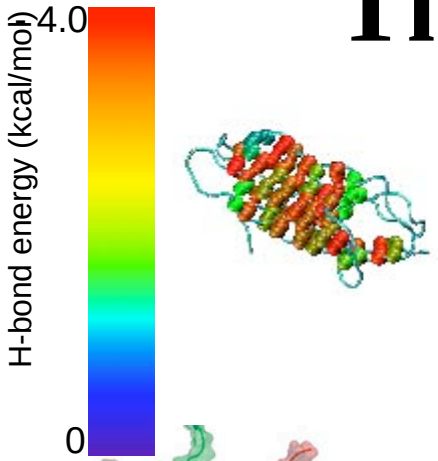
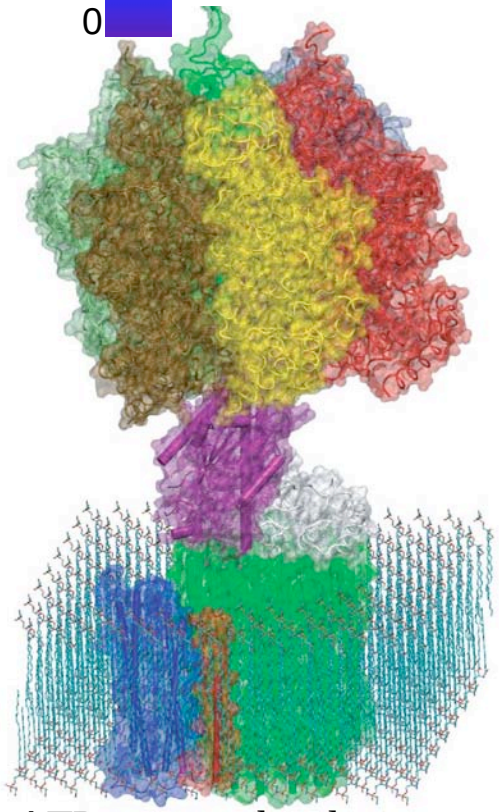
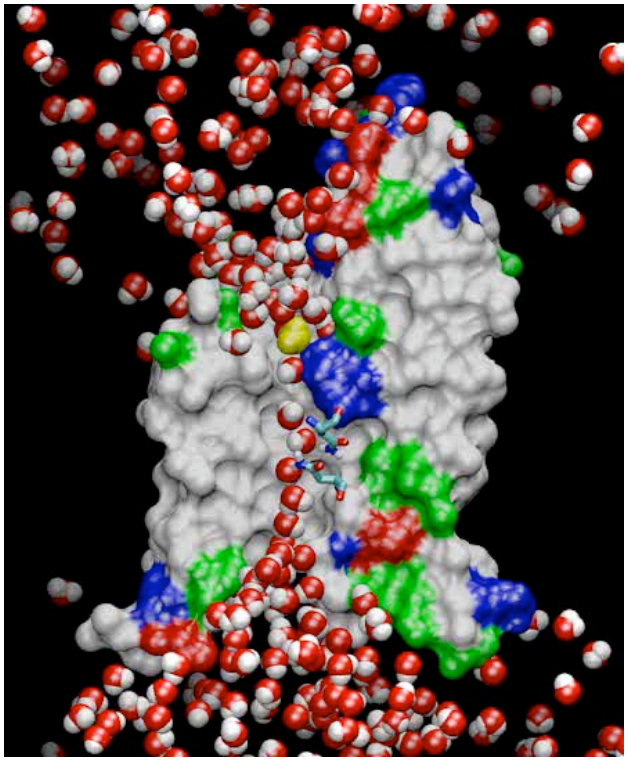
# The Molecular Dynamics Method



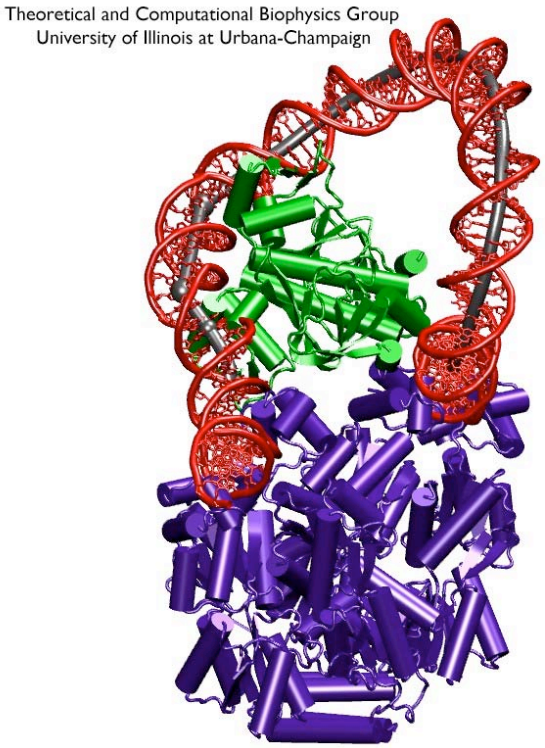

Fibronectin III_1, a mechanical protein that glues cells together in wound healing and in preventing tumor metastasis



ATPase, a molecular motor that synthesizes the body's weight of ATP a day

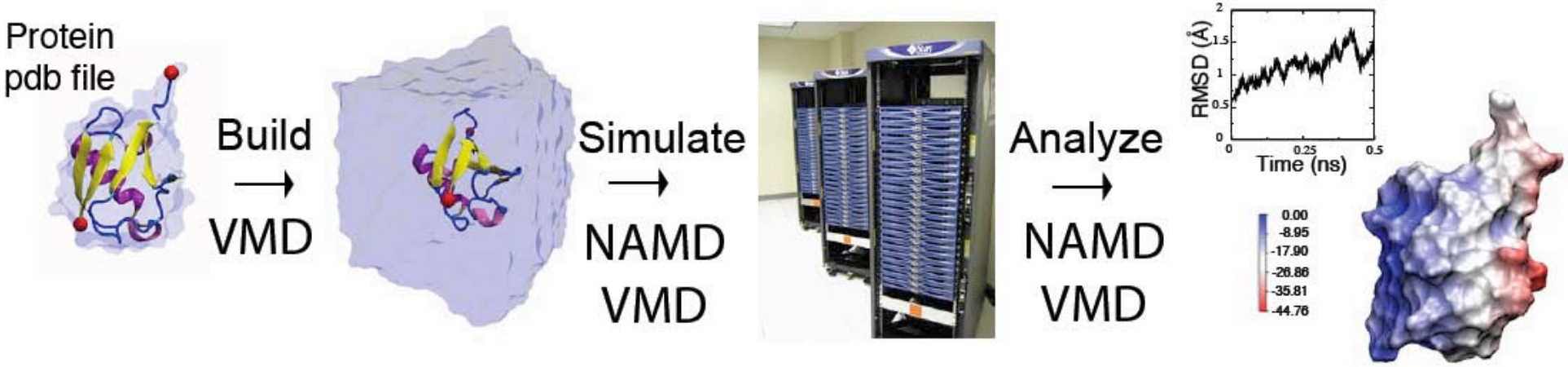


AQP filtering a bath tub of the body's water a day

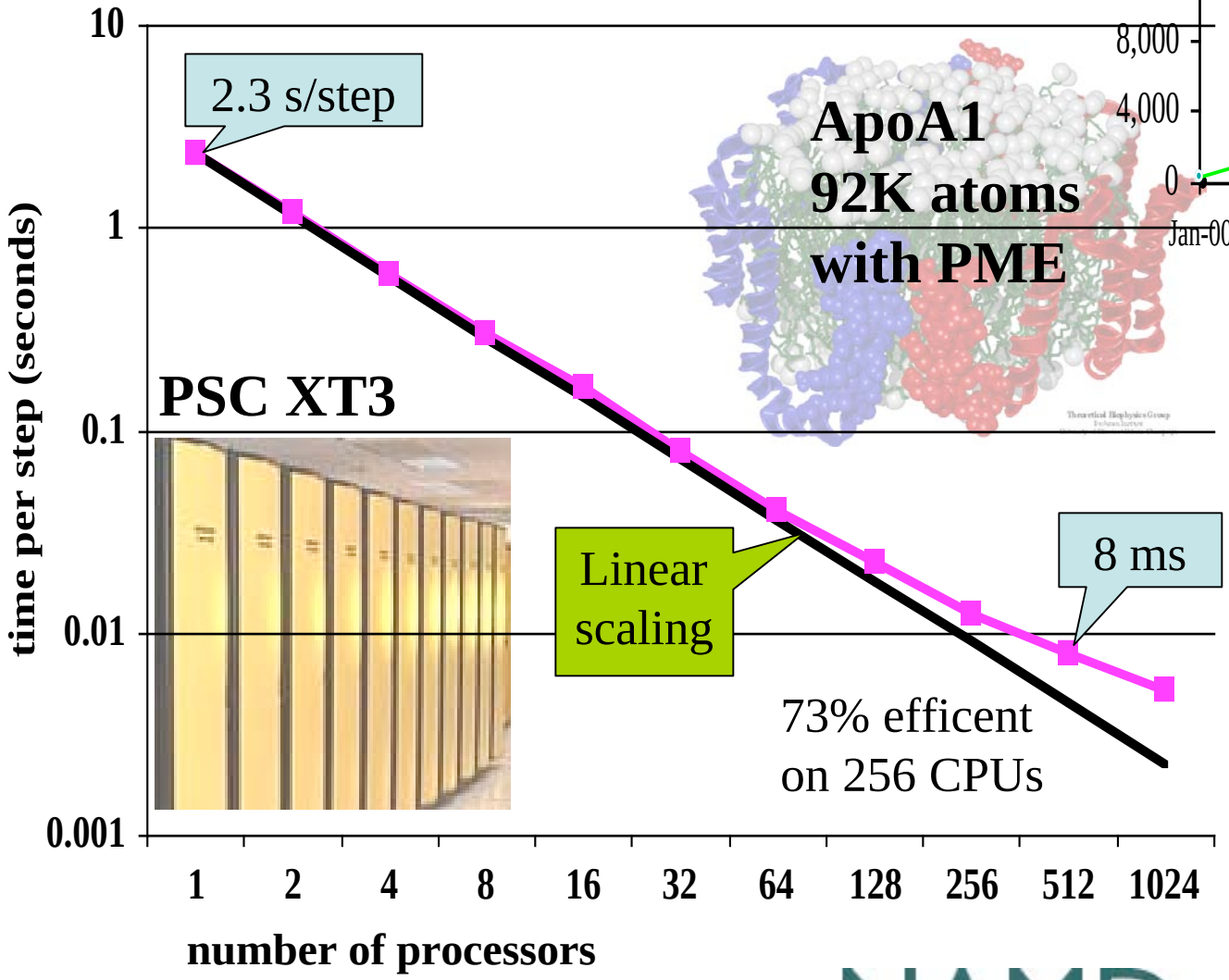



A ternary complex of DNA, lac repressor, and CAP controlling gene expression

# The Molecular Dynamics Simulation Process



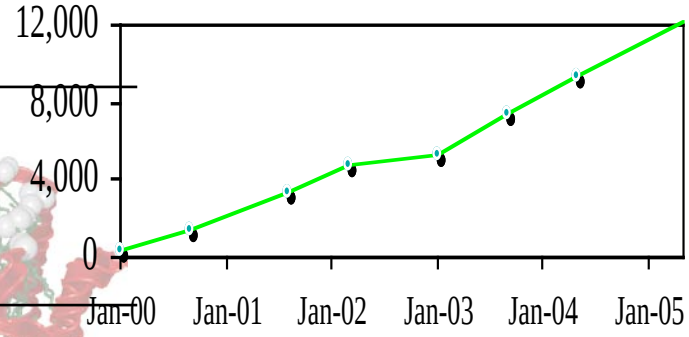
# NAMD Scalable on Parallel Machines







**NAMD Registrants**
12,095 Registrants (16% NIH)
2,122 Repeat Users (18% NIH)




Simulation of large biomolecular systems on parallel computers.

File compatible with original community codes CHARMM & AMBER.

Ten-year collaboration with UIUC Parallel Programming Lab.

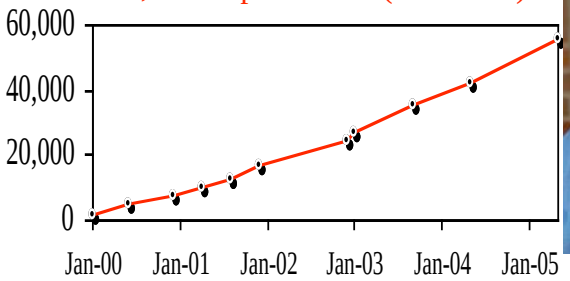
2002 Gordon Bell Award for parallel scalability.

Runs at NSF centers, on clusters, and on desktop.

