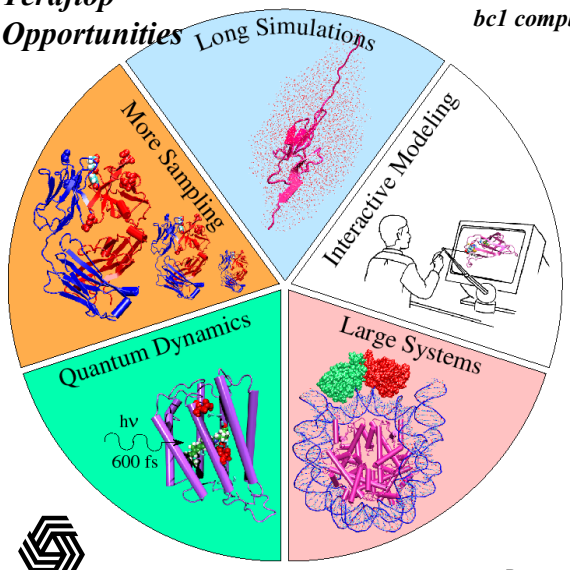
# Introduction to Molecular Dynamics

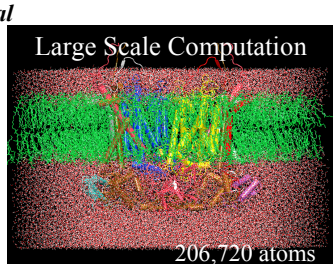
**Theor. Biophysics Group, Beckman Institute, U. Illinois at Urbana-Champaign**

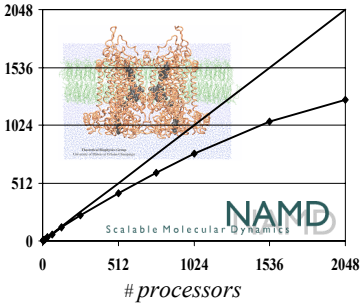
***Teraflop Opportunities***




National Center for Research Resources

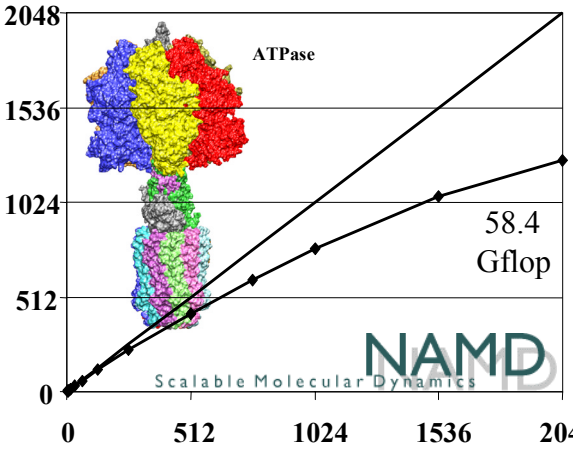
***mitochondrial bc1 complex***




Brunner *et al.,* SC2000, finalist for Gordon Bell award.

# NAMD: Scalable Molecular Dynamics




For SP3, Origin, T3E, clusters…
PSC teraflop, IBM Blue Gene.

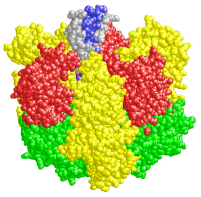
Scalable to 1000's of CPUs.

Data file compatible with CHARMM and X-PLOR.

Fast full electrostatics and constant pressure ensembles.

Flexible Tcl scripting language.

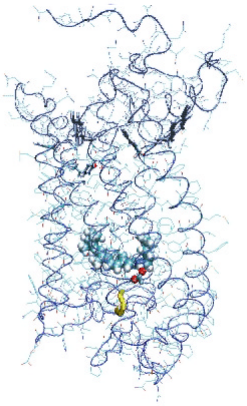
Ready for $10^5$ atoms and beyond…

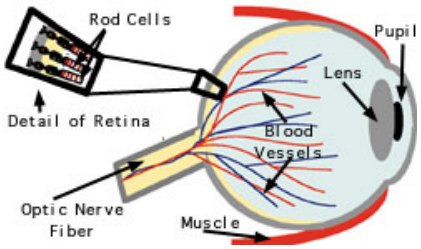


*Design of NAMD:* Kalé *et al.,* J. Comp. Phys., **151**, 283 (1999)

