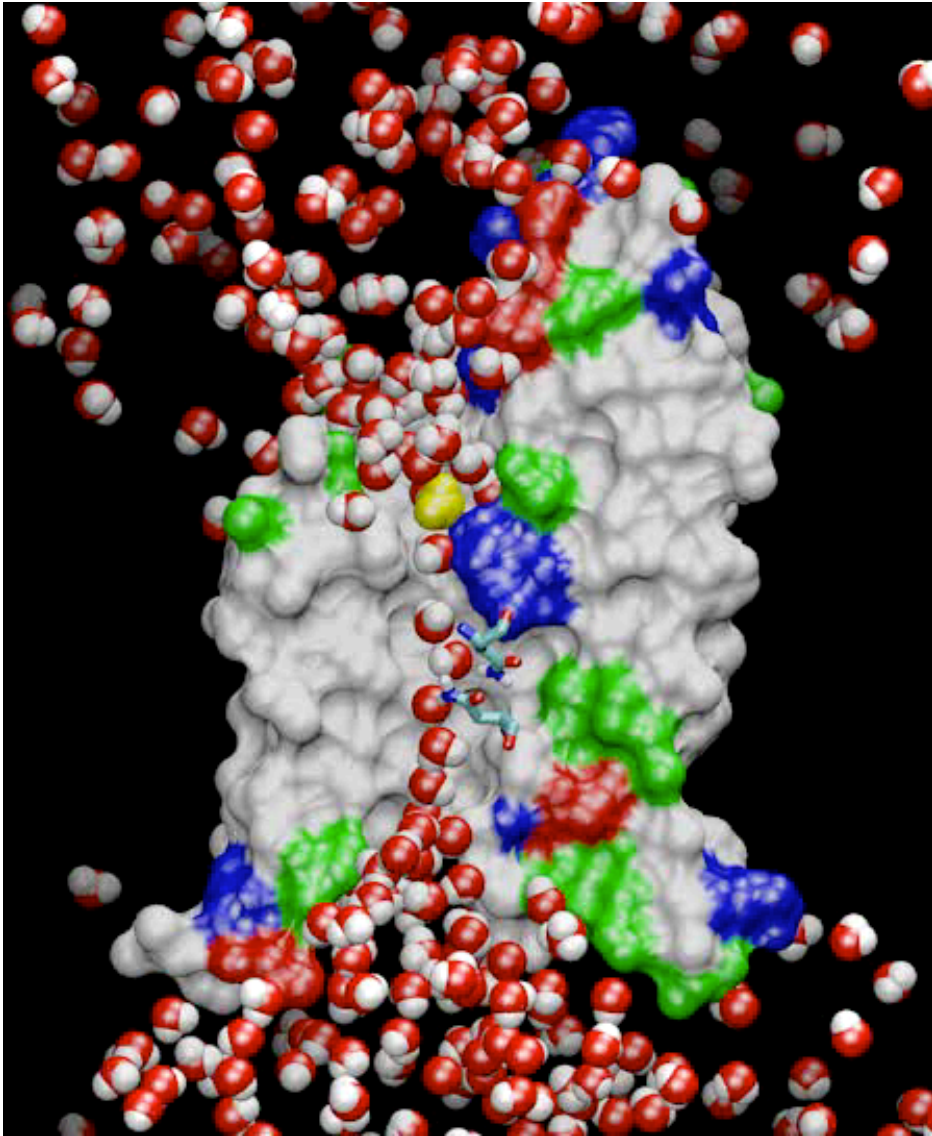


# The Molecular Dynamics Method



Water permeation through channels

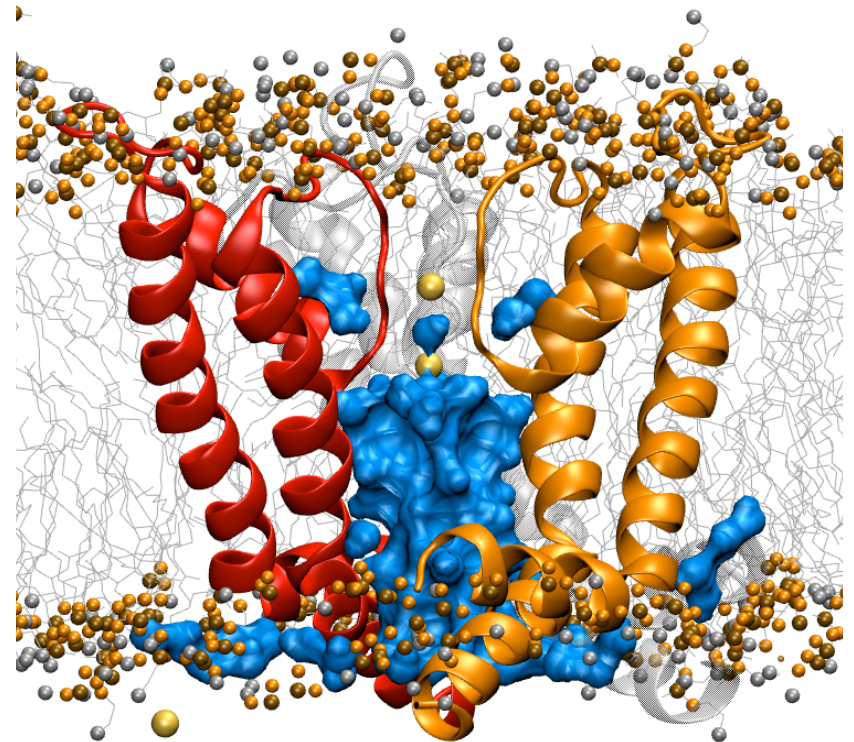
**Emad Tajkhorshid**