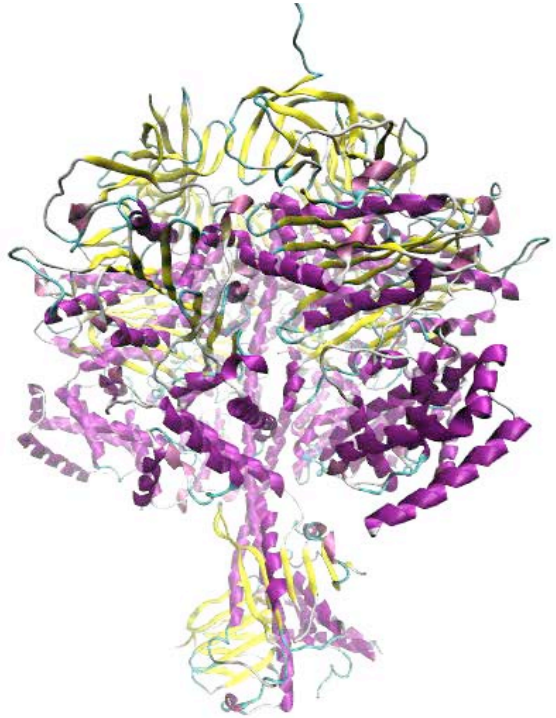
NAMD
Scalable Molecular Dynamics

# VMD Molecular Graphics - Structure

"… VMD is far from a simple 'visualization tool for biologists, it is a true thinking tool. Without it a whole class of biological hypotheses would simply not exist." - *Carl Woese*

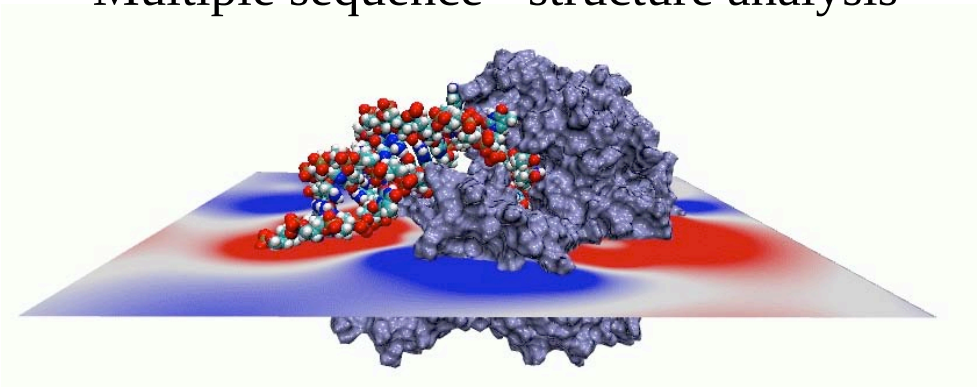






- Platforms: Unix, Windows, MacOS X
- Display of large biomolecules and simulation trajectories
- Multiple sequence - structure analysis

VMD view of F1-ATPase



Electrostatic potential for an ATPase obtained with VMD's PME plugin

# Classical Dynamics

*F=ma 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.

# Langevin Dynamics

*come on, feel the noise*

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

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

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

# 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.

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

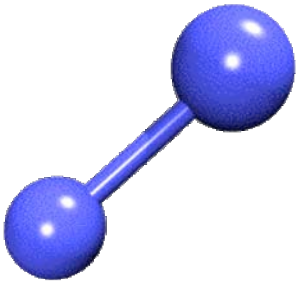
+

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

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

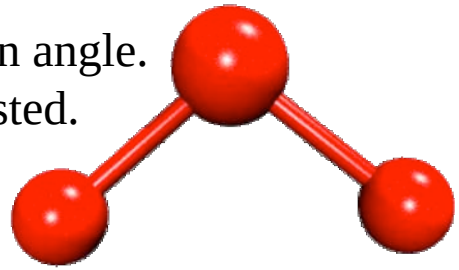
$$\boxed{\mathbf{r}(t+\delta t) \approx 2\mathbf{r}(t) - \mathbf{r}(t-\delta t) + \mathbf{a}(t)\delta t^2}$$

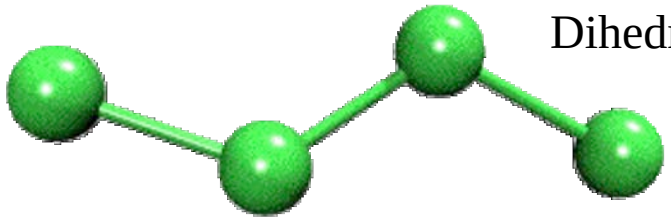
# Molecular Structure (bonds, angles, etc.)



Bonds: Every pair of covalently bonded atoms is listed.

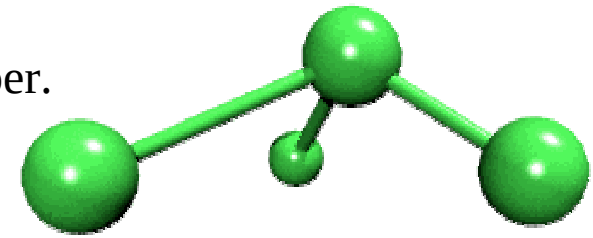
Angles: Two bonds that share a common atom form an angle.
Every such set of three atoms in the molecule is listed.





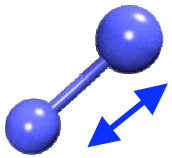
Dihedrals: Two angles that share a common bond form a dihedral.
Every such set of four atoms in the molecule is listed.

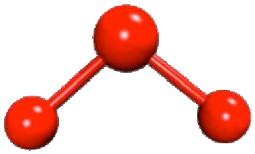
Impropers: Any *planar* group of four atoms forms an improper.
Every such set of four atoms in the molecule is listed.



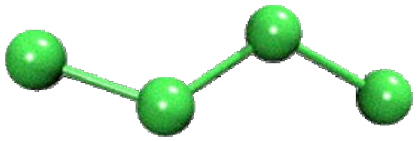
# Potential Energy Function of Biopolymer

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





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

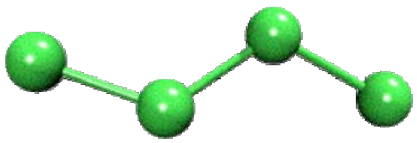


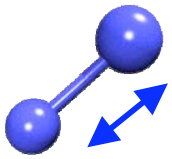
$$\underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} +$$

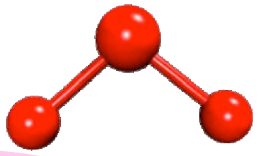
$$\underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}$$

# Potential Energy Function of Biopolymer

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







**heuristic**

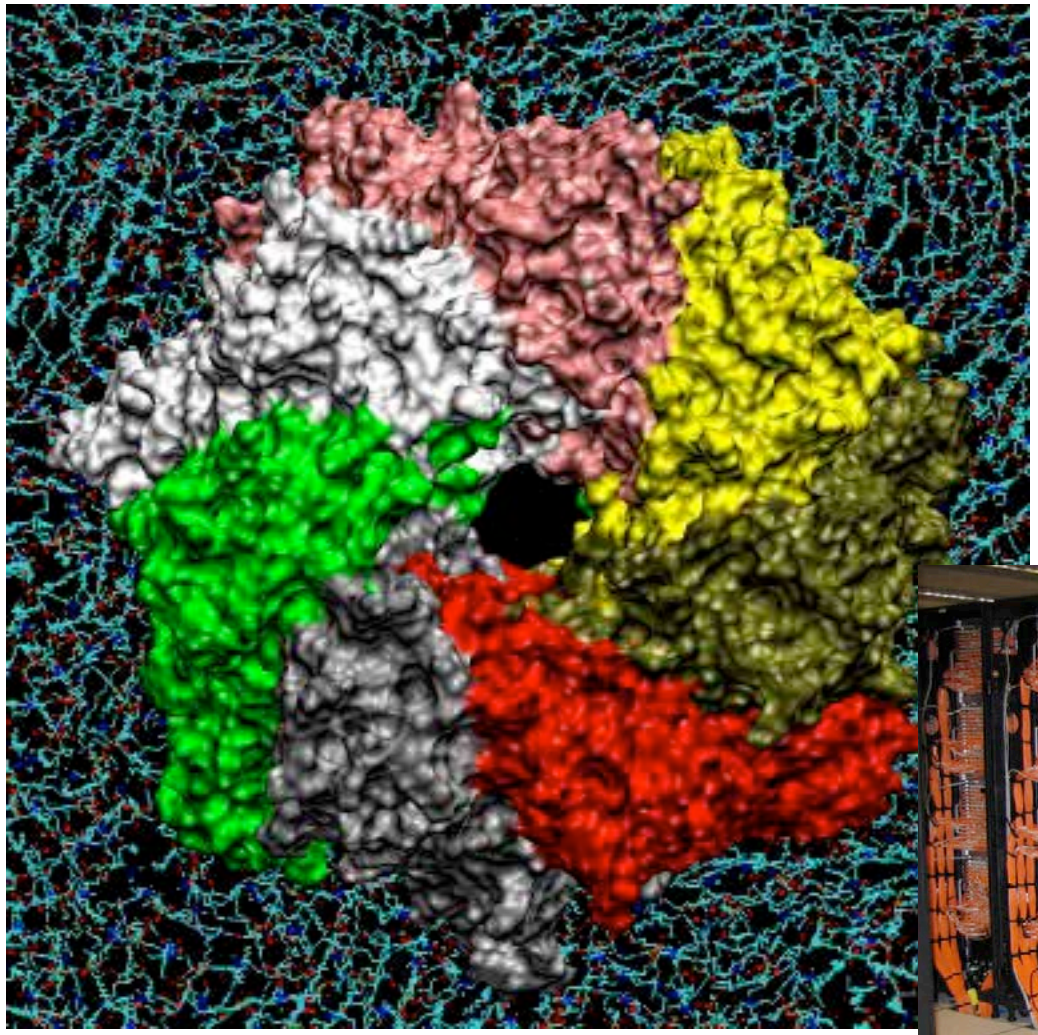
$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} +$$

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

**from physics**

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

# Large is no problem. But …



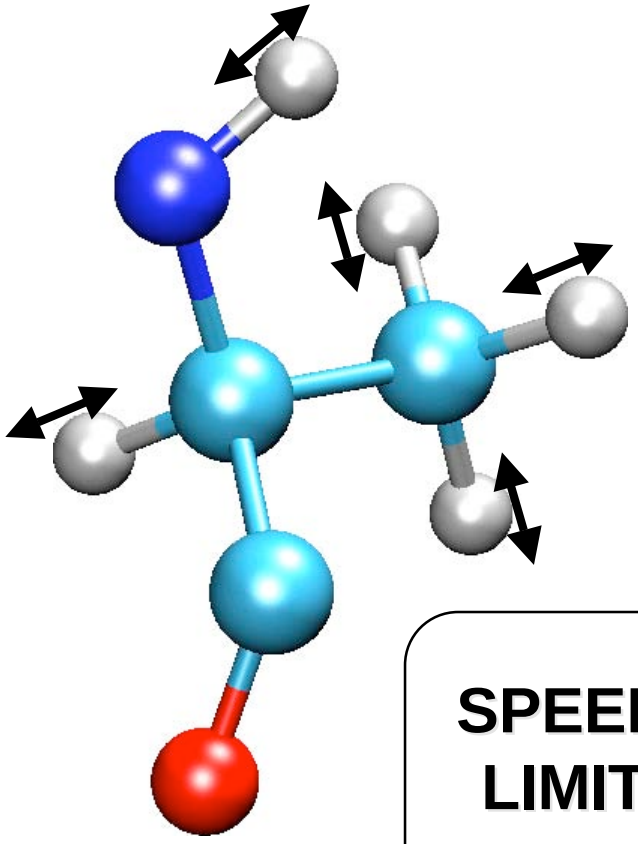
Molecular dynamics simulation of alpha-hemolysin with about 300,000 atoms

NCSA machine room

# But long is!

## *biomolecular timescale and timestep limits*

| | | *steps* |
|---|---|---|
| Rotation of buried sidechains<br>Local denaturations<br>Allosteric transitions | s | $10^{15}$ |
| | ms | $10^{12}$ |
| | μs | $10^{9}$ (year) |
| Hinge bending | ns | $10^{6}$ (day) |
| Rotation of surface sidechains | | |
| Elastic vibrations | ps | $10^{3}$ |
| Bond stretching | | |
| Molecular dynamics timestep → | fs | $10^{0}$ |



**SPEED LIMIT**

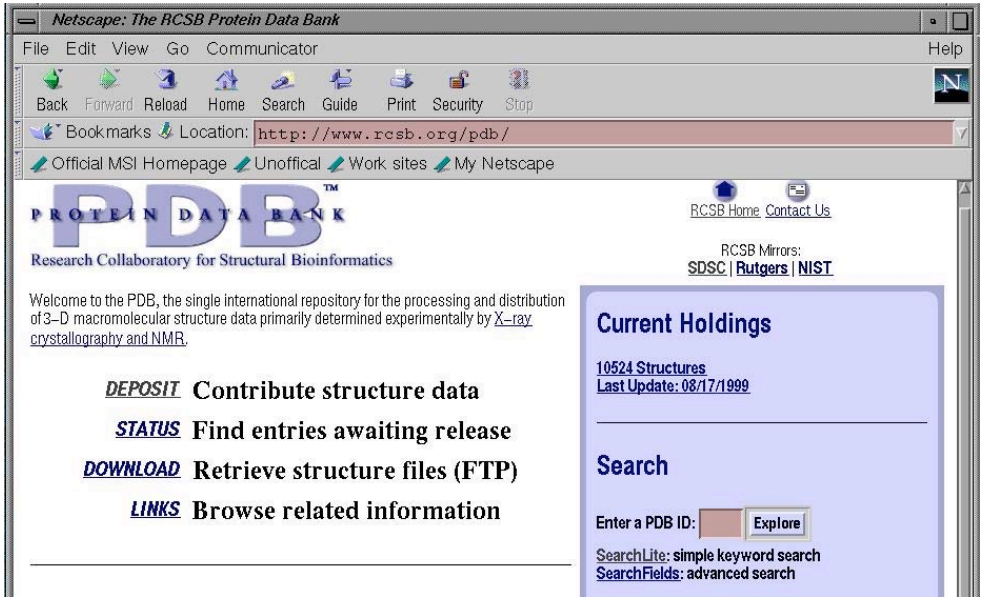
**δt = 1 fs**

# PDB Files

## *a little information*

- Simulations start with a crystal/NMR structure from the Protein Data Bank, in the standard PDB file format.
- PDB files contain standard records for species, tissue, authorship, citations, sequence, secondary structure, etc.
- We only care about the atom records…
  - atom name (N, C, CA)
  - residue name (ALA, HIS)
  - residue id (integer)
  - coordinates (x, y, z)
  - occupancy (0.0 to 1.0)
  - temp. factor (a.k.a. beta)
  - segment id (6PTI)
- No hydrogen atoms!

