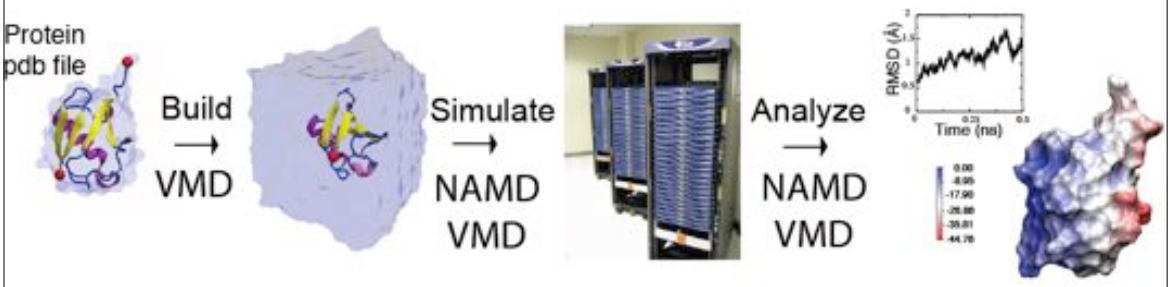
The Molecular Dynamics Simulation Process



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.

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

+

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

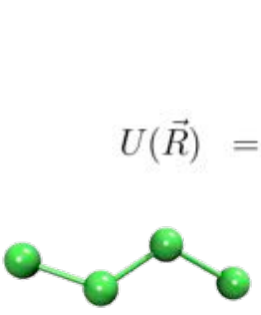
"Verlet algorithm"

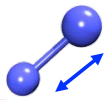
$-\vec{\nabla} U(\vec{R}) / m_i$

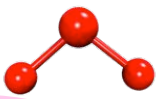
$$\boxed{\mathbf{r}(t+\delta t) \approx 2\mathbf{r}(t) - \mathbf{r}(t-\delta t) + \mathbf{a}(t)\delta t^2}$$

Potential Energy Function of Biopolymer

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







heuristic

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

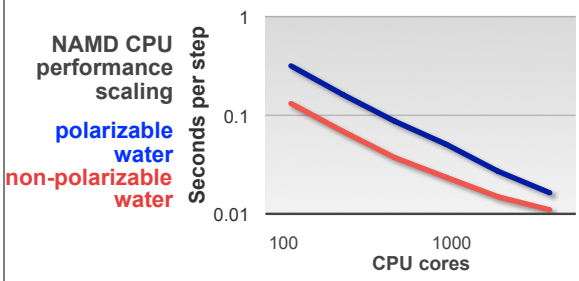
$$\underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} +$$

from physics

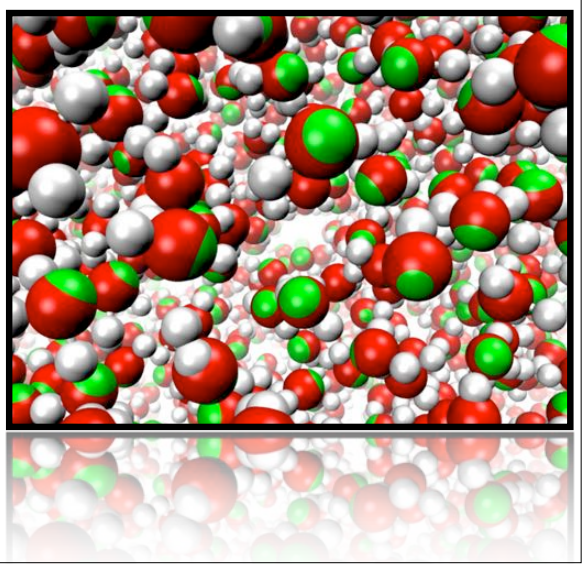
$$\underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}$$

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:

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

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

Langevin Dynamics

for pressure control

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

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

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

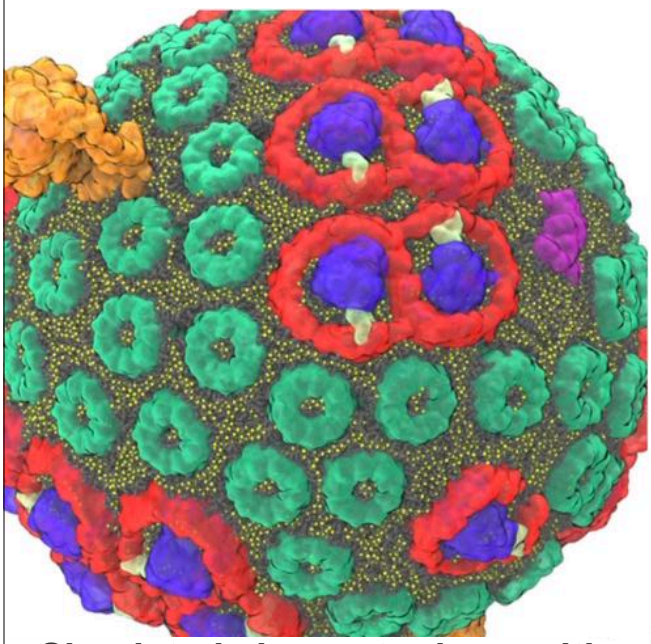
$$\langle R_{\rm bs}(t)\, R_{\rm bs}(t')\rangle \;=\; \frac{2\,k_{\rm B}\,T_{\rm target}\,\delta(t \,-\, t')}{W_{\rm bs}\,\tau_{\rm bs}} \qquad W_{\rm bs} \;=\; d\,N_{\rm atoms}\,k_{\rm B}T_{\rm target}\,\tau^2_{period}$$

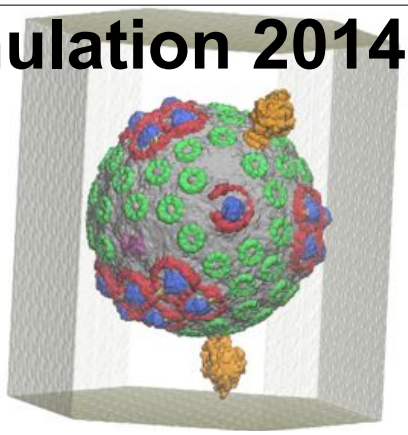
$$\dot{\mathbf{r}}_i = \mathbf{v}_i + s\mathbf{r}_i \qquad\qquad \dot{\mathbf{v}}_i = \mathbf{F}_i \,/\, m_i - s\mathbf{v}_i$$