[csbmb.beckman.illinois.edu](mailto:csbmb.beckman.illinois.edu)

Department of Biochemistry,

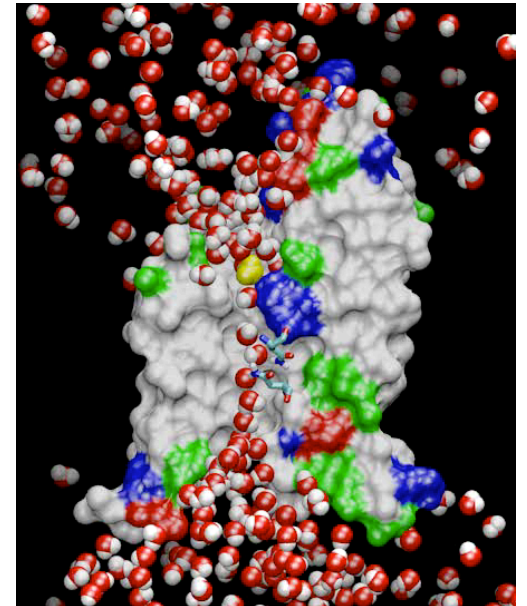
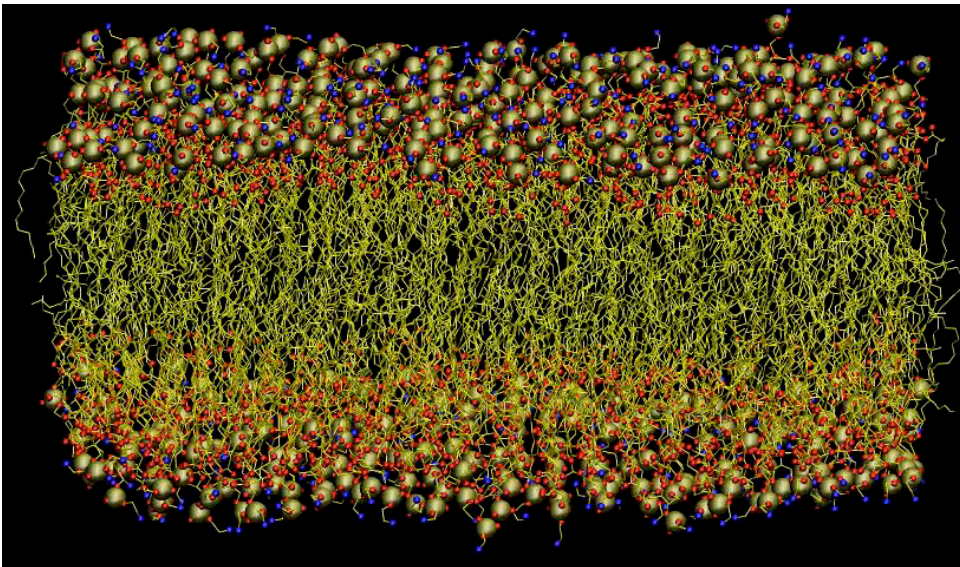
Center for Biophysics and Computational Biology,