Freely available with C++ source code from http://www.ks.uiuc.edu/Research/namd/

# VMD: Molecular Visualization



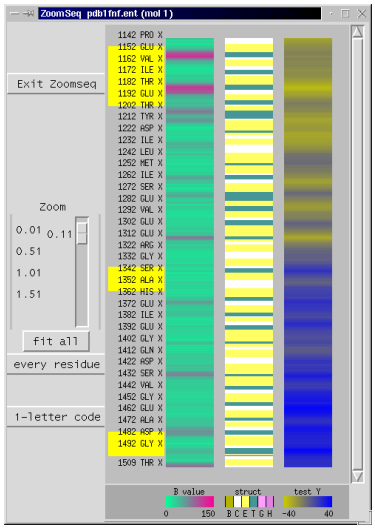


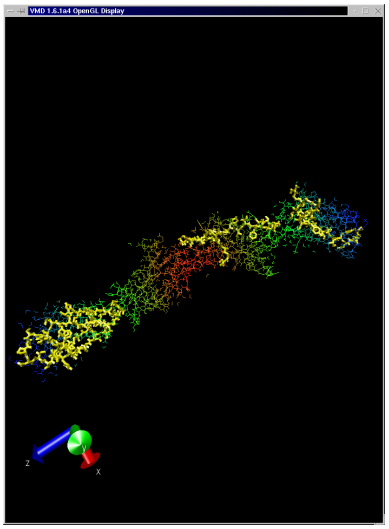

**VMD freely available, with source code from http://www.ks.uiuc.edu**

*Humphrey et. al.*, J. Molec. Graphics, **14**:33-38, 1996

VMD
Visual Molecular Dynamics

# Sequence Browsing in VMD



# An Introduction to Molecular Dynamics Simulations

Macroscopic properties are often determined by molecule-level behavior.

Quantitative and/or qualitative information about macroscopic behavior of macromolecules can be obtained from simulation of a system at atomistic level.

Molecular dynamics simulations calculate the motion of the atoms in a molecular assembly using Newtonian dynamics to determine the net force and acceleration experienced by each atom. Each atom ***i*** at position $\boldsymbol{r_i}$, is treated as a point with a mass $\boldsymbol{m_i}$ and a fixed charge $\boldsymbol{q_i}$.

# MD: Verlet Method

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

used to determine the force on each atom:

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

Newton's equation represents a set of N second order differential equations which are solved numerically at discrete time steps to determine the trajectory of each atom.

$$\vec{r}_i(t + \Delta t) = 2\vec{r}_i(t) - \vec{r}_i(t - \Delta t) + \frac{\Delta t^2}{m_i} \vec{F}_i(t)$$

# Deriving the Verlet algorithm

- Uses positions and accelerations at time t and the positions from time t-δt to calculate new positions at time t+ δ t.
- Uses no explicit velocities.

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

+

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

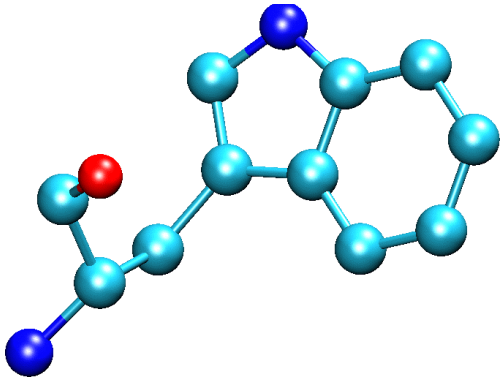
$$\Downarrow$$

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

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

# What is the Force Field $-\vec{\nabla}U(\vec{R})$?

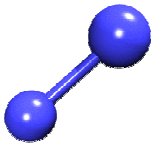
In molecular dynamics a molecule is described as a series of charged points (atoms) linked by springs (bonds).



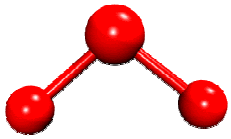
To describe the time evolution of bond lengths, bond angles and torsions, also the non-bonding van der Waals and elecrostatic interactions between atoms, one uses a forcefield.
The forcefield is a collection of equations and associated constants designed to reproduce molecular geometry and selected properties of tested structures.