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

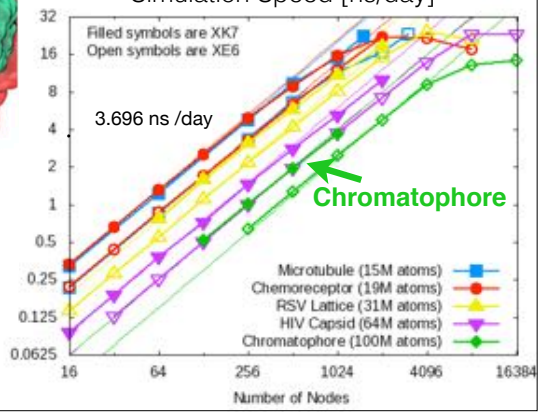
d - dimension

100-million Atom Simulation 2014

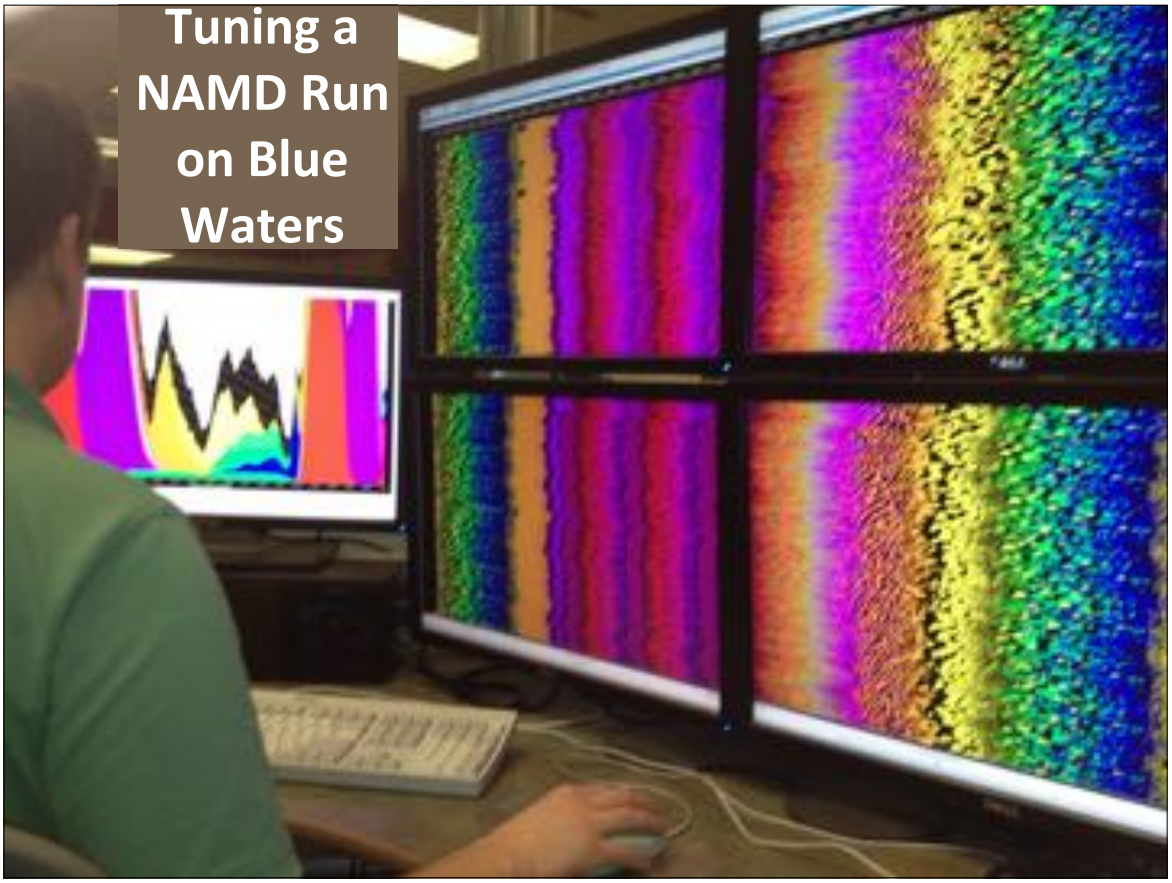




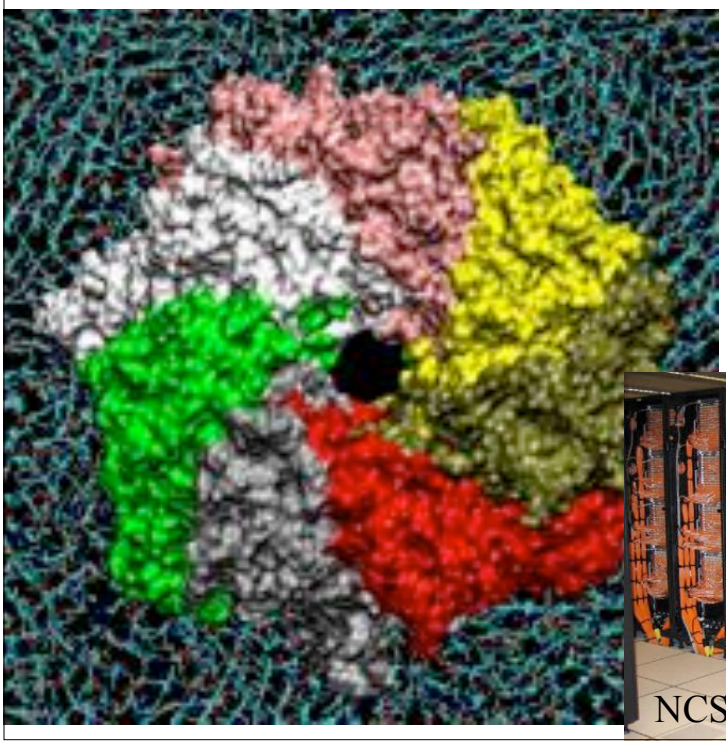
Simulation Speed [ns/day]



Simulated chromatophore with 101 protein complexes and 16,000 lipids



Large is no problem. But …



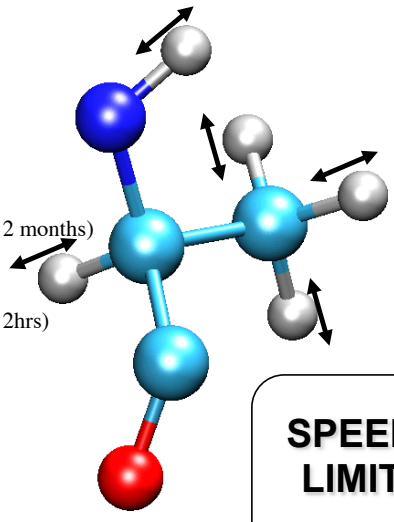
Molecular dynamics simulation of alpha-hemolysin with about 300,000 atoms; 10 million atom simulations are routine today, 200 million atom simulations are possible.

