}_i$$

$$\dot{V} = dVs \qquad \dot{s} = dV\,(P - P_{\rm target})\,/\,W - s\,/\,\tau_{\rm bs} \qquad + R(t)$$

d - dimension

Large is no problem. But …



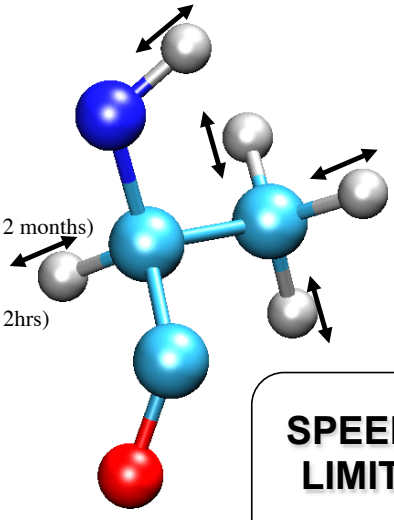
Molecular dynamics simulation of alpha-hemolysin with about 300,000 atoms; 10 million atom simulations are routine today, 200 million atom simulations are possible.

NCSA machine room

But long is still a problem!

biomolecular timescale and timestep limits

		steps
Rotation of buried sidechains Local denaturations Allosteric transitions	s	10^{15}
	ms	10^{12} (30 years, 2 months)
small protein folding	μs	10^{9} (10 days, 2hrs)
Hinge bending Rotation of surface sidechains Elastic vibrations	ns	10^{6} (15 min)
	ps	10^{3}
Bond stretching Molecular dynamics timestep →	fs	10^{0}



SPEED LIMIT

δt = 1 fs

(NSF center, Shaw Res.)

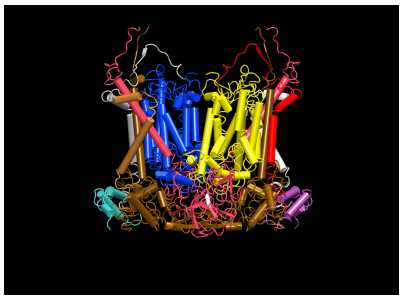
Preparing Your System for MD
Solvation

Biological activity is the result of interactions between molecules and occurs at the interfaces between molecules (protein-protein, protein-DNA, protein-solvent, DNA-solvent, etc).

Why model solvation?
• many biological processes occur in aqueous solution
• solvation effects play a crucial role in determining molecular conformation, electronic properties, binding energies, etc

How to model solvation?
• explicit treatment: solvent molecules are added to the molecular system
• implicit treatment: solvent is modeled as a continuum dielectric or so-called implicit force field

mitochondrial bc1 complex



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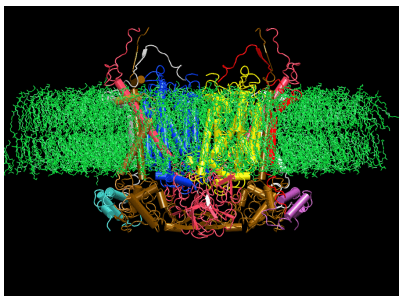

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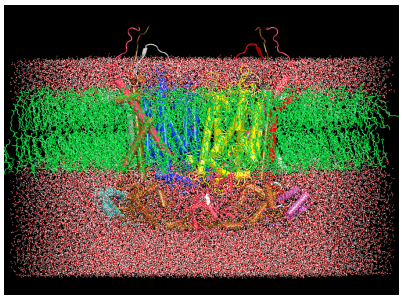
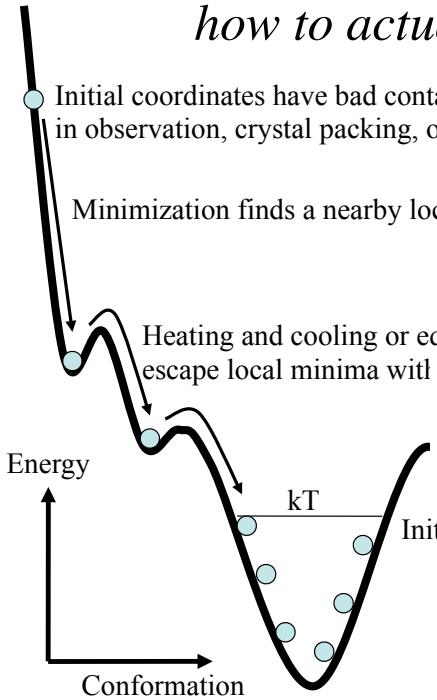


(Usually periodic! Avoids surface effects)

From the Mountains to the Valleys

how to actually describe a protein



Initial coordinates have bad contacts, causing high energies and forces (due to averaging in observation, crystal packing, or due to difference between theoretical and actual forces)

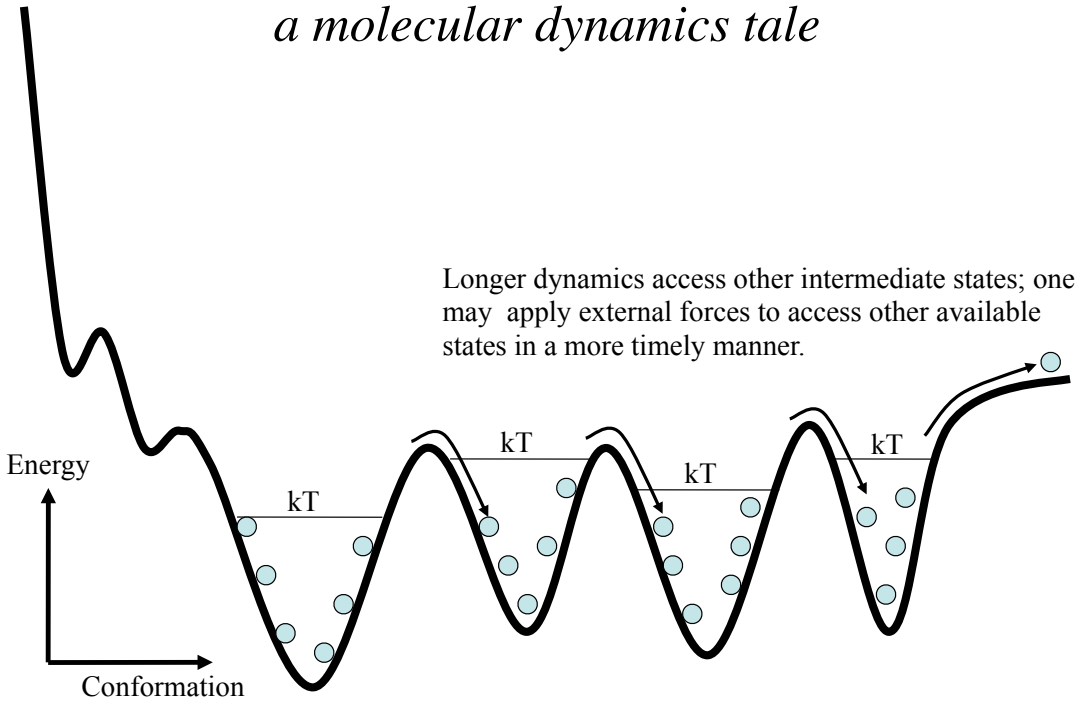
Minimization finds a nearby local minimum.

Heating and cooling or equilibration at fixed temperature permits biopolymer to escape local minima wit

Initial dynamics samples thermally accessible states.

From the Mountains to the Valleys

a molecular dynamics tale



VMD-NAMD plugin Keith