# Energy Terms Described in the CHARMm Force Field

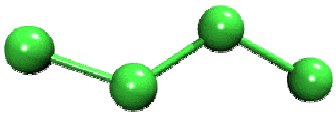
Bond



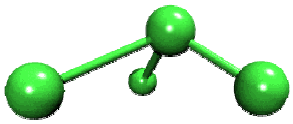
Angle



Dihedral



Improper



# Energy Functions

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

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

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

$U_{bond}$ = oscillations about the equilibrium bond length
$U_{angle}$ = oscillations of 3 atoms about an equilibrium angle
$U_{dihedral}$ = torsional rotation of 4 atoms about a central bond
$U_{nonbond}$ = non-bonded energy terms (electrostatics and Lenard-Jones)

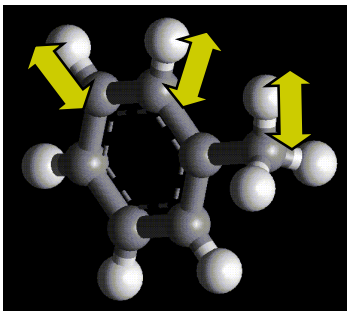
# Time scales

- Time scale of biological events

| Motion | Time Scale (sec) |
|---|---|
| Bond stretching | $10^{-14}$ to $10^{-13}$ |
| Elastic vibrations | $10^{-12}$ to $10^{-11}$ |
| Rotations of surface sidechains | $10^{-11}$ to $10^{-10}$ |
| Hinge bending | $10^{-11}$ to $10^{-7}$ |
| Rotation of buried side chains | $10^{-4}$ to 1 sec |
| Allosteric transistions | $10^{-5}$ to 1 sec |
| Local denaturations | $10^{-5}$ to 10 sec |

# The 1 fs Time Barrier

- Dynamics simulations are limited by the highest frequency vibration
- Ideally the timestep should be 1/10 highest frequency
- In most cases C-H bond stretching ($10^{-14}$ s) is the fastest mode



**SPEED LIMIT**

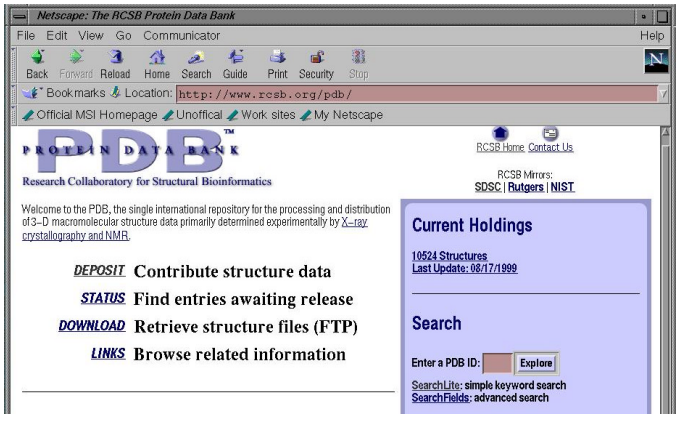
**1 fs**

# 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
  - Collect your data
  - Evaluate observables (macroscopic level properties)
  - Or relate to single molecule experiments

# Obtaining files

- Files can be downloaded through the Web



# First, You Need a 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
```

# What you need to know to build a realistic atomistic model of your system

- What is a force field?
- How to prepare your system for MD?
- What specific conditions (temperature, pressure, volume, etc) will be used in MD?

# Energy Functions

$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} +$$
$$\underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} +$$
$$\underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}$$

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# Topology and Parameter Files

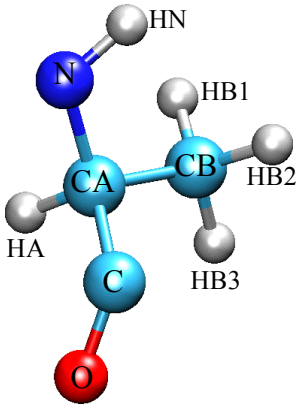
Topology files contain:
• atom types are assigned to identify different elements and different molecular orbital environments
• charges are assigned to each atom
• connectivities between atoms are established

Parameter files contain:
• force constants necessary to describe the bond energy, angle energy, torsion energy, nonbonded interactions (van der Waals and electrostatics)
• suggested parameters for setting up the energy calculations

# Example of Topology 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
          |
```