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.)

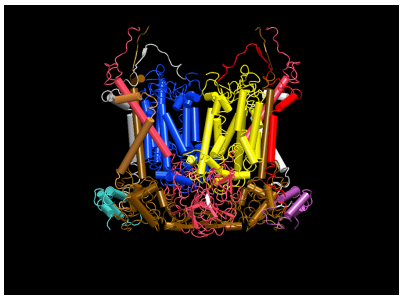
Preparing Your System for MD
Solvation

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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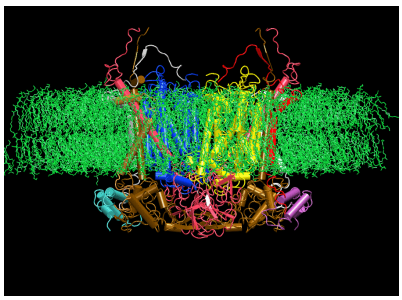

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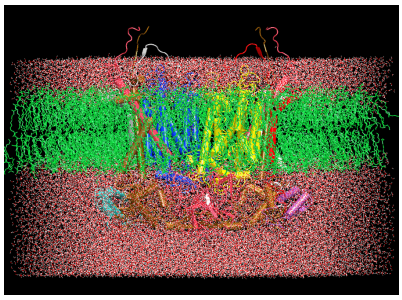
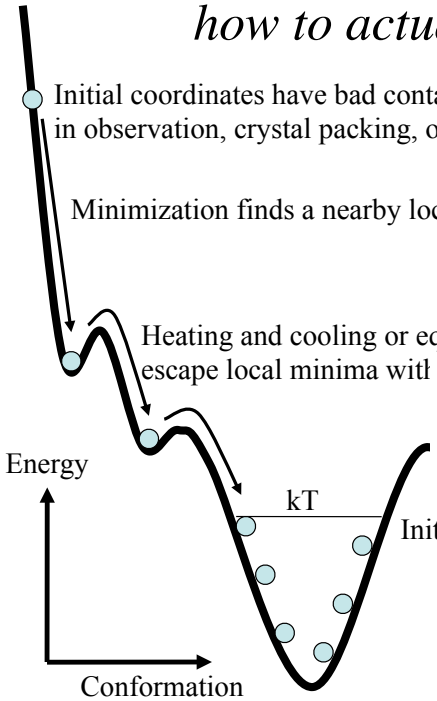


(Usually periodic! Avoids surface effects)

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)

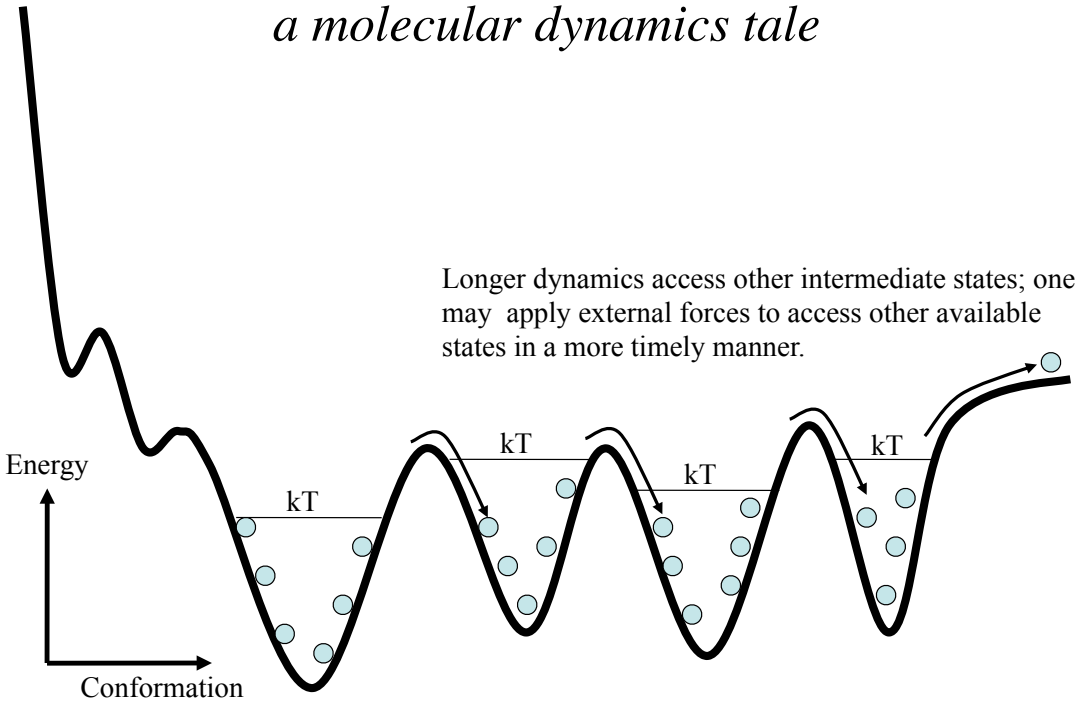
Minimization finds a nearby local minimum.

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

Initial dynamics samples thermally accessible states.