  (We must add them ourselves.)



# PDB File

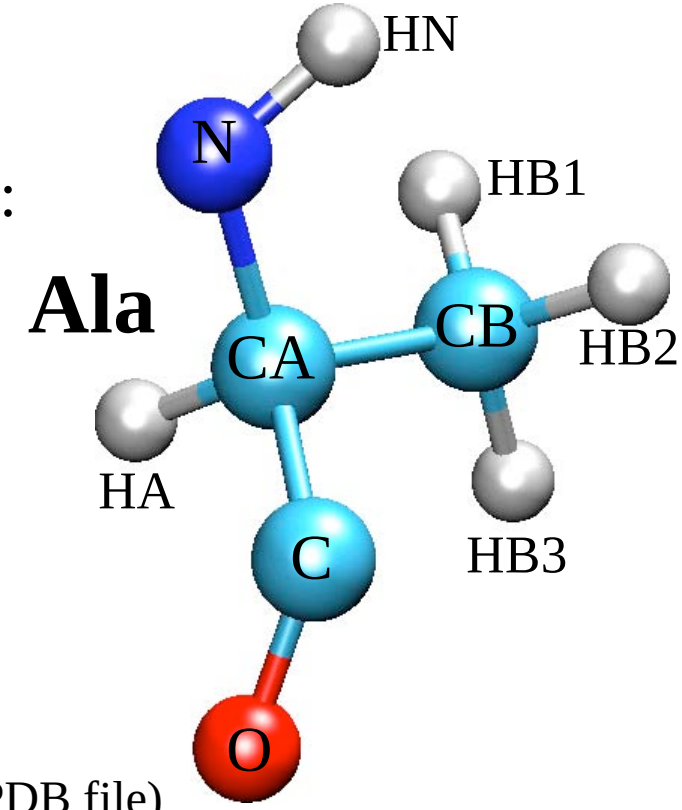
(available from **www.rcsb.org** if structure of biopolymer solved)

```
REMARK FILENAME="bpti19.pdb“
REMARK    PROTEINASE INHIBITOR (TRYPSIN)        13-MAY-87   6PTI
REMARK    BOVINE PANCREATIC TRYPSIN INHIBITOR
REMARK    BOVINE (BOS TAURUS) PANCREAS
REMARK    A.WLODAWER
REMARK DATE:26-Jun-00  21:34:42       created by user:
ATOM       1  HT1 ARG     1      13.150  -7.331  10.849  1.00  0.00      BPTI
ATOM       2  HT2 ARG     1      11.747  -7.115  11.780  1.00  0.00      BPTI

etc etc etc

ATOM    554  CA   GLY    56      15.319   0.828  11.790  1.00 17.33      BPTI
ATOM    555  C    GLY    56      16.029  -0.385  12.375  1.00 18.91      BPTI
ATOM    556  OT1 GLY    56      15.443  -1.332  12.929  1.00 21.00      BPTI
ATOM    557  OT2 GLY    56      17.308  -0.138  12.617  1.00 21.95      BPTI
END
```

# PSF Files

## *atomic properties (mass, charge, type)*

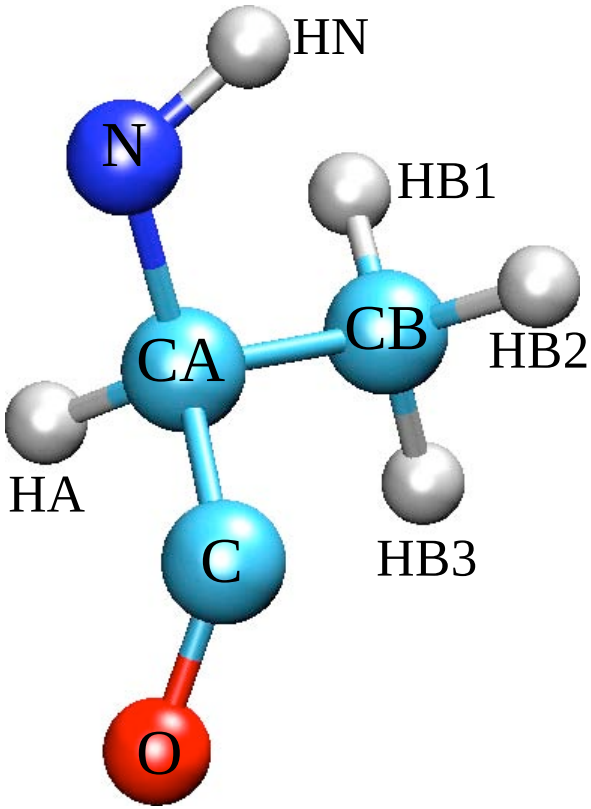
- Every atom in the simulation is listed.
- Provides all static atom-specific values:
  - atom name (N, C, CA)
  - atom type (NH1, CT1)
  - residue name (ALA, HIS)
  - residue id (integer)
  - segment id (6PTI)
  - atomic mass (in atomic mass units)
  - partial charge (in electronic charge units)
- What is not in the PSF file?
  - coordinates (dynamic data, initially read from PDB file)
  - velocities (dynamic data, initially from Boltzmann distribution)
  - force field parameters (non-specific, used for many molecules)



# Example of PSF File

```
 MASS HS     1.0080 ! thiol hydrogen
 MASS C     12.0110 ! carbonyl C, peptide backbone
 MASS CA    12.0110 ! aromatic C
 ..... (missing data here)
!-----------------------------------------------------------
 AUTOGENERATE ANGLES=TRUE  DIHEDRALS=TRUE  END
!-----------------------------------------------------------
 RESIDUE ALA

 GROUP
     ATOM  N    TYPE=NH1  CHARGE=   -.4700  END !
     ATOM  HN    TYPE=H    CHARGE=    .3100  END  !
     ATOM  CA    TYPE=CT1  CHARGE=    .0700  END !
     ATOM  HA    TYPE=HB   CHARGE=    .0900  END !
 GROUP                                          !
     ATOM  CB    TYPE=CT3  CHARGE=   -.2700  END !
     ATOM  HB1   TYPE=HA   CHARGE=    .0900  END !
     ATOM  HB2   TYPE=HA   CHARGE=    .0900  END !
     ATOM  HB3   TYPE=HA   CHARGE=    .0900  END !
 GROUP                  !
     ATOM  C     TYPE=C    CHARGE=    .5100  END
     ATOM  O     TYPE=O    CHARGE=   -.5100  END
 !END GROUP
    BOND  CB    CA
    BOND  N     HN
    BOND  N     CA
    BOND  O     C
    BOND  C     CA
    BOND  CA    HA
    BOND  CB    HB1
    BOND  CB    HB2
    BOND  CB    HB3
    DONOR  HN    N
    ACCEPTOR  O     C
  END {ALA }
```

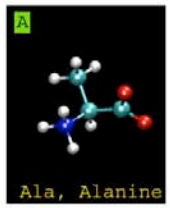
```
          |
        N--HN
          |    HB1
          |   /
    HA-CA--CB-HB2
          |   \
          |    HB3
        O=C
          |
```

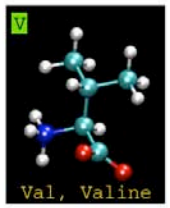


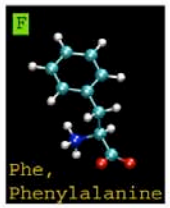
# Protein Primary Structure

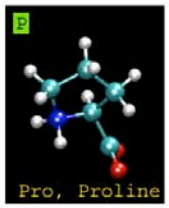
## *The twenty amino acids*

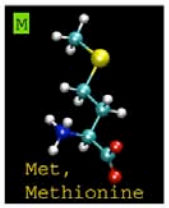
non-polar

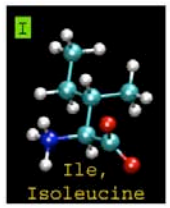


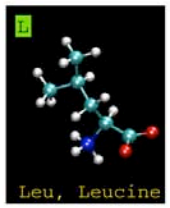



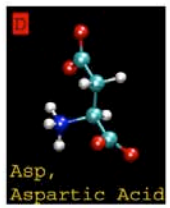



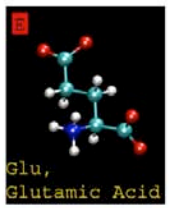



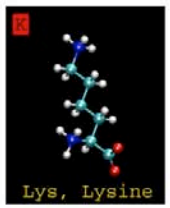



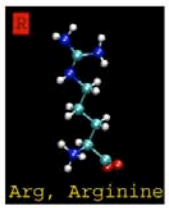




charged

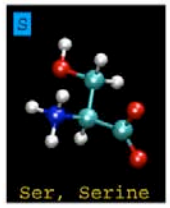


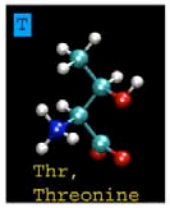



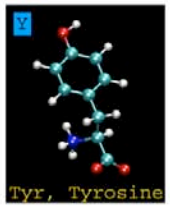



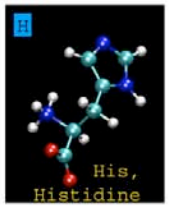



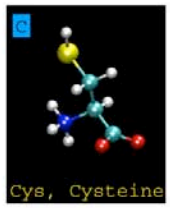

polar

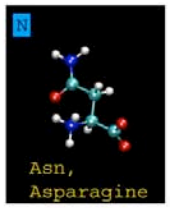


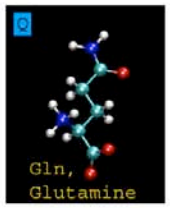



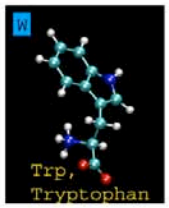



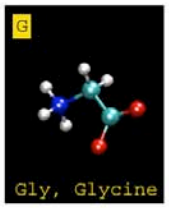




***Introduction to Protein Structure,*** *2nd ed.*
Carl Branden & John Tooze, 1999

***Protein Structure and Function,***
Greg Petsko & Dagmar Ringe, 2003

***Molecular Biology of The Cell***
Alberts, Johnson, Lewis, Raff, Roberts, Walter, 2002

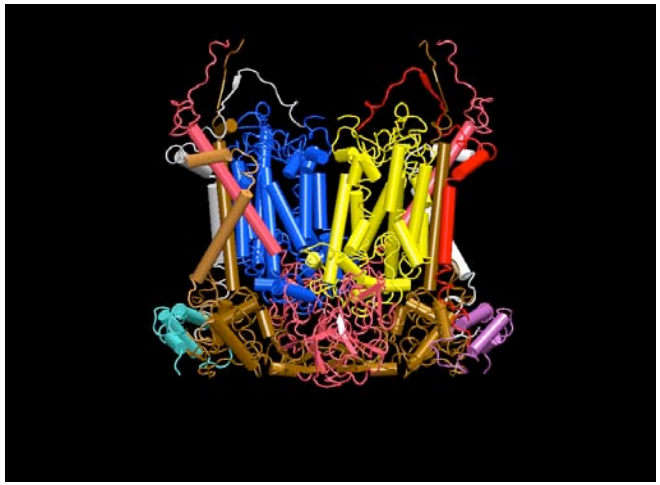
**URL: http://lectures.molgen.mpg.de/ProteinStructure**

# 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).

***mitochondrial bc1 complex***



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

# Preparing Your System for MD

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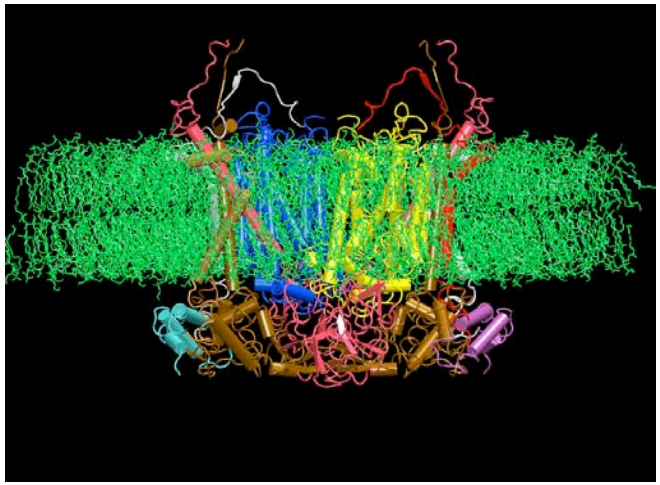