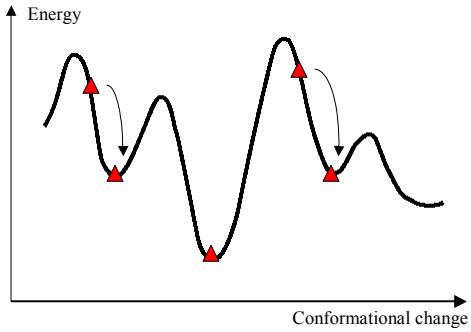



# Example of Parameter File

```
!BOND PARAMETERS:  Force Constant, Equilibrium Radius
 BOND  C   C       600.000 {SD=.022}      1.335 ! ALLOW ARO HEM
 BOND  CA  CA    305.000 {SD=.031}      1.375 ! ALLOW   ARO

!ANGLE PARAMETERS:  Force Constant, Equilibrium Angle,
Urie-Bradley Force Const., U.-B. equilibrium  (if any)
 ANGLE  CA   CA   CA       40.00 {SD=.086}    120.0000    UB  35.000  2.416
 ANGLE  CP1  N    C        60.00 {SD=.070}    117.0000 ! ALLOW PRO

!DIHEDRAL PARAMETERS:  Energy Constant, Periodicity, Phase Shift, Multiplicity
 DIHEDRAL  C   CT2  NH1  C          1.60 {SD=.430}    1    180.0000 ! ALLOW PEP
 DIHEDRAL  C   N    CP1   C          .80 {SD=.608}    3      .0000 ! ALLOW PRO PEP

!IMPROPER PARAMETERS:  Energy Constant, Periodicity(0), Phase Shift(0)
!   Improper angles are introduced for PLANARITY maintaining
 IMPROPER  HA  C   C   HA        20.00 {SD=.122}    0      .0000 ! ALLOW   PEP POL ARO
 IMPROPER  HA  HA  C   C         20.00 {SD=.122}    0    180.0000 ! ALLOW   PEP POL ARO

! -----NONBONDED-LIST-OPTIONS-----------------------------
  CUTNB=  13.000 TOLERANCE=    .500 WMIN=   1.500 ATOM
  INHIBIT=    .250
! -----ELECTROSTATIC OPTIONS------------------------------
  EPS=   1.000 E14FAC=   1.000 CDIELECTRIC SHIFT
! -----VAN DER WAALS OPTIONS------------------------------
  VSWITCH
! -----SWITCHING /SHIFTING PARAMETERS----------------------
  CTONNB=  10.000 CTOFNB=  12.000
! -----EXCLUSION LIST OPTIONS-----------------------------
  NBXMOD=   5
! ------------
!               EPS     SIGMA    EPS(1:4)  SIGMA(1:4)

 NONBONDED  C       .1100   4.0090    .1100   4.0090 ! ALLOW   PEP POL ARO
 NONBONDED  CA      .0700   3.5501    .0700   3.5501 ! ALLOW   ARO
```

# Preparing Your System for MD

## Minimization




The energy of the system can be calculated using the forcefield. The conformation of the system can be altered to find lower energy conformations through a process called minimization.

Minimization algorithms:

- steepest descent (slowly converging – use for highly restrained systems
- conjugate gradient (efficient, uses intelligent choices of search direction – use for large systems)
- BFGS (quasi-newton variable metric method)
- Newton-Raphson (calculates both slope of energy and rate of change)

# 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).

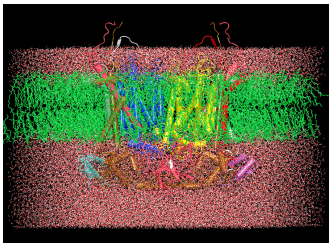
Why model solvation?

- 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

***mitochondrial bc1 complex***



## What you need to know to build a realistic atomistic model of your system

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## Molecular Dynamics Ensembles

Constant energy, constant number of particles (NE)

Constant energy, constant volume (NVE)

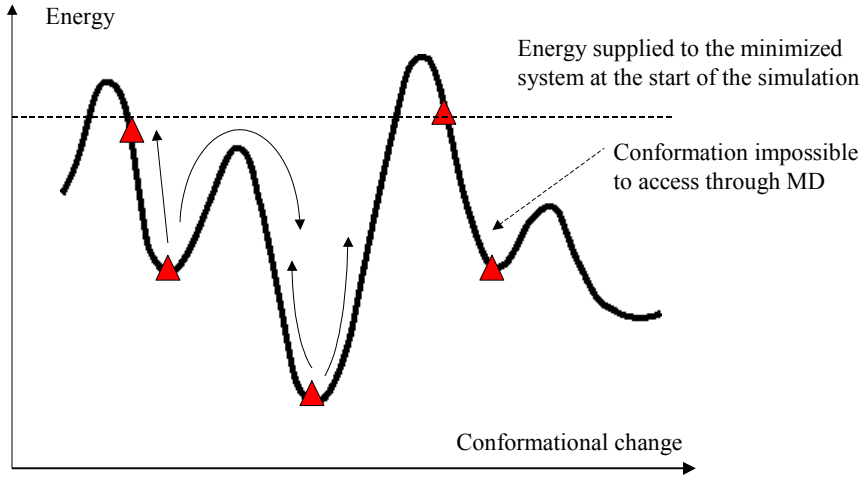
Constant temperature, constant volume (NVT)