From the Mountains to the Valleys

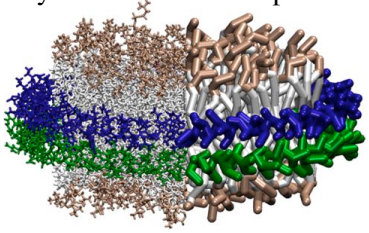
a molecular dynamics tale



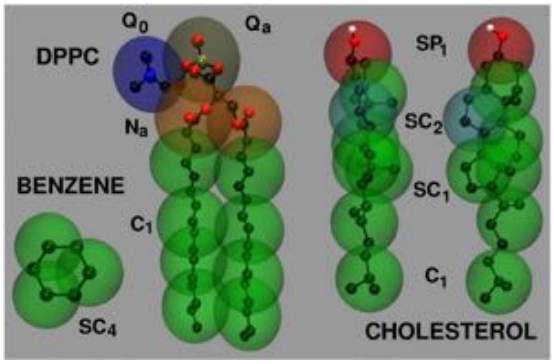
Cutting Corners

cutoffs, PME, rigid bonds, and multiple timesteps

- Nonbonded interactions require order N^2 computer time!
  - Truncating at R_{cutoff} reduces this to order $N\ R_{cutoff}^3$
  - Particle mesh Ewald (PME) method adds long range electrostatics at order N log N, only minor cost compared to cutoff calculation.
- Can we extend the timestep, and do this work fewer times?
  - Bonds to hydrogen atoms, which require a 1fs timestep, can be held at their equilibrium lengths, allowing 2fs steps.
  - Long range electrostatics forces vary slowly, and may be evaluated less often, such as on every second or third step.
- Coarse Graining

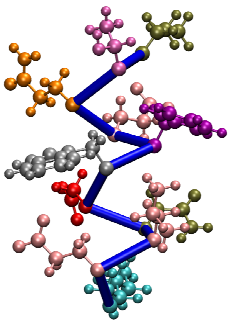


Residue-Based Coarse-Grained Model

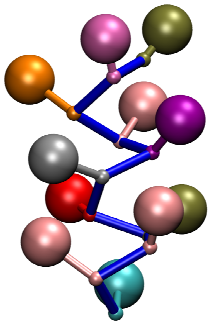


- Lipid model: MARTINI
- Level of coarse-graining: ~4 heavy atoms per CG bead
- Interactions parameterized based on experimental data and thermodynamic properties of small molecules

- Protein model uses two CG beads per residue
- One CG bead per side chain another for backbone



All-atom peptide

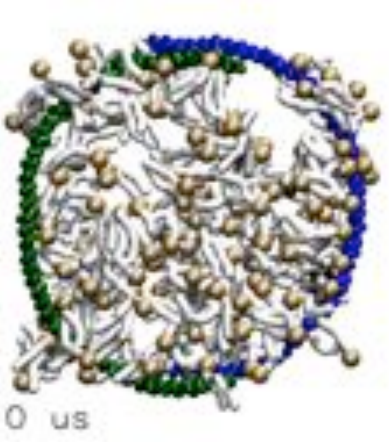


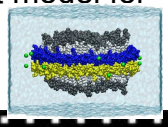
CG peptide

Peter L. Freddolino, Anton Arkhipov, Amy Y. Shih, Ying Yin, Zhongzhou Chen, and Klaus Schulten. **Application of residue-based and shape-based coarse graining to biomolecular simulations.** In Gregory A. Voth, editor, *Coarse-Graining of Condensed Phase and Biomolecular Systems*, chapter 20, pp. 299-315. Chapman and Hall/CRC Press, Taylor and Francis Group, 2008.

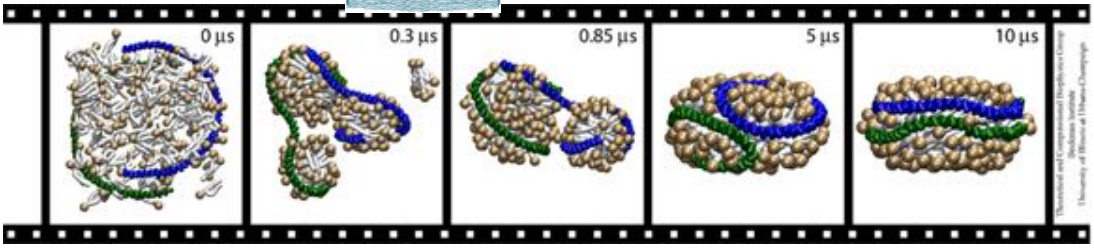
Nanodisc Assembly CG MD Simulation

- 10 μs simulation
- Assembly proceeds in two steps:
  - Aggregation of proteins and lipids driven by the hydrophobic effect
  - Optimization of the protein structure driven by increasingly specific protein-protein interactions
- Formation of the generally accepted double-belt model for discoidal HDL





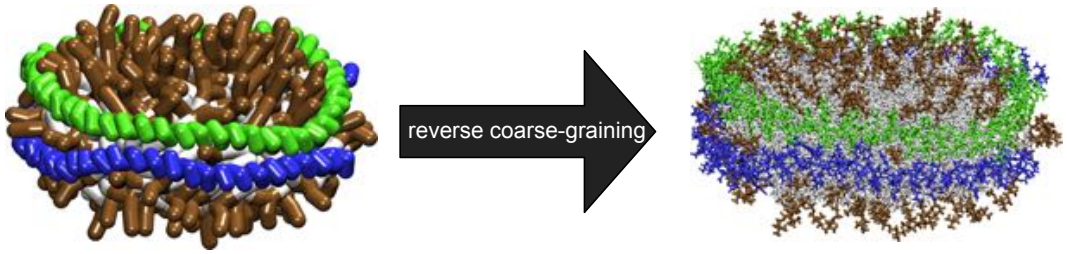
Fully hydrated



A. Shih, A. Arkhipov, P. Freddolino, and K. Schulten. *J. Phys. Chem. B*, 110:3674–3684, 2006; A. Shih, P. Freddolino, A. Arkhipov, and K. Schulten. *J. Struct. Biol.*, 157:579–592,2007; A. Shih, A. Arkhipov, P. Freddolino, S. Sligar, and K. Schulten. *Journal of Physical Chemistry B*, 111: 11095 - 11104, 2007; A. Shih, P. Freddolino, S. Sligar, and K. Schulten. *Nano Letters*, 7:1692-1696, 2007.