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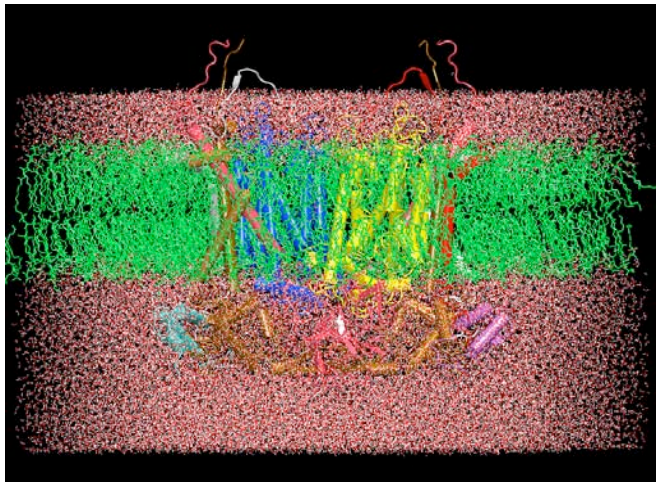

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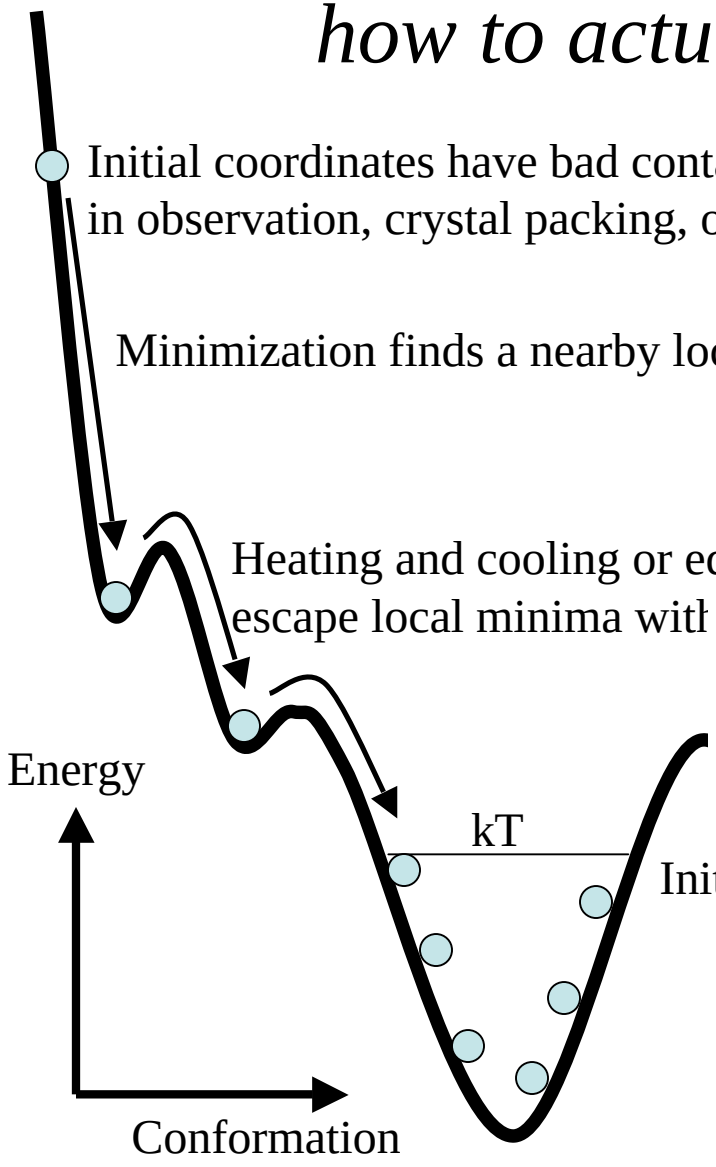
# From the Mountains to the Valleys

## *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)

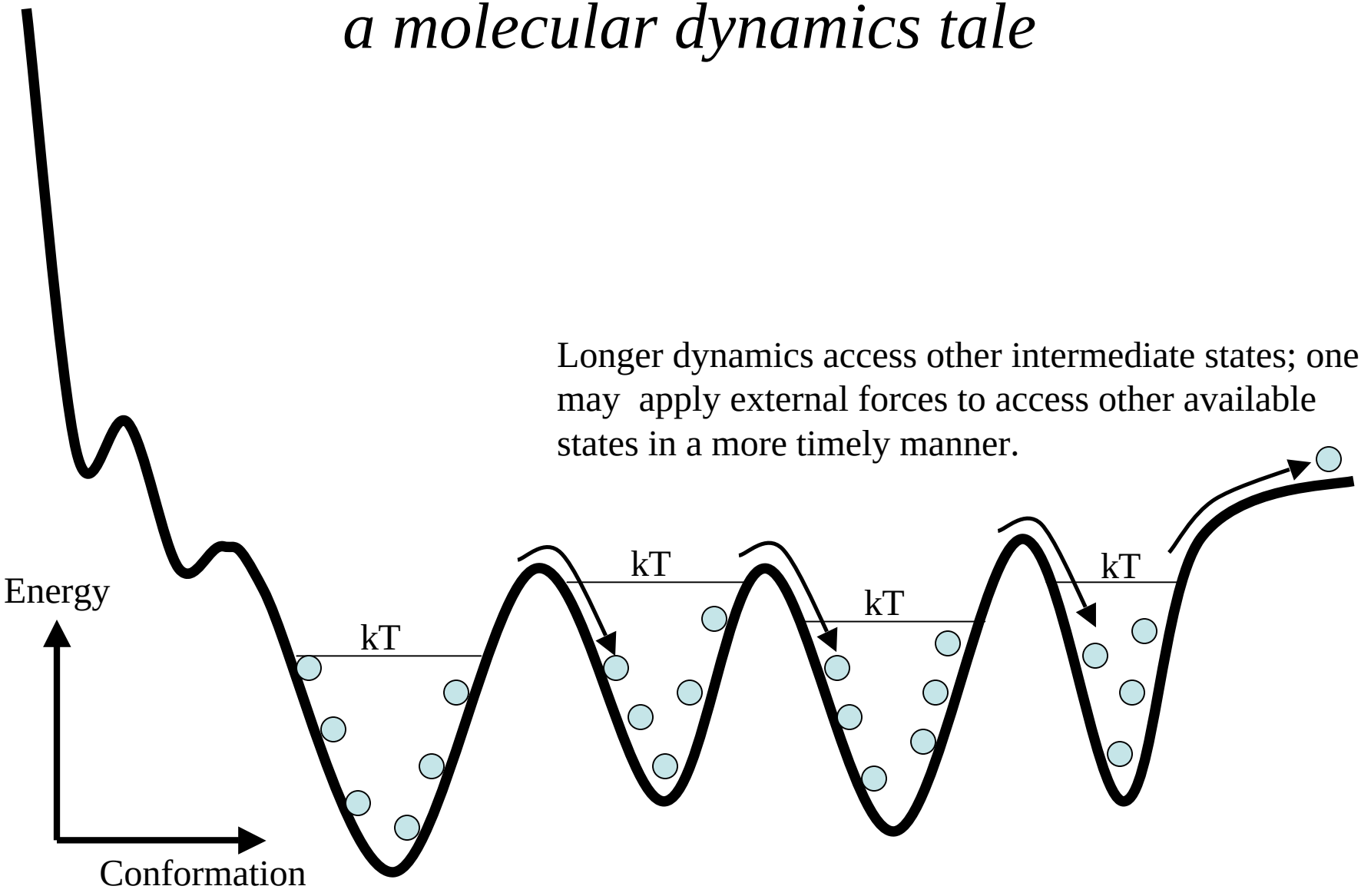
Minimization finds a nearby local minimum.

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*



# Molecular Dynamics Ensembles

Constant energy, constant number of particles (NE)

Constant energy, constant volume (NVE)

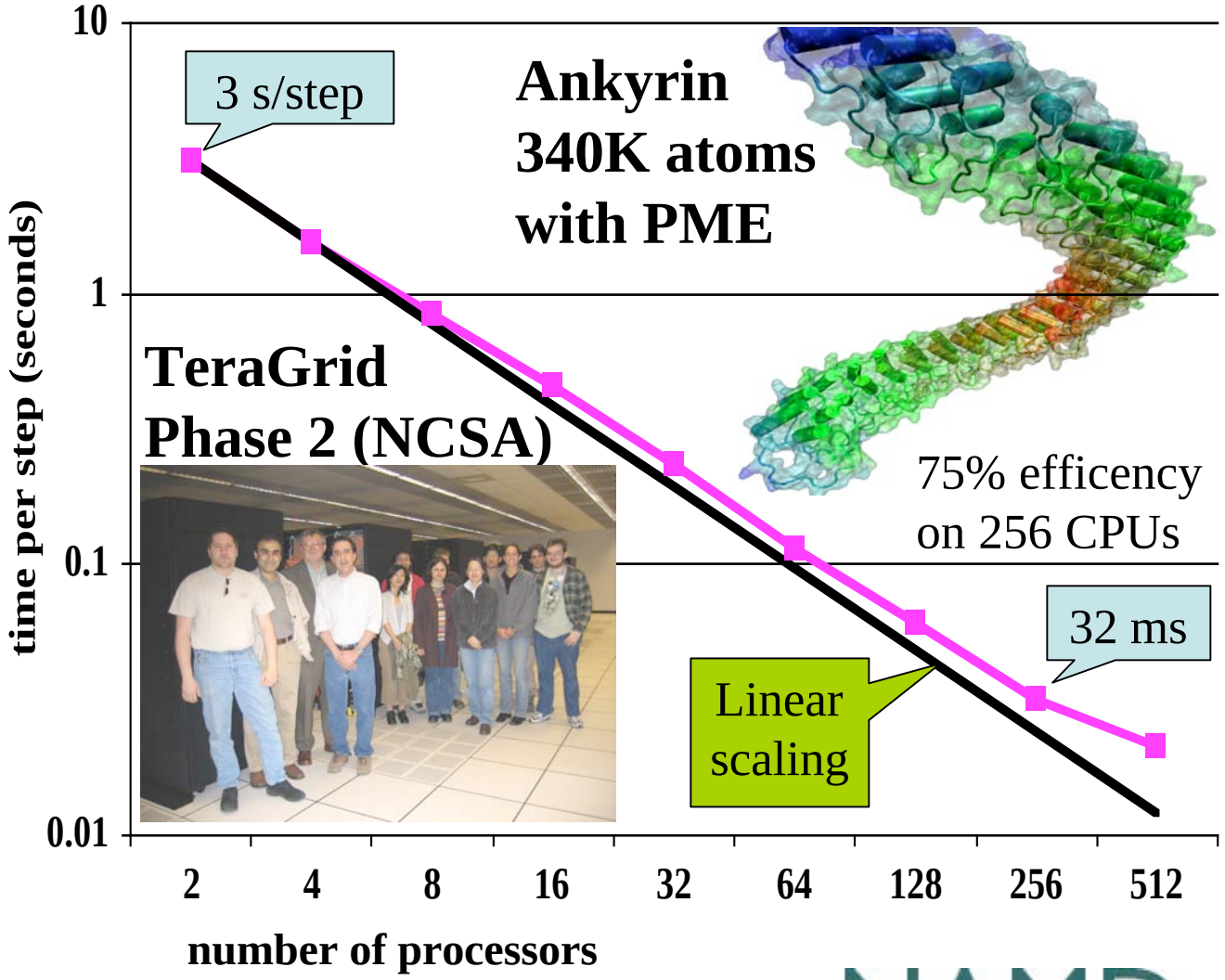
Constant temperature, constant volume (NVT)

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

# NAMD: The Program we will Use

*NAMD programmer J. Phillips Ph.D. UIUC Physics*




Simulation of large biomolecular systems

2002 Gordon Bell Award for parallel scalability.

Runs at NSF centers, on clusters, and on desktop.

Available for **FREE** as precompiled binaries; includes source code.

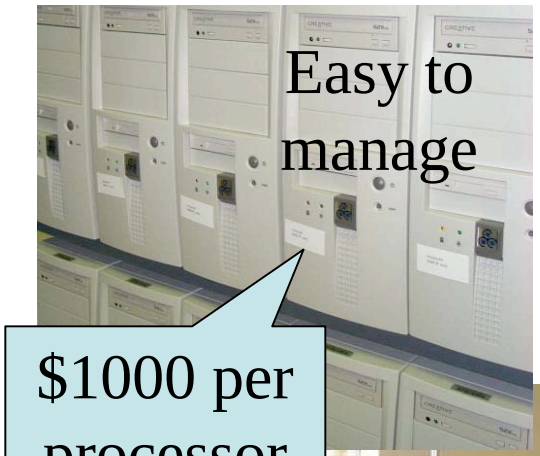
10,000 registered users.