Constant temperature, constant pressure (NPT)

Choose the ensemble that best fits your system and start the simulations

# Molecular Dynamics

MD = change in conformation over time using a forcefield

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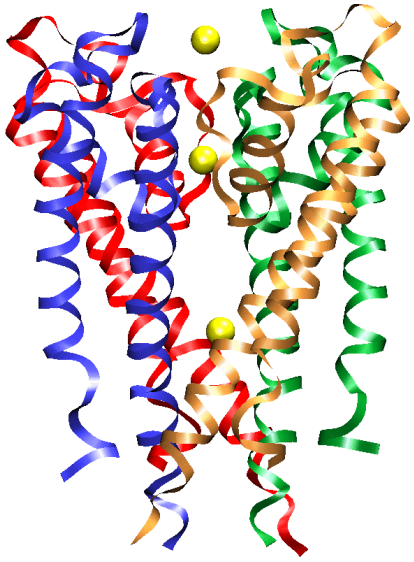
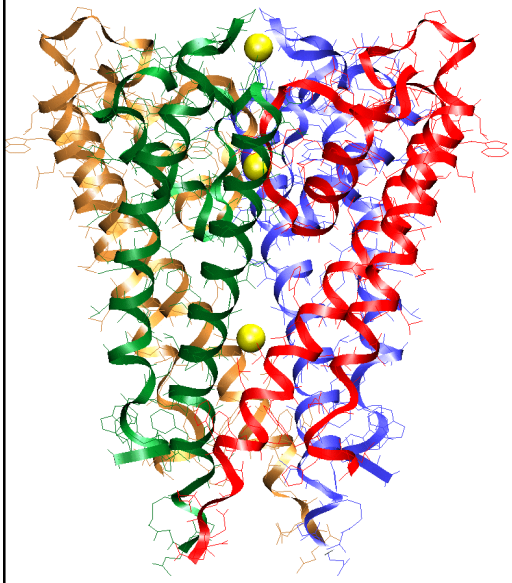
# 1st Example: MD Simulations of the $K^+$ Channel Protein

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.

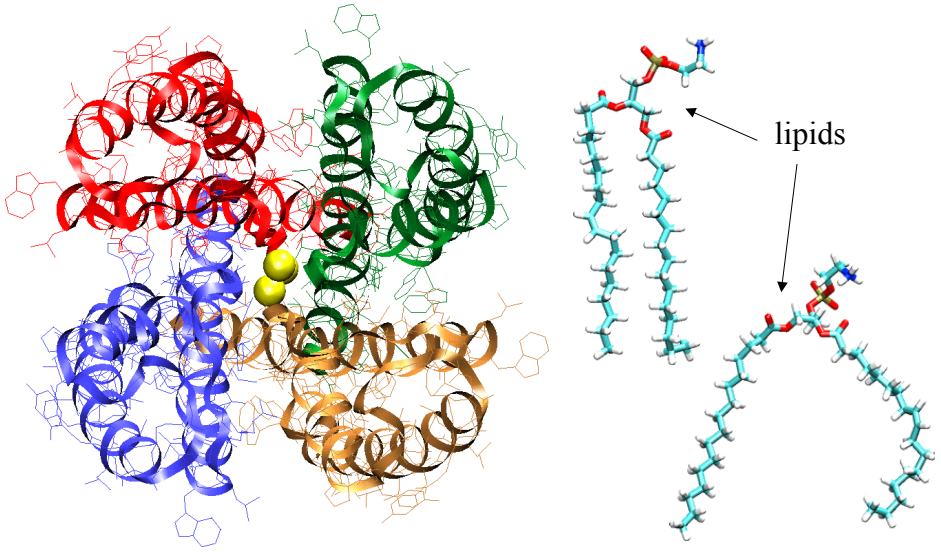


# Setting up the system (1)



- retrieve the PDB (coordinates) file from the Protein Data Bank
- add hydrogen atoms using X-PLOR
- use topology and parameter files to set up the structure
- minimize the protein structure using NAMD2