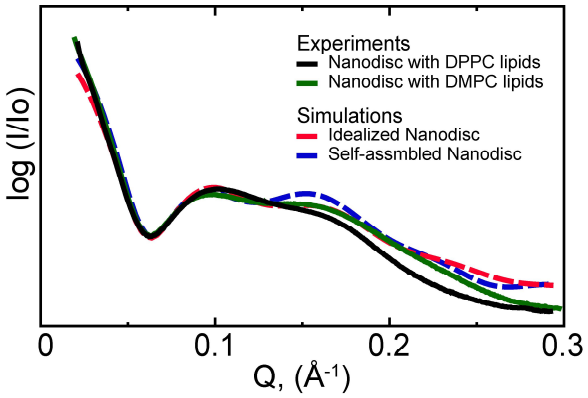
Validation of Simulations

reverse coarse-graining and small-angle X-ray scattering

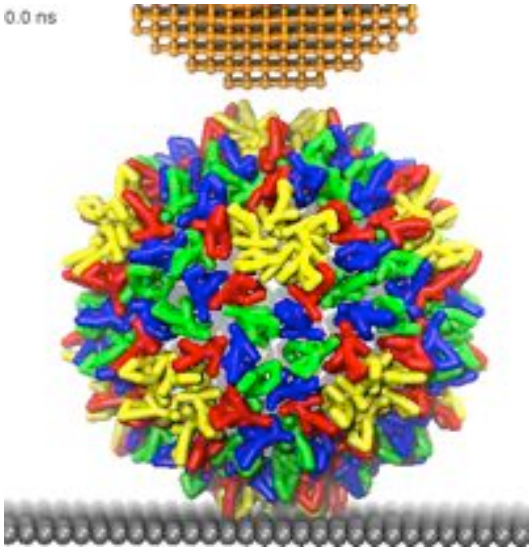


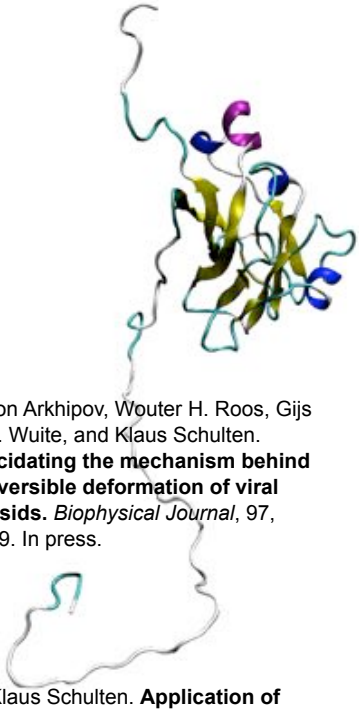
Reverse coarse-graining:
1. Map center of mass of the group of atoms represented by a single CG bead to that beads location
2. MD minimization, simulated annealing with restraints, and equilibration to get all-atom structure

Small-angle X-ray scattering:
Calculated from reverse coarse-grained all-atom model and compared with experimental measurements



Shape-Based Coarse-Grained (CG) model





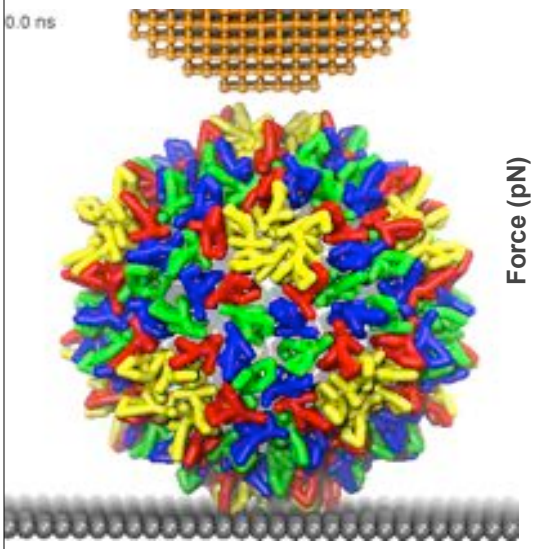
Anton Arkhipov, Wouter H. Roos, Gijs J. L. Wuite, and Klaus Schulten. **Elucidating the mechanism behind irreversible deformation of viral capsids.** *Biophysical Journal*, 97, 2009. In press.

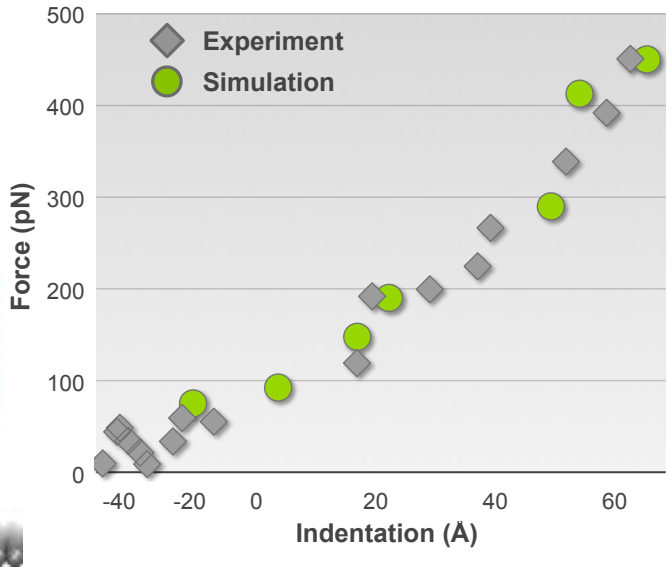
- **Fully automatic**
- **Number of CG beads is chosen by a user (we used ~200 atoms per CG bead)**

Peter L. Freddolino, Anton Arkhipov, Amy Y. Shih, Ying Yin, Zhongzhou Chen, and Klaus Schulten. **Application of residue-based and shape-based coarse graining to biomolecular simulations.** In Gregory A. Voth, editor, *Coarse-Graining of Condensed Phase and Biomolecular Systems*, chapter 20, pp. 299-315. Chapman and Hall/CRC Press, Taylor and Francis Group, 2008.