NAMD
Scalable Molecular Dynamics

# Linux Clusters 101

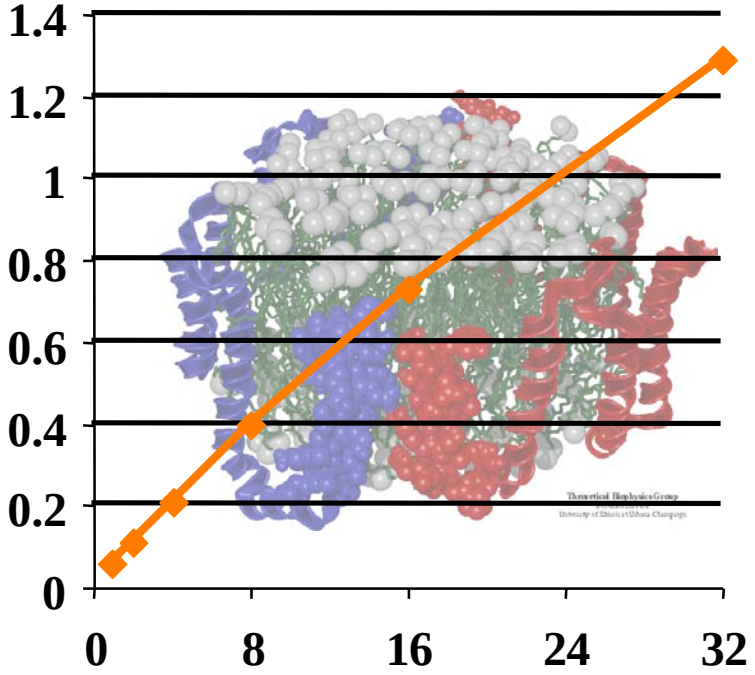
*parallel computing on a professor's salary*

**Learn to build your own Linux cluster!**




$1000 per processor

92K atoms with PME
(ns simulated per week)



# 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

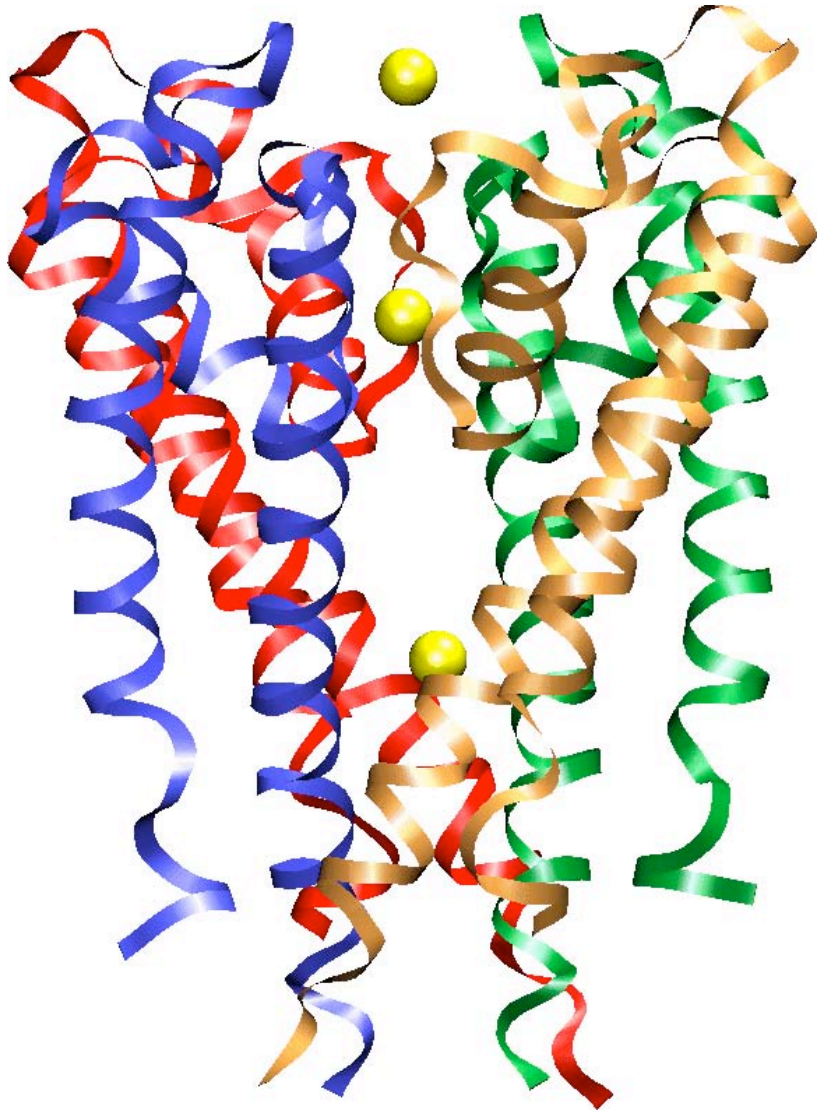
# Steps in a Typical MD Simulation

- 1. Prepare molecule
  - Read in pdb and psf file
- 2. Minimization
  - Reconcile observed structure with force field used (T = 0)
- 3. Heating
  - Raise temperature of the system
- 4. Equilibration
  - Ensure system is stable
- 5. Dynamics
  - Simulate under desired conditions (NVE, NpT, etc)
  - Collect your data
- 6. Analysis
  - Evaluate observables (macroscopic level properties)
  - Or relate to single molecule experiments
  - Many tools available in VMD

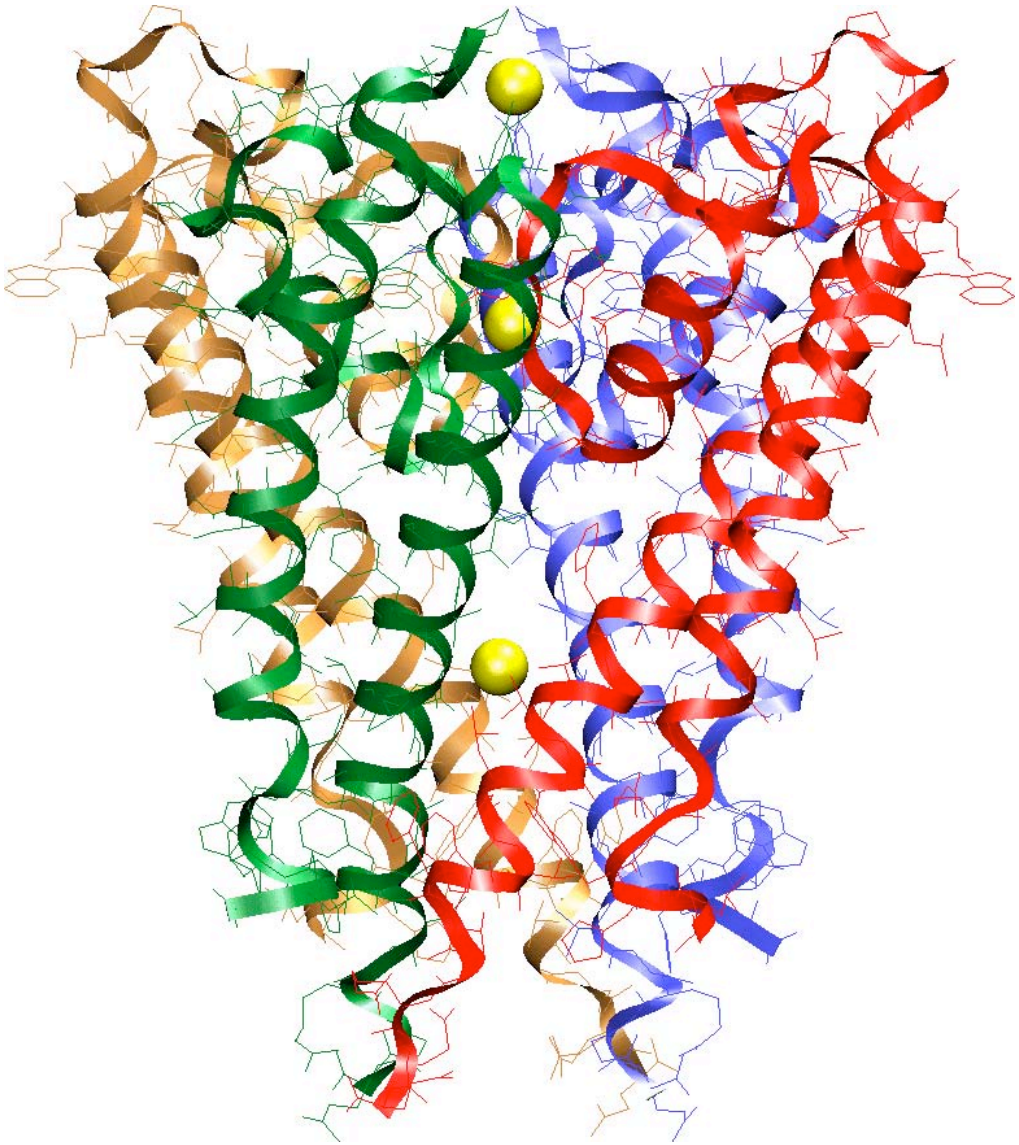
# Example: MD Simulations of the $K^+$ Channel Protein

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.

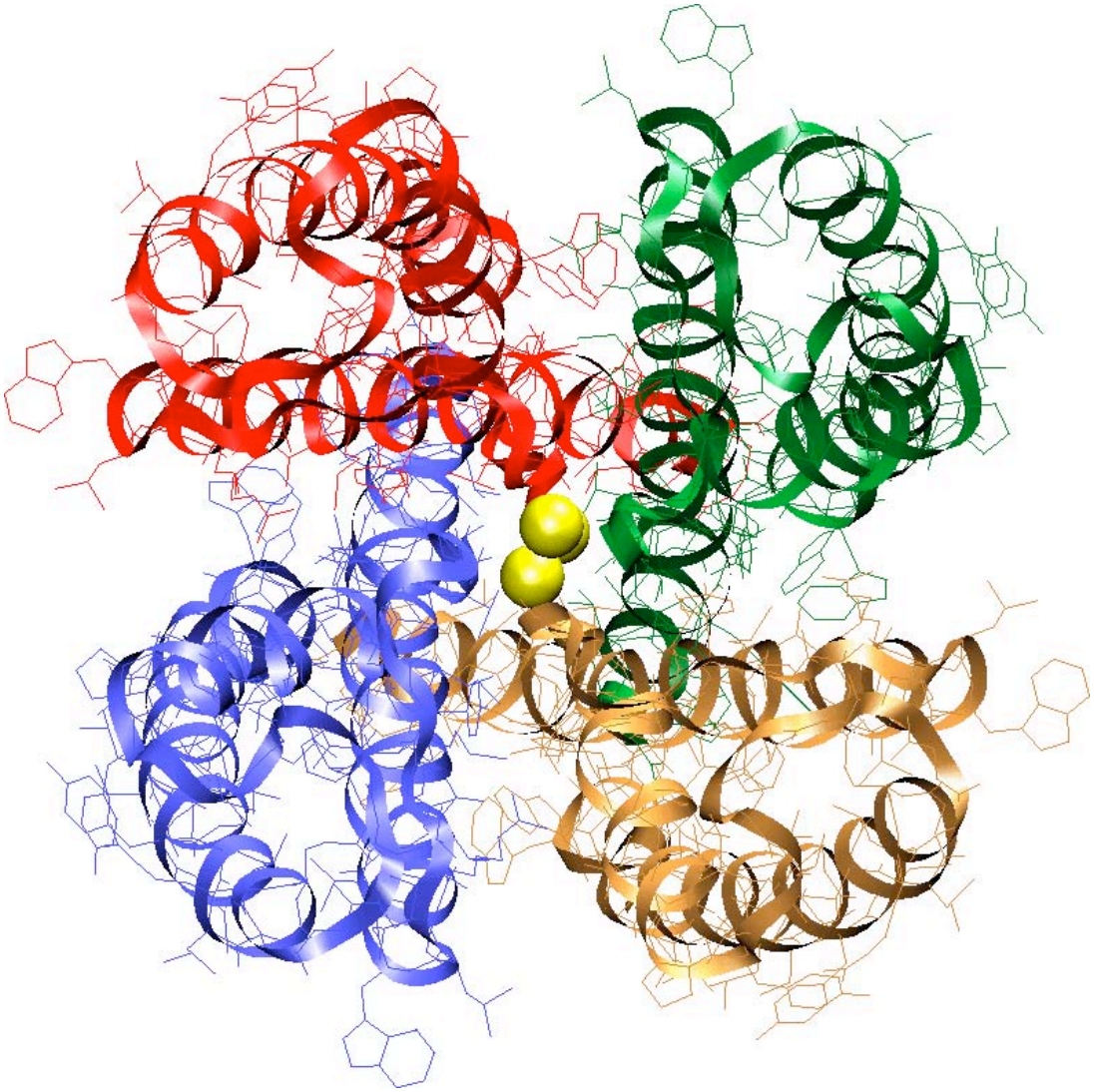


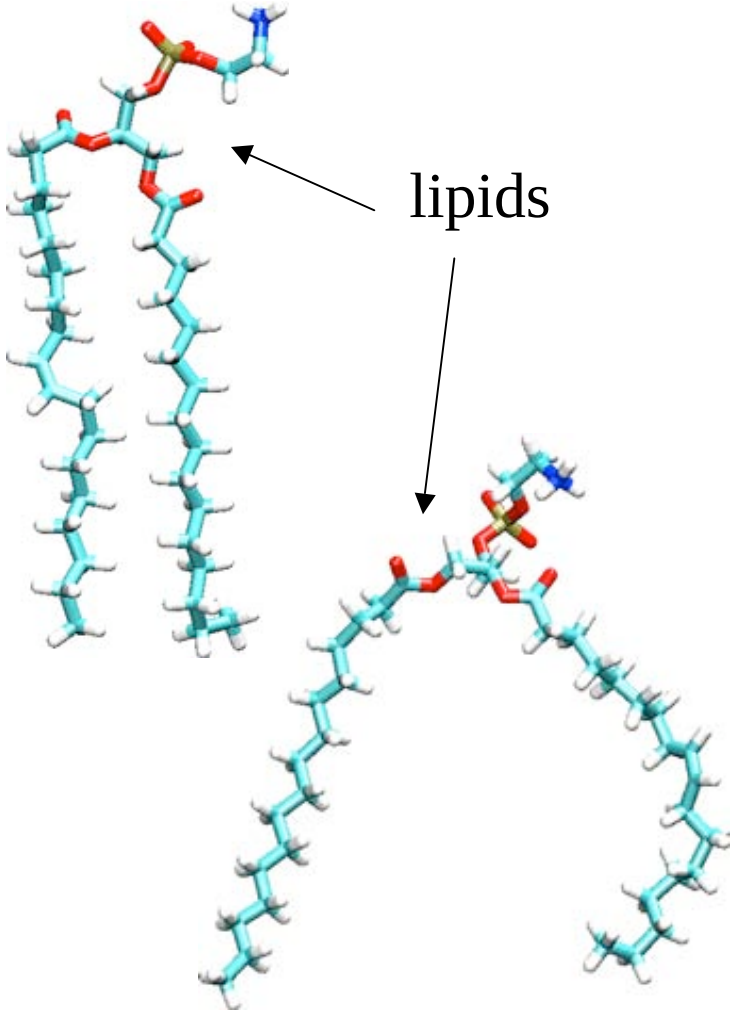
# Setting up the system (1)