Beckman Institute for Advanced Science and  
Technology

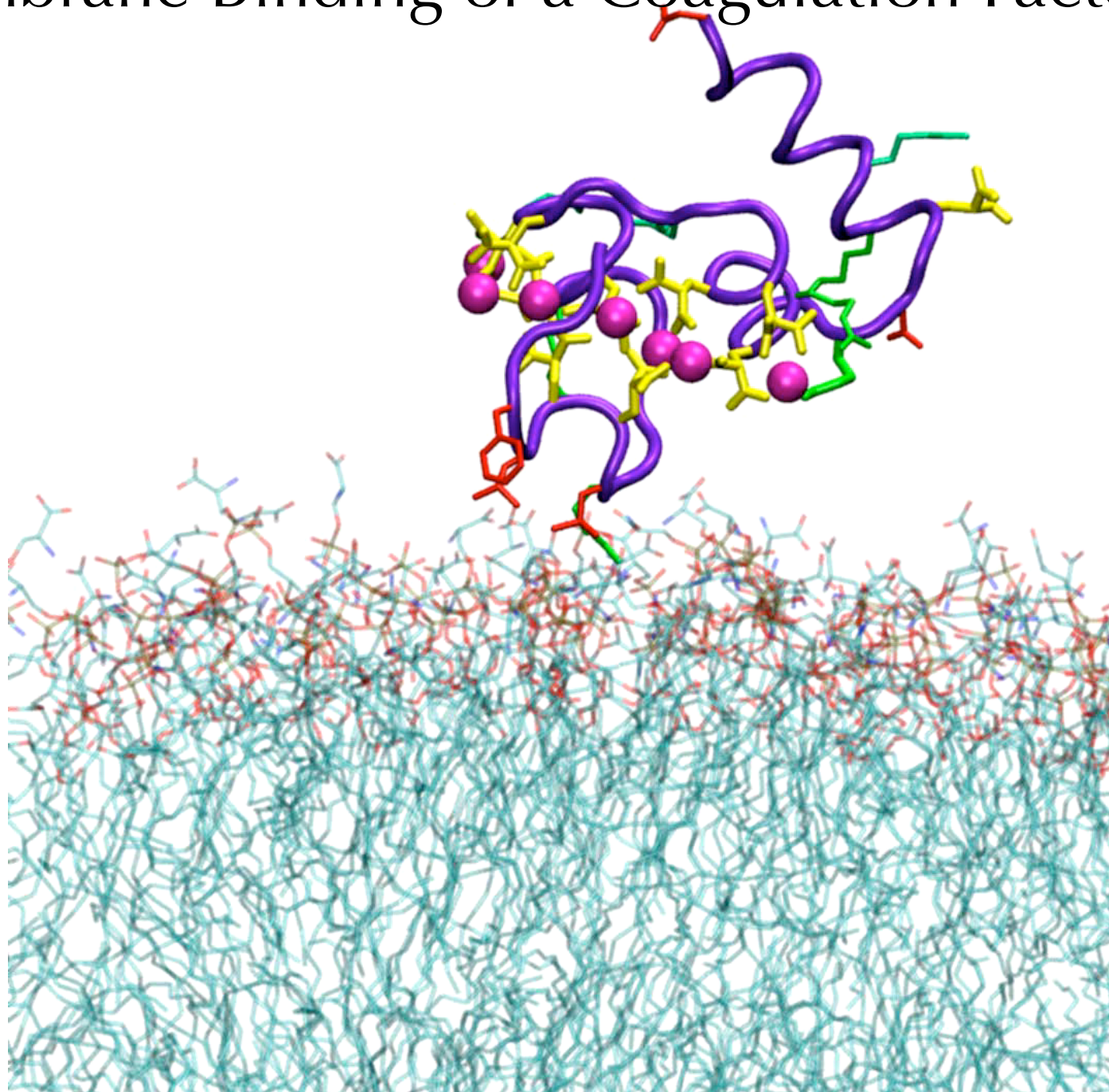


# When do we use MD?

- Generating a thermodynamic ensemble (Sampling / Statistic)
- Taking into account fluctuations/dynamics in interpretation of experimental observables
- Describing molecular processes + free energy
- Help with molecular modeling