Virus Capsid Mechanics
Atomic Force Microscope

— Hepatitis B Virus —

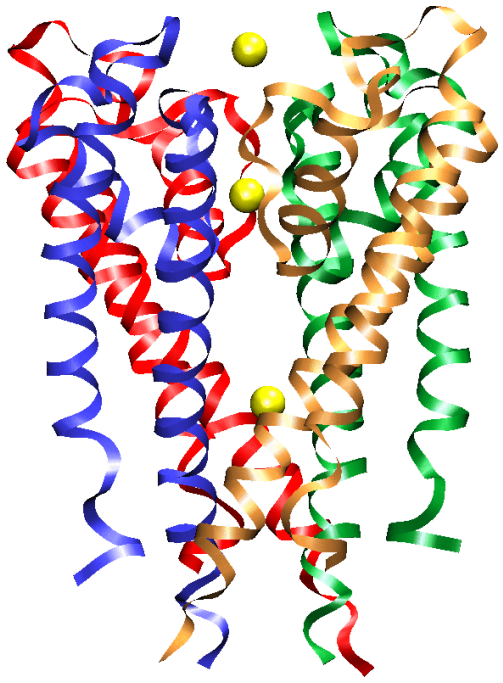




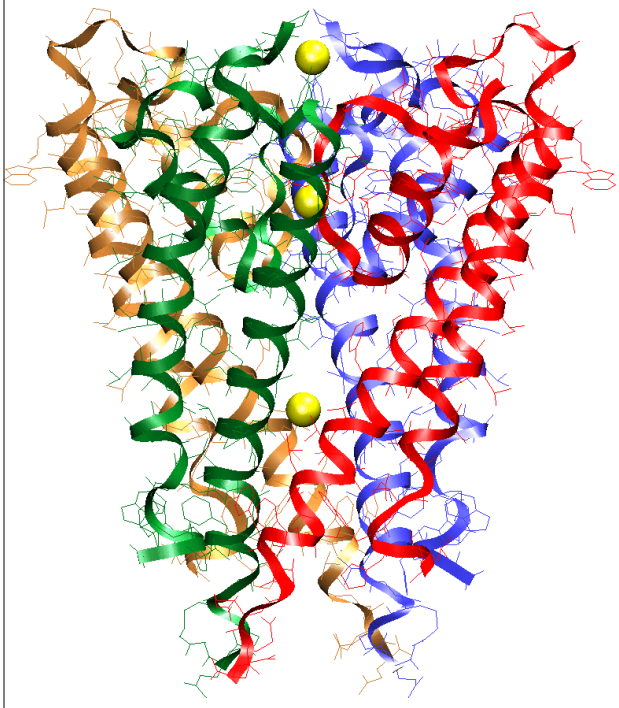
Example: MD Simulations of the K^+ Channel Protein

Ion channels are membrane - spanning proteins that form a pathway for the flux of inorganic ions across cell membranes.

Potassium channels are a particularly interesting class of ion channels, managing to distinguish with impressive fidelity between K^+ and Na^+ ions while maintaining a very high throughput of K^+ ions when gated.

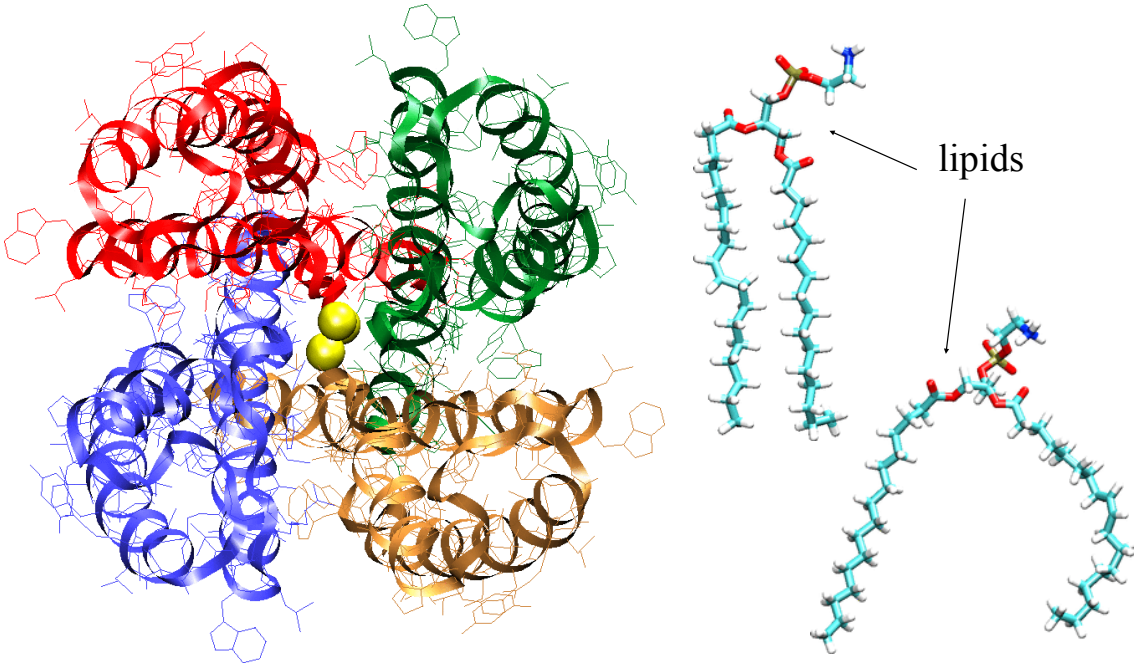


Setting up the system (1)



- retrieve the PDB (coordinates) file from the Protein Data Bank
- add hydrogen atoms using PSFGEN
- use psf and parameter files to set up the structure; needs to be better than available in Charmm to describe well the ions, e.g., K/Na ion selectivity or Ca^{++} ion
- minimize the protein structure using NAMD2