- 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
- minimize the protein structure using NAMD2

# Setting up the system (2)

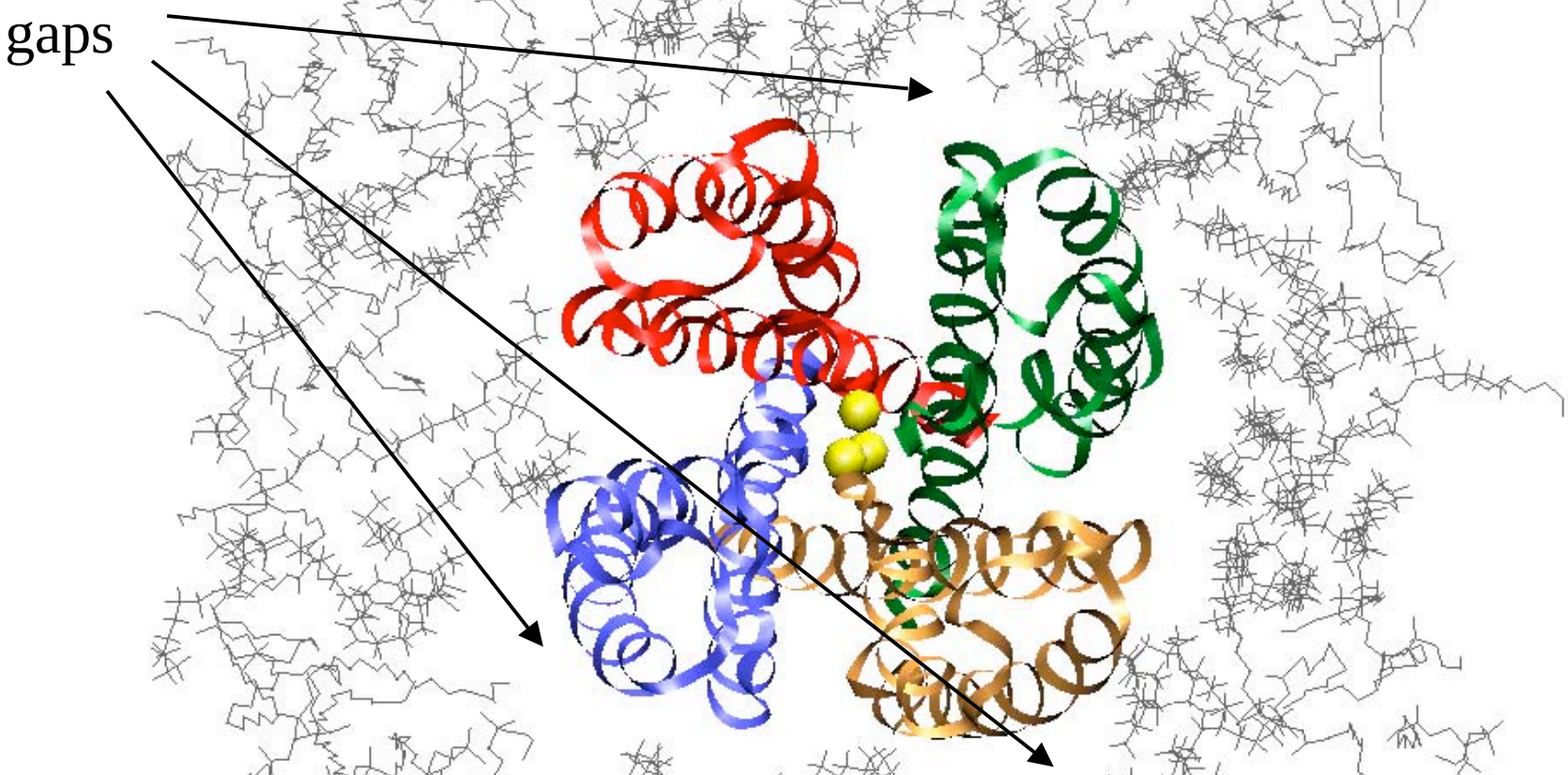





Simulate the protein in its natural environment: solvated lipid bilayer

# Setting up the system (3)

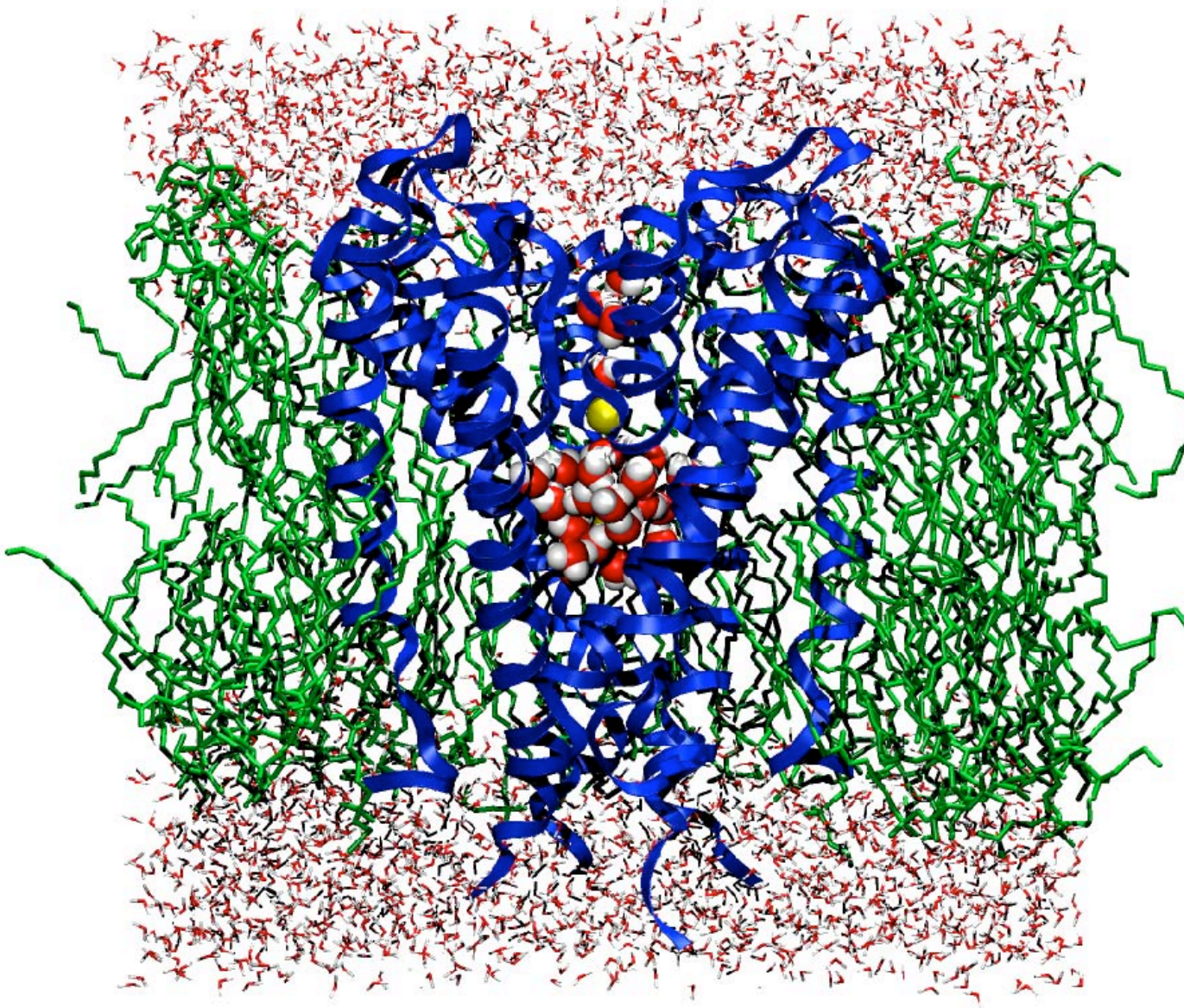
## Inserting the protein in the lipid bilayer




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

# The system

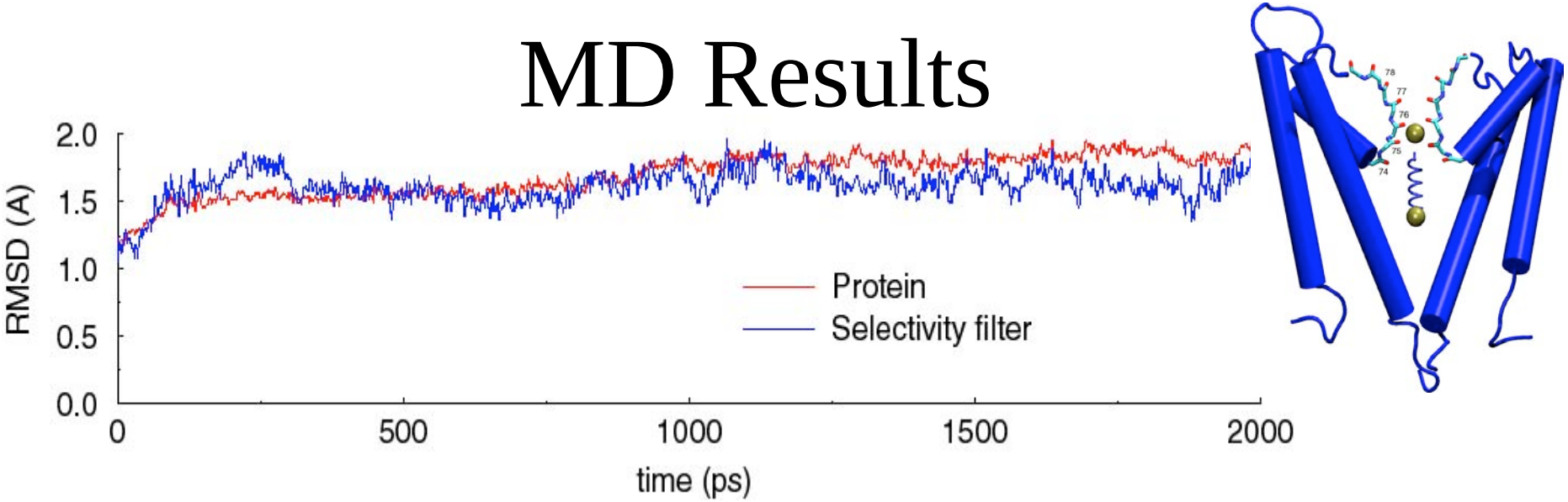


solvent

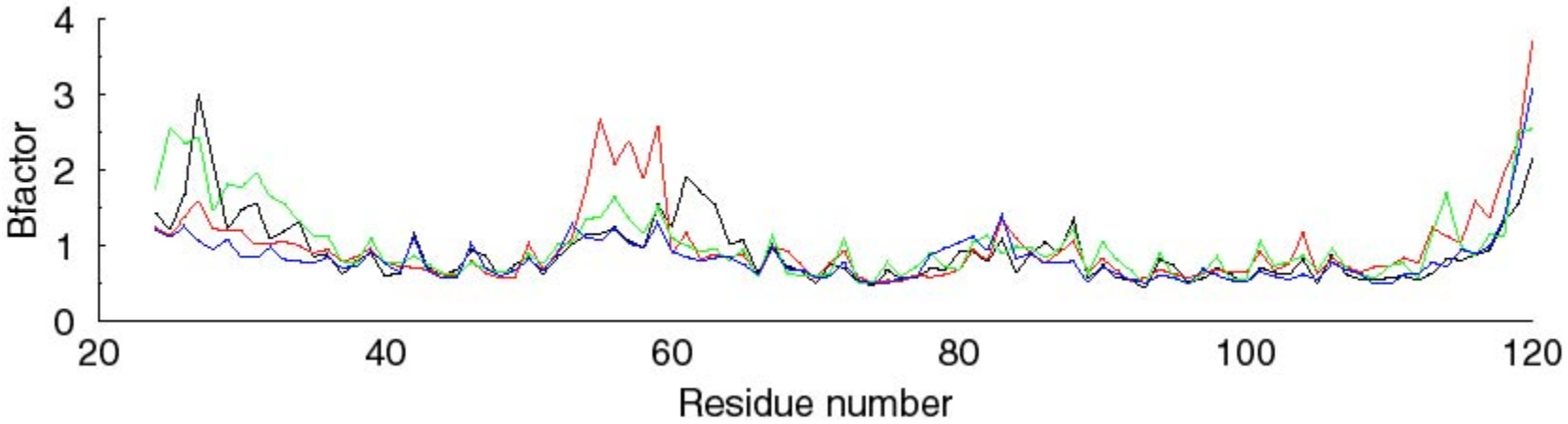
Kcsa channel protein (in blue) embedded in a (3:1) POPE/POPG lipid bilayer. Water molecules inside the channel are shown in vdW representation.