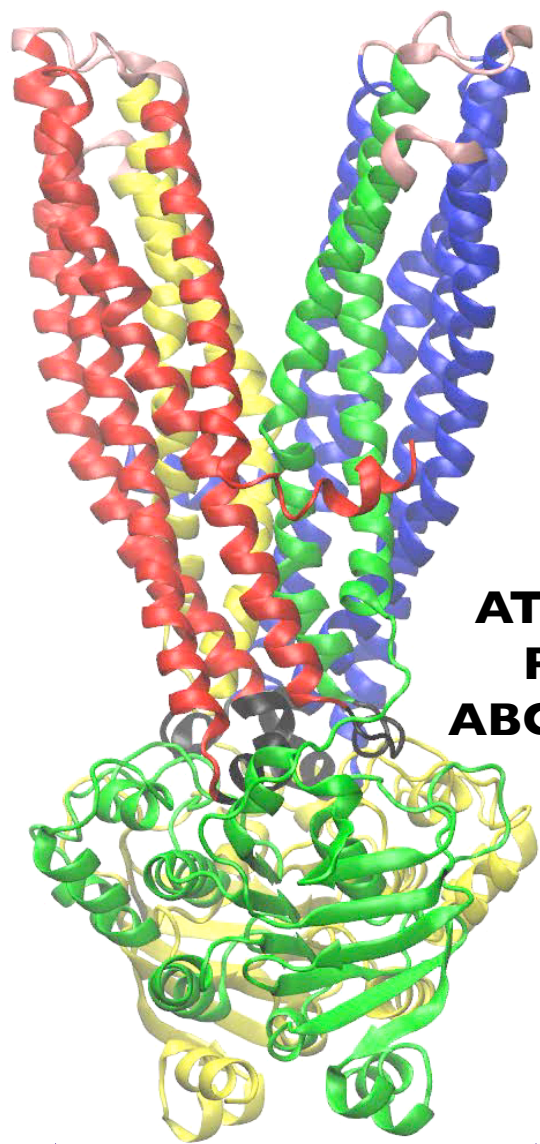


# Membrane Binding of a Coagulation Factor

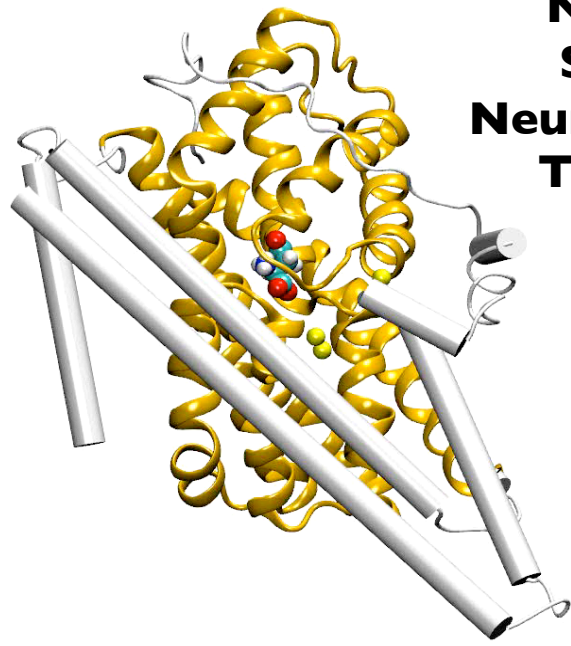


**COMPLEX**

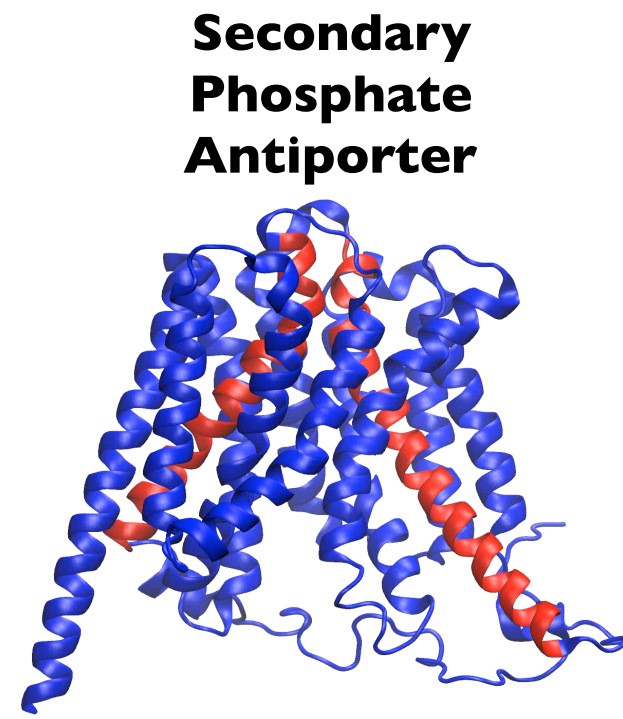