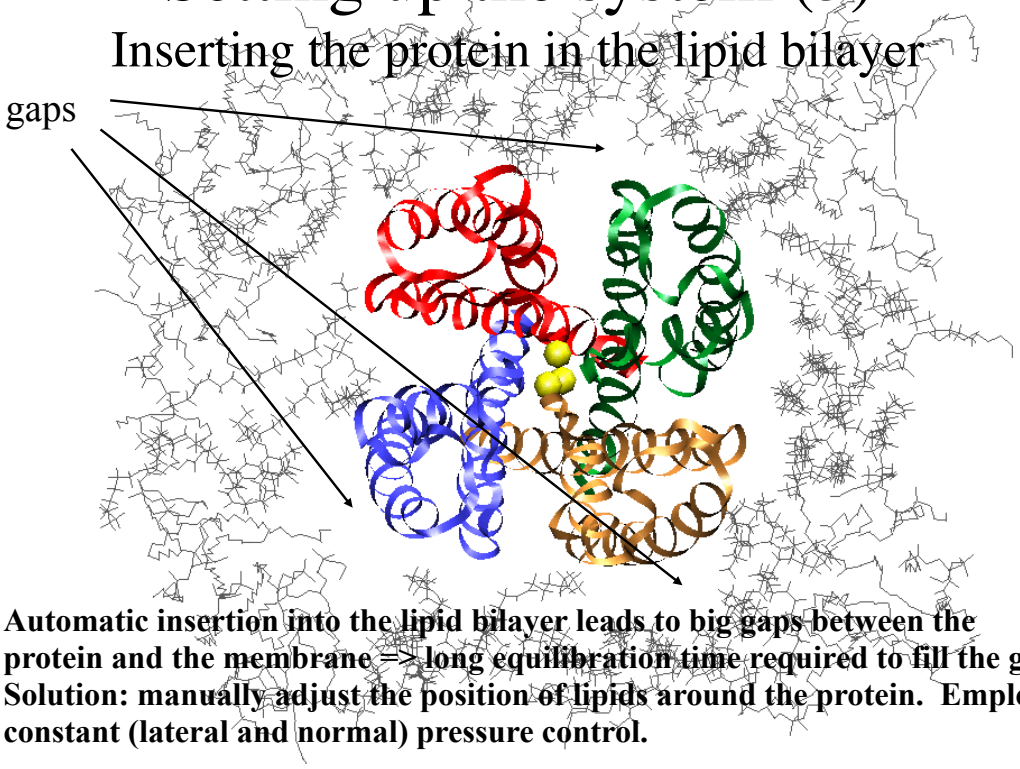
Setting up the system (2)



Simulate the protein in its natural environment: solvated lipid bilayer

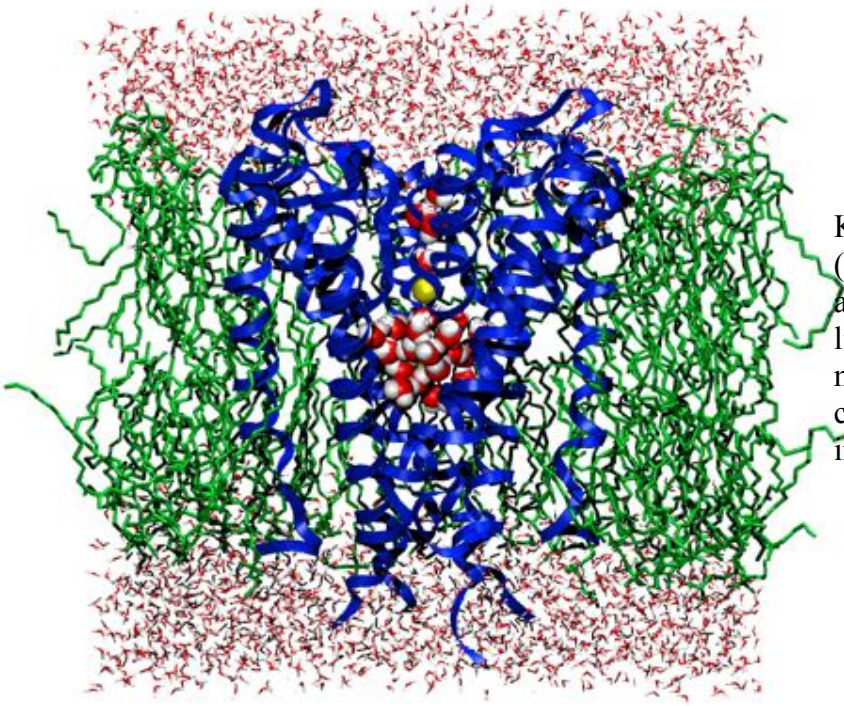
Setting up the system (3)

Inserting the protein in the lipid bilayer



Automatic insertion into the lipid bilayer leads to big gaps between the protein and the membrane => long equilibration time required to fill the gaps. Solution: manually adjust the position of lipids around the protein. Employ constant (lateral and normal) pressure control.

The system



solvent

Kcsa channel protein (in blue) embedded in a (3:1) POPE/POPG lipid bilayer. Water molecules inside the channel are shown in vdW representation.

solvent

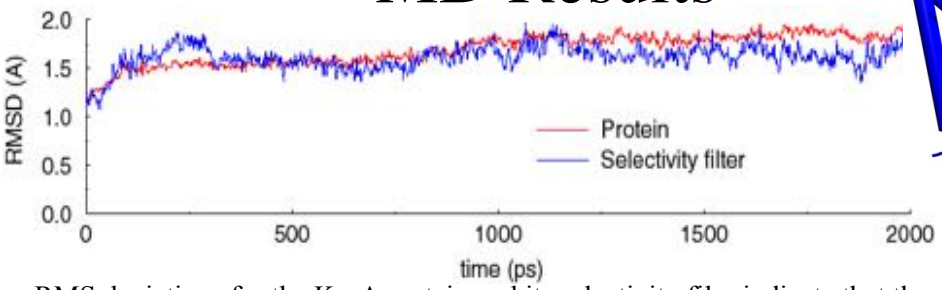
Simulating the system: Free MD

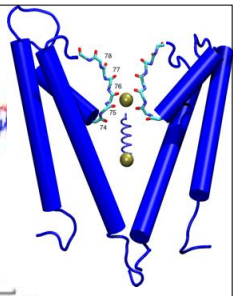
Summary of simulations:
• protein/membrane system contains 38,112 atoms, including 5117 water molecules, 100 POPE and 34 POPG lipids, plus K^+ counterions
• CHARMM26 forcefield
• periodic boundary conditions, PME electrostatics
• 1 ns equilibration at 310K, NpT
• 2 ns dynamics, NpT