solvent

# 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.

# Simulating the system: Free MD

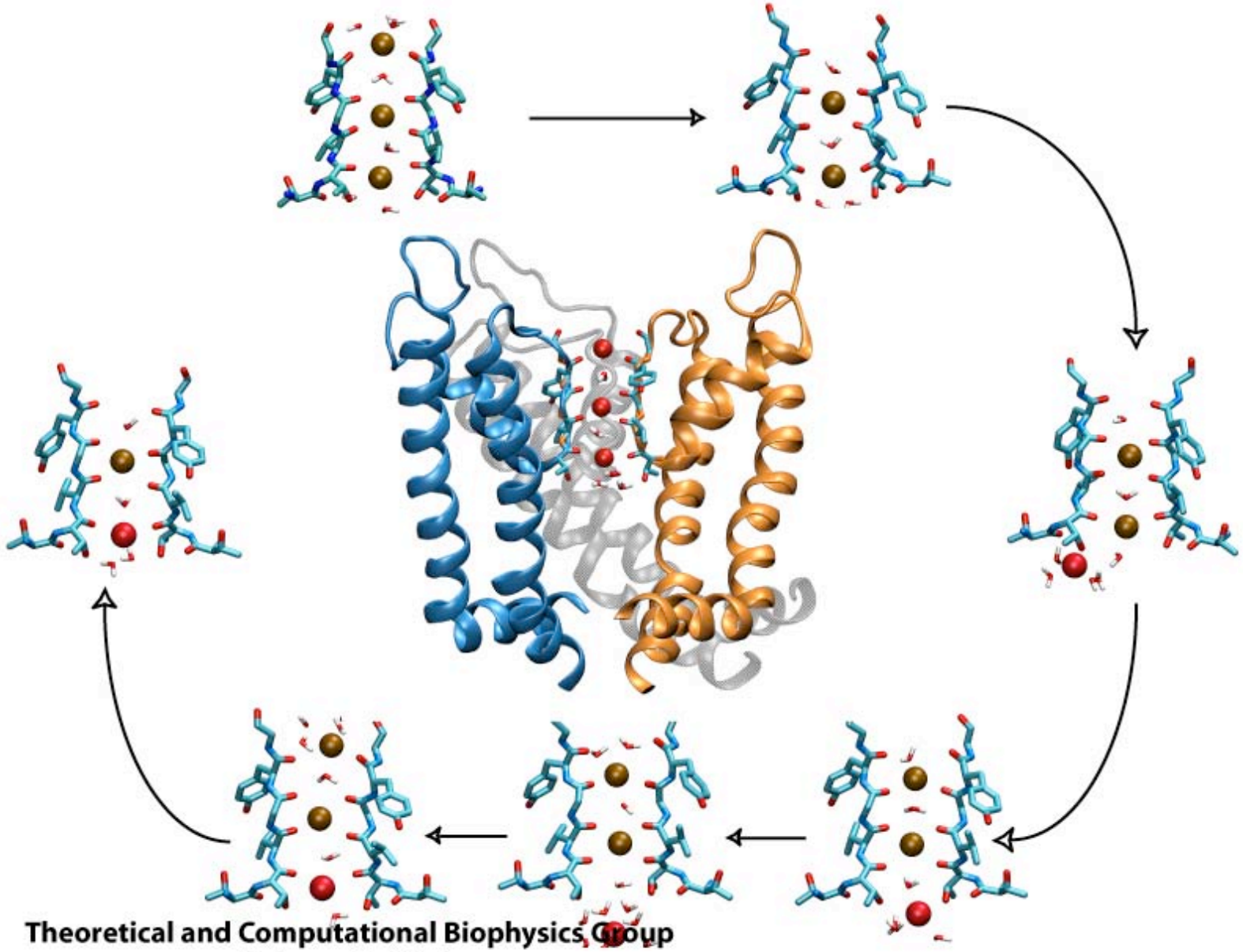
Summary of simulations:

- 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)

# Simulation of Ion Conduction (here for Kv1.2)



**Theoretical and Computational Biophysics Group**
Beckman Institute
University of Illinois at Urbana-Champaign

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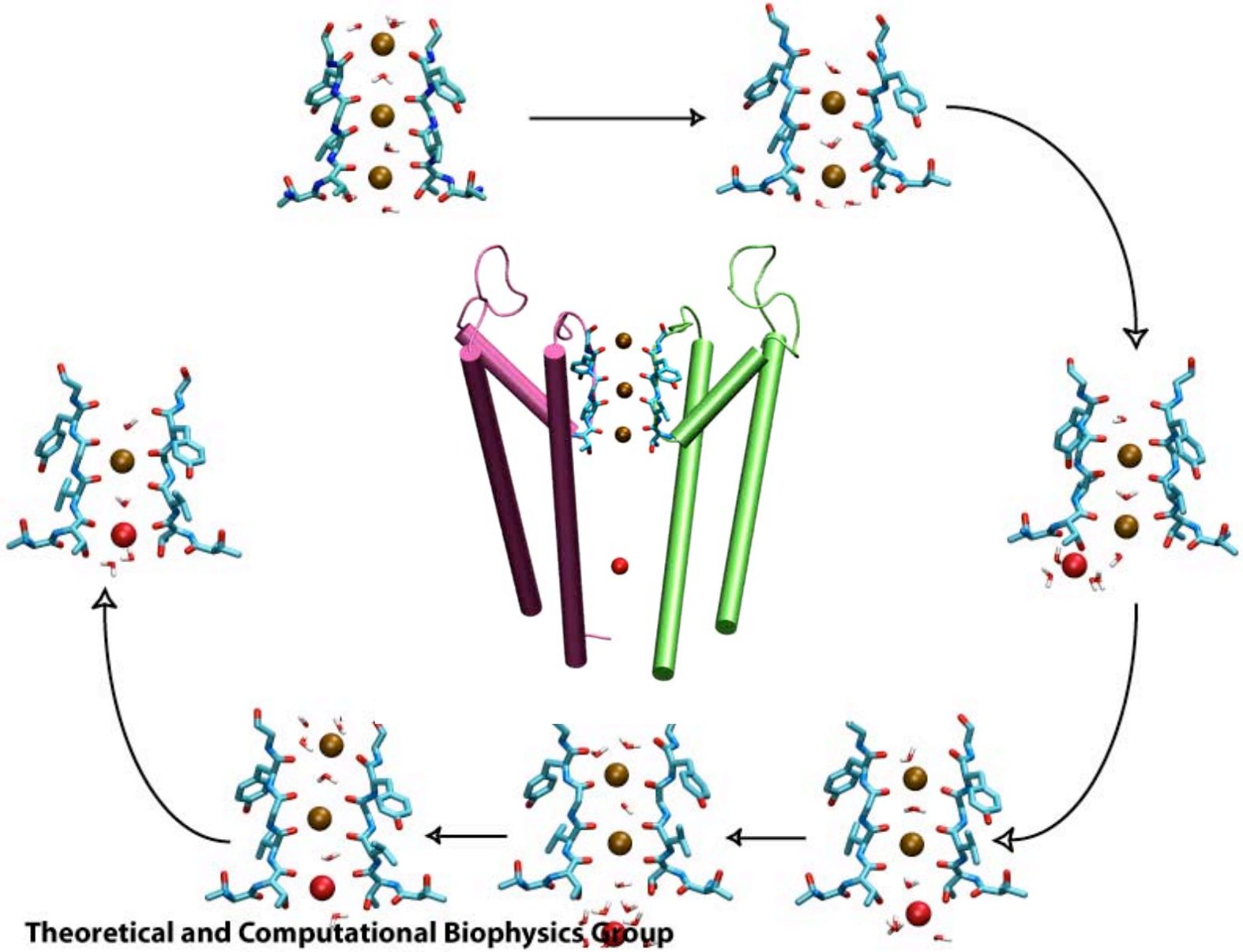
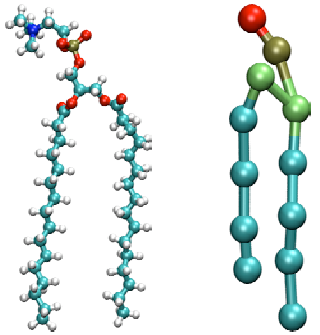


**Theoretical and Computational Biophysics Group**
Beckman Institute
University of Illinois at Urbana-Champaign

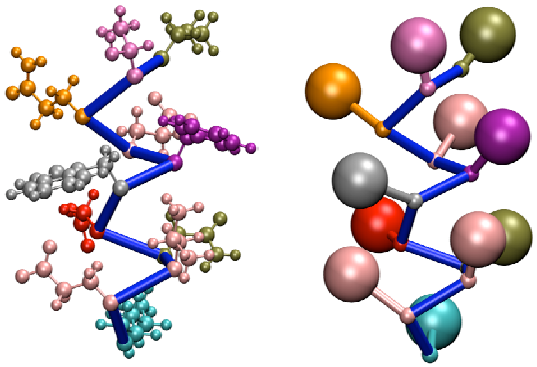
# Coarse-grained protein-lipid model for simulating lipoprotein assembly

- Lipid model: 12 beads per DPPC lipid



$$V = \sum_{bond} \tfrac{1}{2} K_b \left(b - b_0\right)^2 + \sum_{\substack{lipid \\ angle}} \tfrac{1}{2} K_\theta^{lipid} \left(\cos\left(\theta^{lipid}\right) - \cos\left(\theta_0^{lipid}\right)\right)^2 + \sum_{\substack{protein \\ angle}} K_\theta^{protein} \left(\theta^{protein} - \theta_0^{protein}\right)^2$$

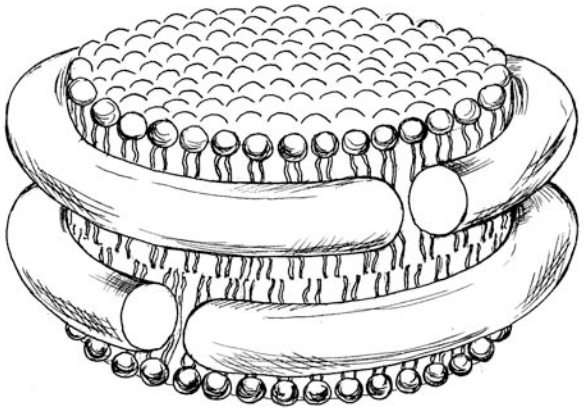
$$+ \sum_{dihedral} K_\chi \left(1 + \cos\left(n\chi - \delta\right)\right) + \sum_{m,n} 4\varepsilon_{mn} \left[\left(\frac{\sigma_{mn}}{r_{mn}}\right)^{12} - \left(\frac{\sigma_{mn}}{r_{mn}}\right)^{6}\right] + \sum_{m,n} \frac{q_m q_n}{4\pi\varepsilon\varepsilon_0 r_{mn}}$$



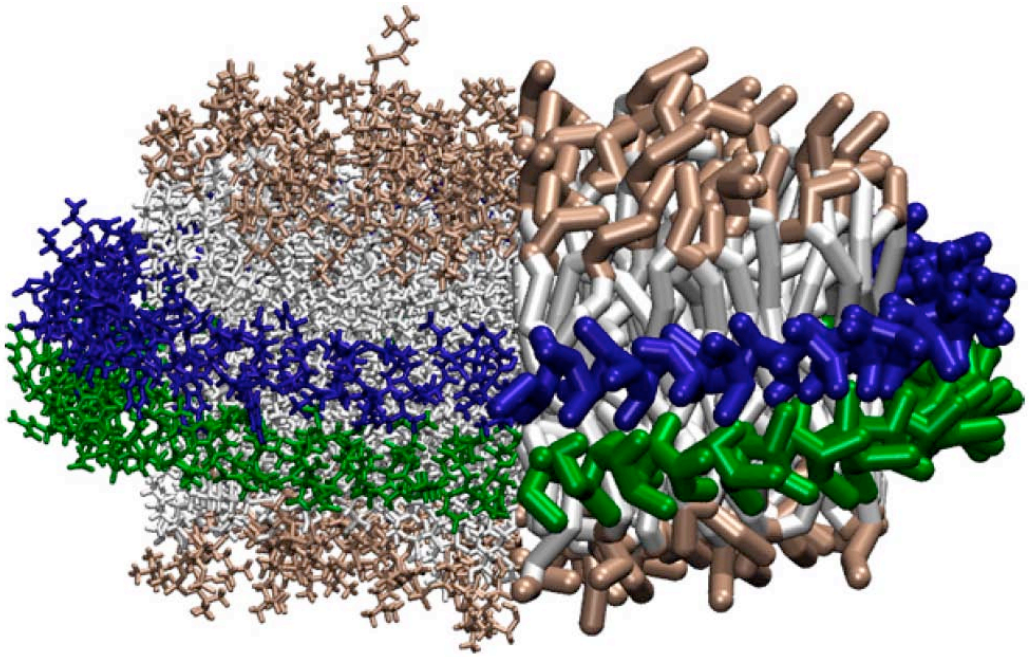
- Protein model: Each residue is represented by two CG beads: backbone & side chain
- Dihedral force obtained using an inverse Boltzman technique (protein backbone only)