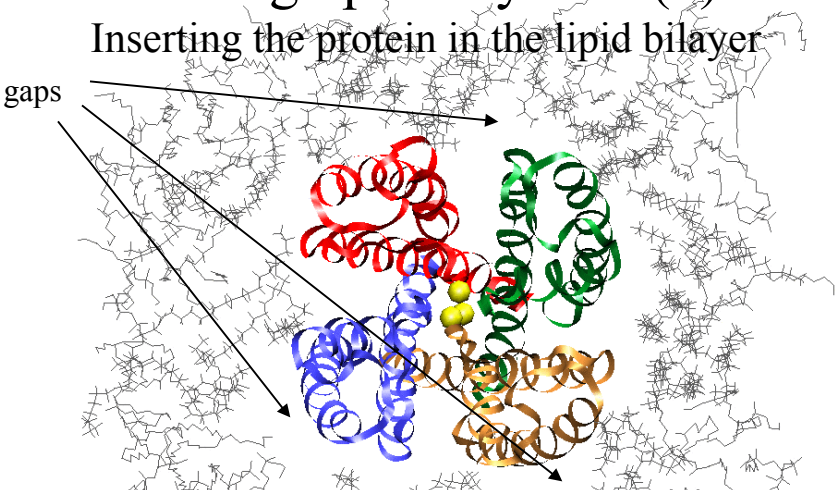
# Setting up the system (2)




Simulate the protein in its natural environment: solvated lipid bilayer

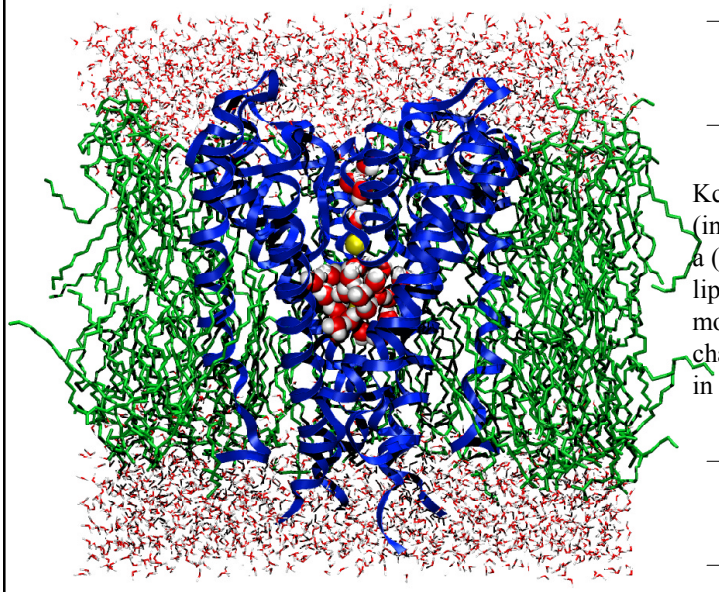
# Setting up the system (3)