Program: NAMD2

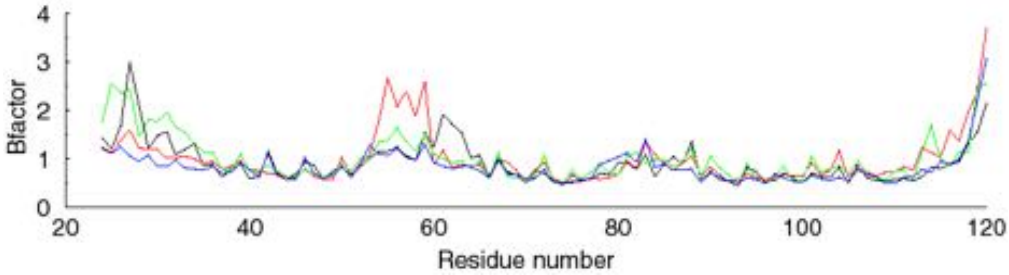
Platform: Cray T3E (Pittsburgh Supercomputer Center) or local computer cluster; choose ~1000 atoms per processor.

MD Results



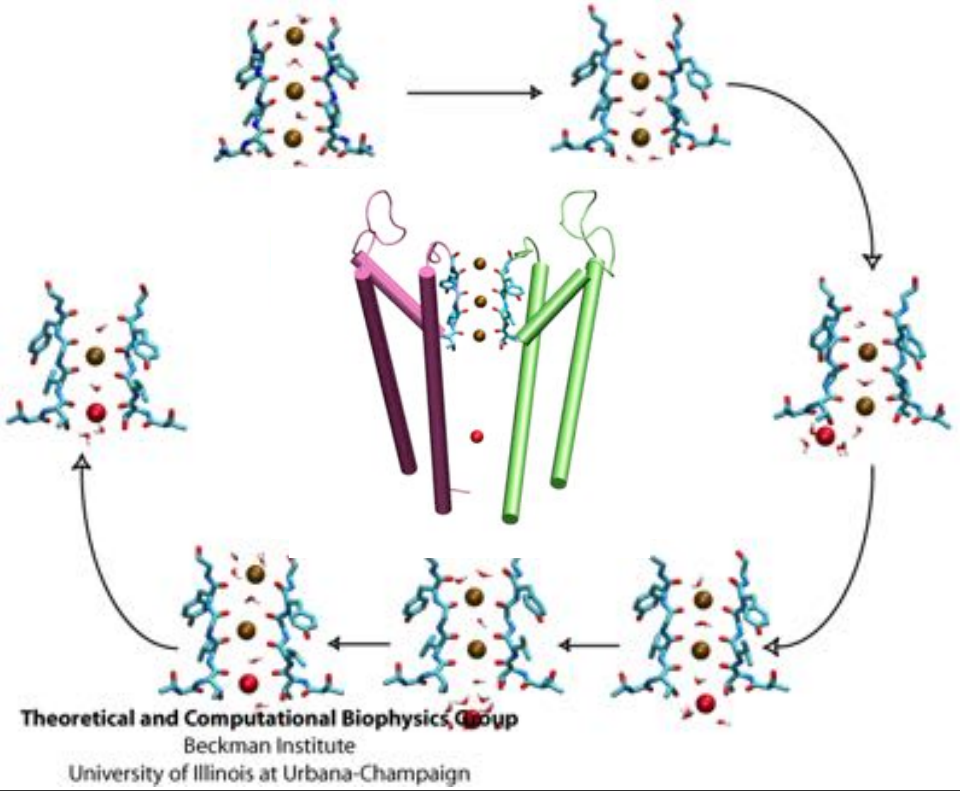


RMS deviations for the KcsA protein and its selectivity filer indicate that the protein is stable during the simulation with the selectivity filter the most stable part of the system.

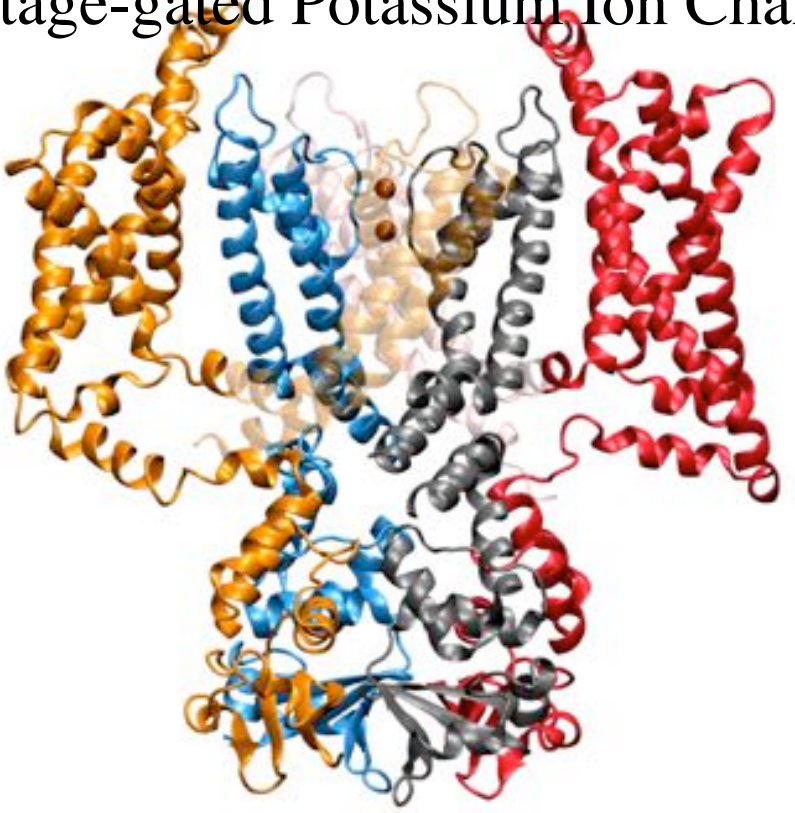


Temperature factors for individual residues in the four monomers of the KcsA channel protein indicate that the most flexible parts of the protein are the N and C terminal ends, residues 52-60 and residues 84-90. Residues 74-80 in the selectivity filter have low temperature factors and are very stable during the simulation.

Simulation of Ion Conduction (here for Kv1.2)



Voltage-gated Potassium Ion Channel



Voltage-gated Potassium Ion Channel