# Diverse Structural Transitions Involved



**ATP-Driven  
Primary  
ABC Exporter**



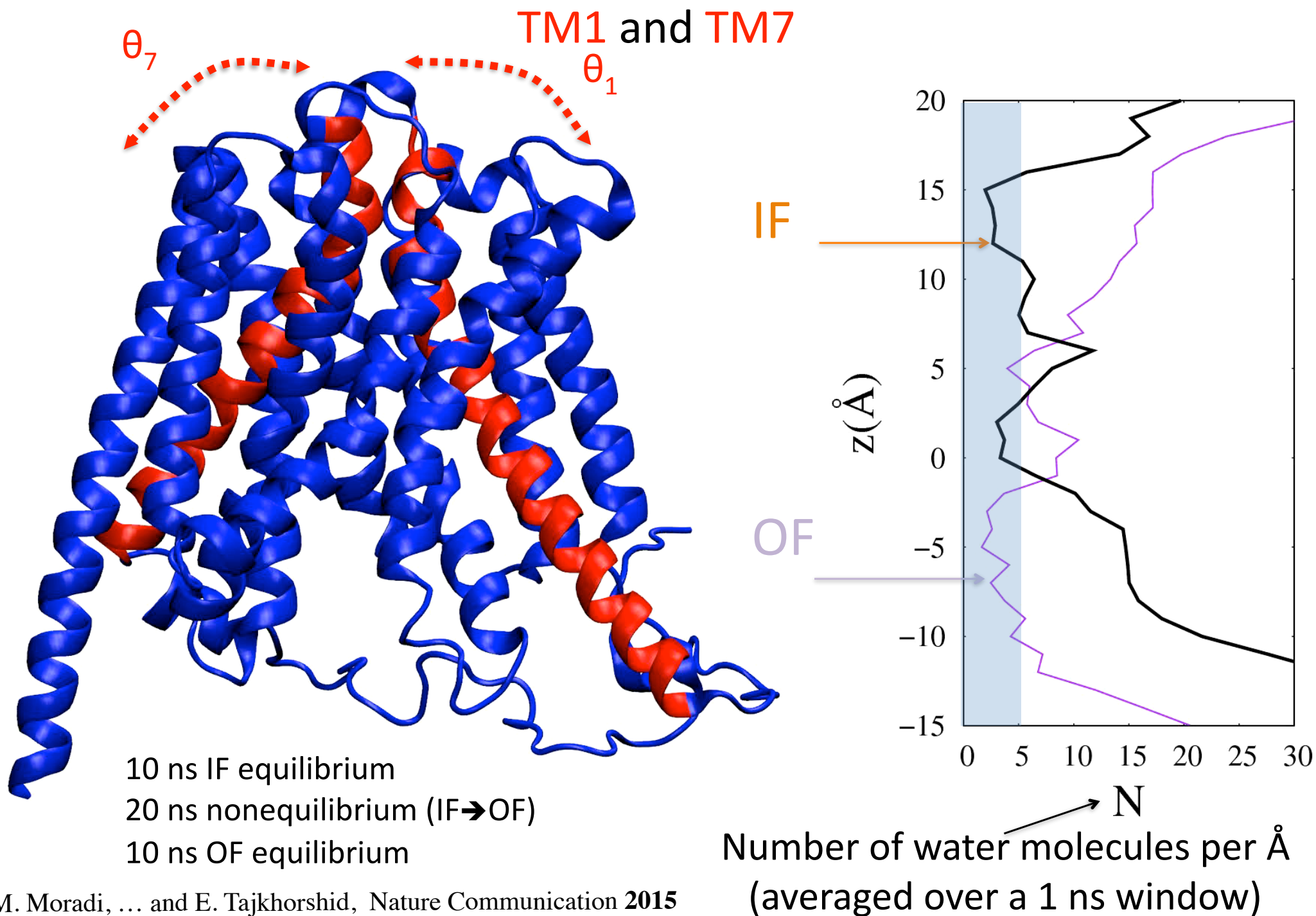
**Na-coupled  
Secondary  
Neurotransmitter  
Transporter**