## 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

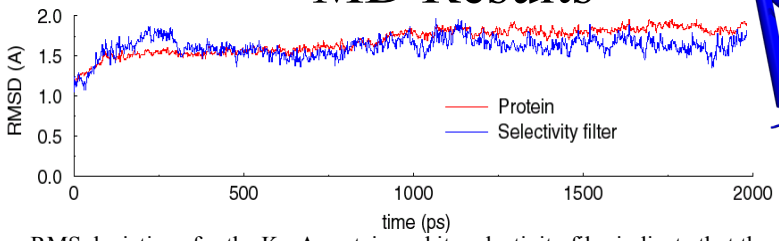


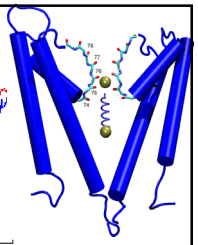
solvent

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

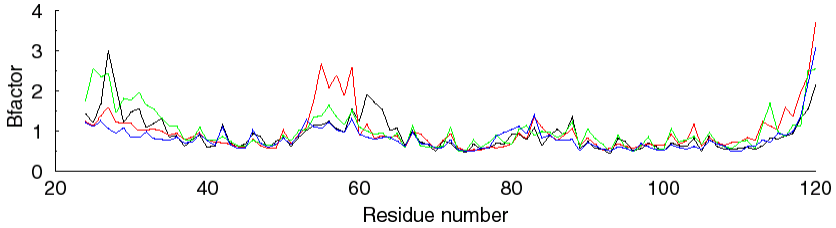
solvent

# 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

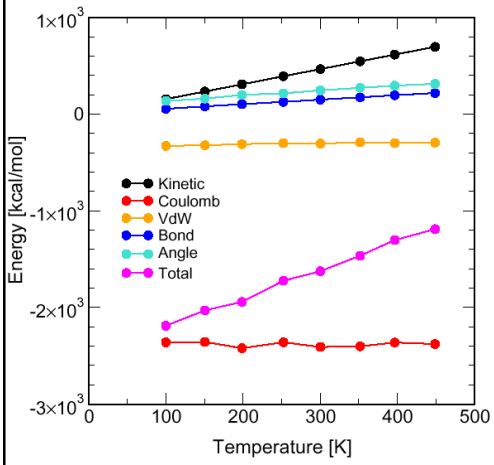
Program: NAMD2

Platform: Cray T3E (Pittsburgh Supercomputer Center)

# Analysis of Trajectories

- Energetic analysis
  - Kinetic energy
  - Potential energy
  - Total energy
  - Generate ensemble averages
    - Assumption that trajectory properly sampled distribution
  - Intermolecular interactions

# Energies: kinetic and potential

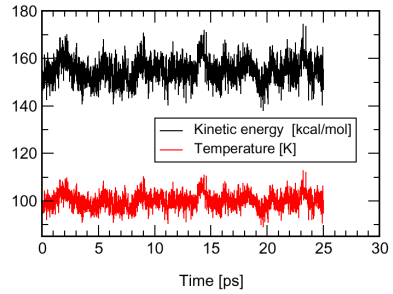


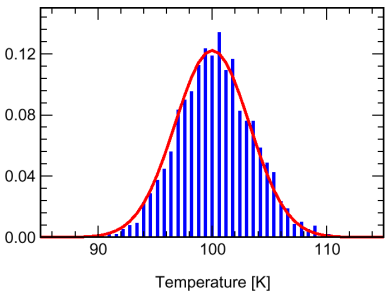

Langevin dynamics

$$m_n \frac{d^2 x_n}{dt^2}(t) = \nabla_{x_n} V - m_n b_n \frac{dx_n}{dt}(t) + f_n(t)$$

$$\begin{aligned} \langle f_n(t) \rangle &= 0 \\ \langle f_n(t)\, f_n(0) \rangle &= 2 k_B T_0\, b_n\, m_n\, \delta(t)\,. \end{aligned}$$

# Analysis of $E_{kin}$, T (free dynamics)




**Definition of Temperature**

$$\langle \sum_j \frac{1}{2} m_j v_j^2 \rangle = \frac{3}{2} N\, k_B\, T$$

$$T = \frac{2}{3N\, k_B} \langle \sum_j \frac{1}{2} m_j v_j^2 \rangle$$

## Temperatur Fluctuations

Maxwell distribution

$$dP(v_n) \;=\; c\,\exp(-m\,v_n^2/2k_BT)\,dv_n \tag{7}$$

Individual kinetic energy $\epsilon_n \;=\; mv_n^2/2$

$$dP(\epsilon_n) \;=\; (\pi T_0\epsilon_n)^{-1/2}\exp(-\epsilon_n/k_BT_0)\,d\epsilon_n \tag{8}$$

One can derive

$$\langle\epsilon_n\rangle \;=\; T_0/2 \tag{9}$$

$$\langle\epsilon_n^2\rangle \;=\; 3\,T_0^2/4 \tag{10}$$

$$\langle\epsilon_n^2\rangle - \langle\epsilon_n\rangle^2 \;=\; T_0^2/2 \tag{11}$$

The distribution of the total kinetic energy $E_{kin} \;=\; \sum_j \frac{1}{2}m_jv_j^2$, according to the central limit theorem, is approximately Gaussian

$$P(E_{kin}) \;=\; c\,\exp\left(\frac{-(E_{kin}\;-\;\langle E_{kin}\rangle)^2}{2\left(\frac{3Nk_B^2T_0^2}{2}\right)}\right) \tag{12}$$

The distribution function for the temperature ($T \;=\; 2E_{kin}/3k_B$) fluctuations $\Delta T \;=\; T \;-\; T_0$ is then

$$P(\Delta T) \;=\; c\,\exp[-(\Delta T)^2/2\sigma^2]\,, \qquad \sigma^2 \;=\; 2\,T^2/3N \tag{13}$$

For $T_0 \;=\; 100$K and $N \;=\; 557$, this gives $\sigma \;=\; 3.6$.