A. Shih, A. Arkhipov, P. Freddolino, and K. Schulten. J. Phys. Chem. B, 110:3674-3684, 2006; J. Struct.Biol. (invited)

# Coarse Grained Molecular Dynamics of Lipid Nanodiscs



scaffold protein



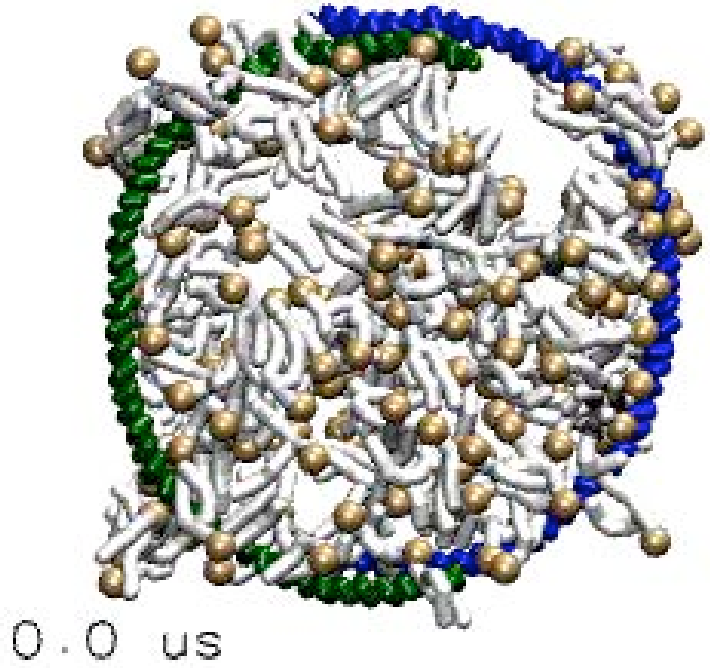
Full atom representation

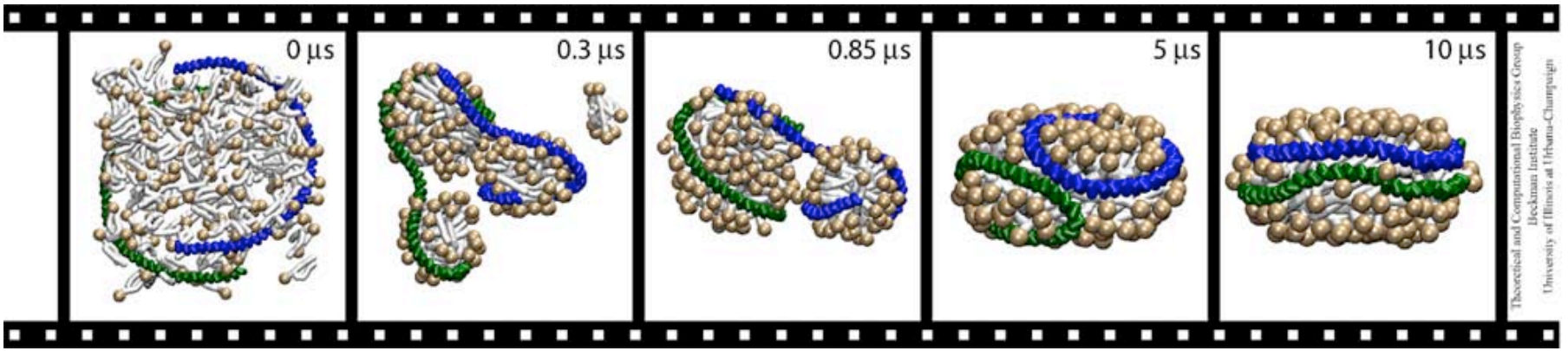
Coarse-grained representation

A. Shih, A. Arkhipov, P. Freddolino, and K. Schulten. J. Phys. Chem. B, 110:3674-3684, 2006; J. Struct.Biol. (invited)

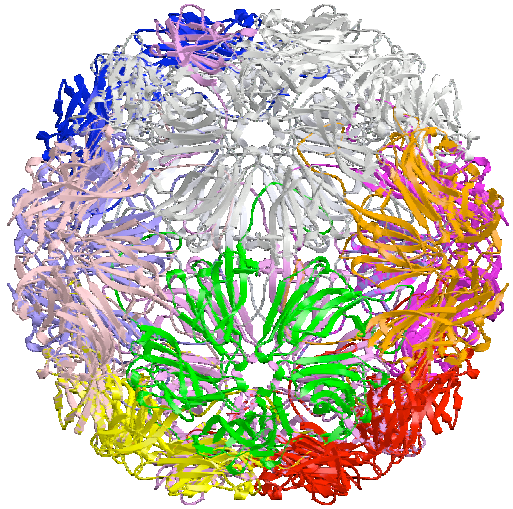
# Nanodisc Assembly CG MD Simulation

- 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

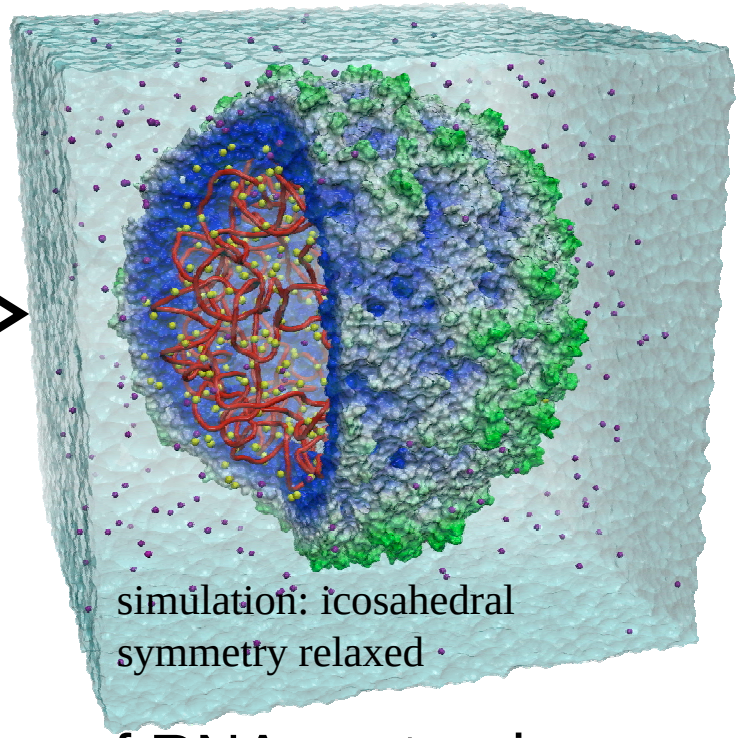


# Study of Very Large Systems by Coarse Graining
## *(Satellite Tobacco Mosaic Virus)*



crystal structure: icosahedral
symmetry imposed

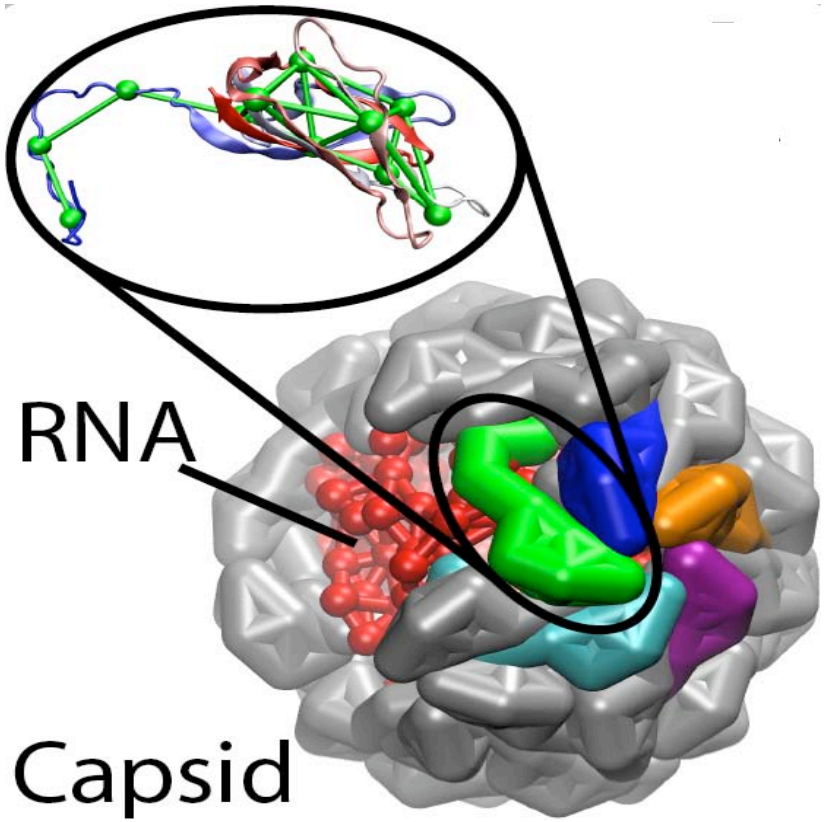


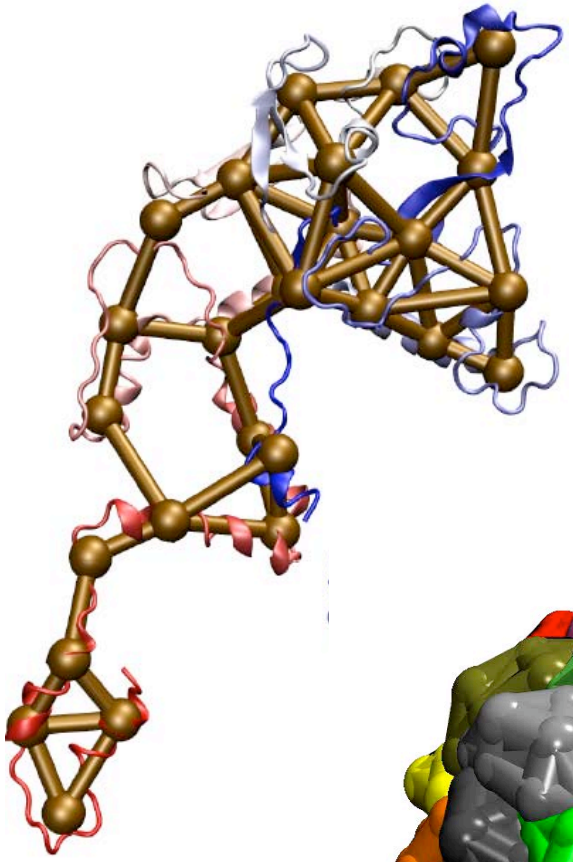
simulation: icosahedral
symmetry relaxed

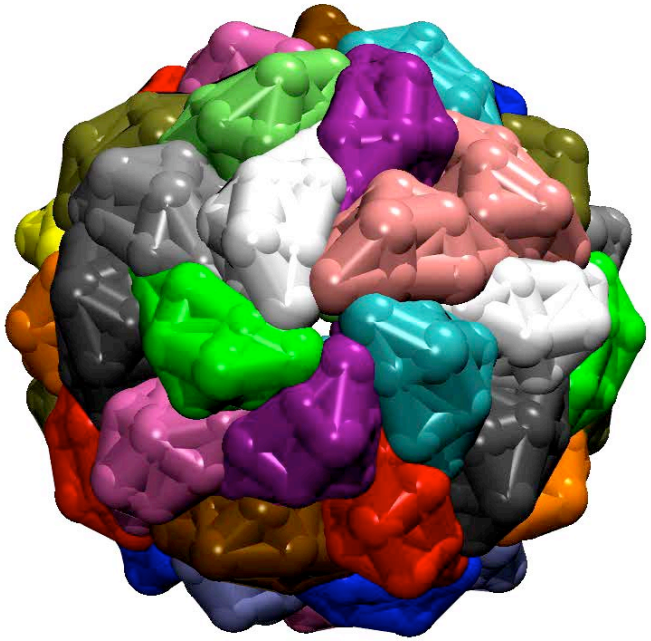
132,000 atoms of protein, 30,000 atoms of RNA, water, ions
~1,000,000 atoms in total

Peter Freddolino, Anton Arkhipov, Steven Larson, Alexander McPherson, and Klaus Schulten, *Structure*, **14**:437 (2006)

# Coarse-Grained Simulation of Virus Capsid





Each protein unit is represented by 15 beads (~170 atoms per bead)

Anton Arkhipov, Peter L. Freddolino, and Klaus Schulten. *Structure*, 2006. In press.