# A Brief Tutorial on NAMD

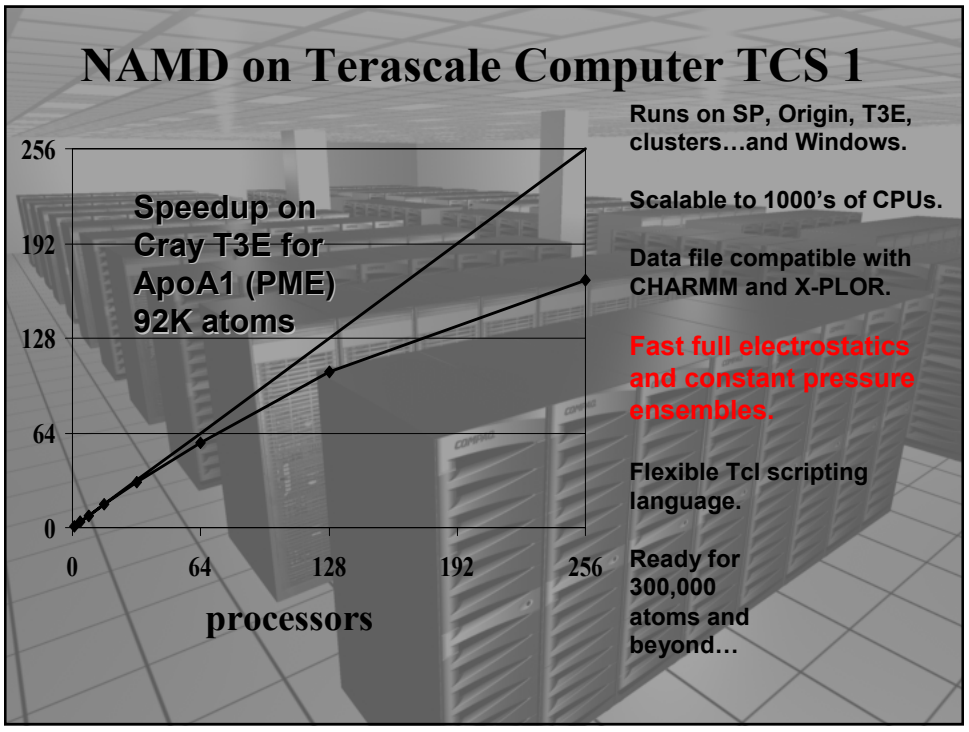
Not (Just) Another MD Program

Theoretical Biophysics Group

University of Illinois

# What Is NAMD Designed For?

- Classical molecular dynamics simulations
- CHARMM energy function
- Large systems (10,000 to 1,000,000 atoms)
- Parallel supercomputers (T3E, TCS)
- Clusters of Unix workstations (Beowulf)
- Full electrostatics (PME recommended)
- Multiple timestep integration



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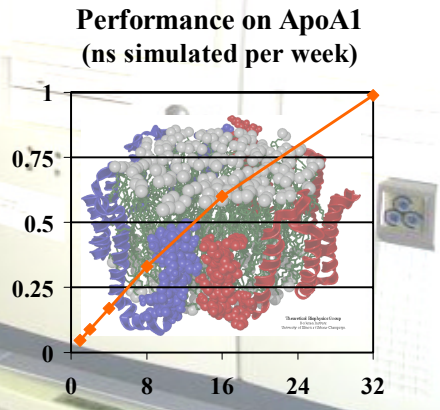
## NAMD 2.3 on Athlon Cluster

- 67% efficiency on 32, *commodity hardware*.
- Equivalent to owning a 100 CPU Cray T3E for only $30K.
- Available in the lab



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How to run BPTI simulation jobs: see web site

www.ks.uiuc.edu/~demouser/script.shtml

Follow instructions; Justin, Ioan and Jim will help.

run NAMD jobs in the following order
(specify 8 threads / processors; specify 600 s time):

- minimize.namd
- equil.namd (specify temperature
set TARGETTEMP 350
, choose temperature 100 + 10 x machine number)
- langevin.namd (specify temperature
set TARGETTEMP 350
, choose temperature 100 + 10 x machine number)
- free.namd