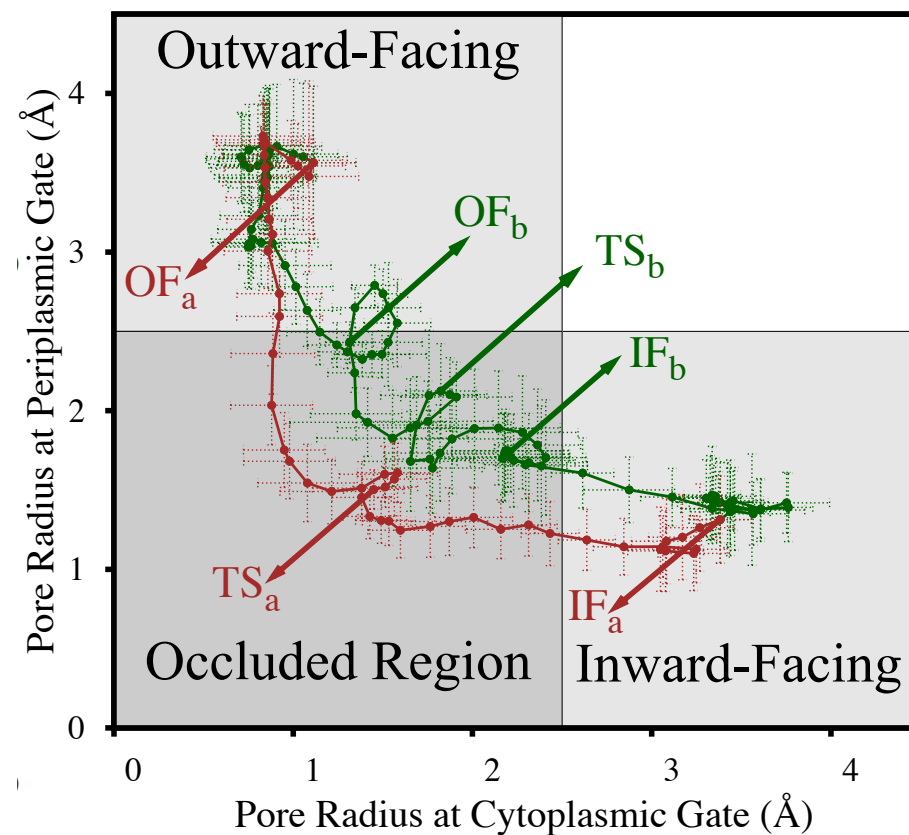
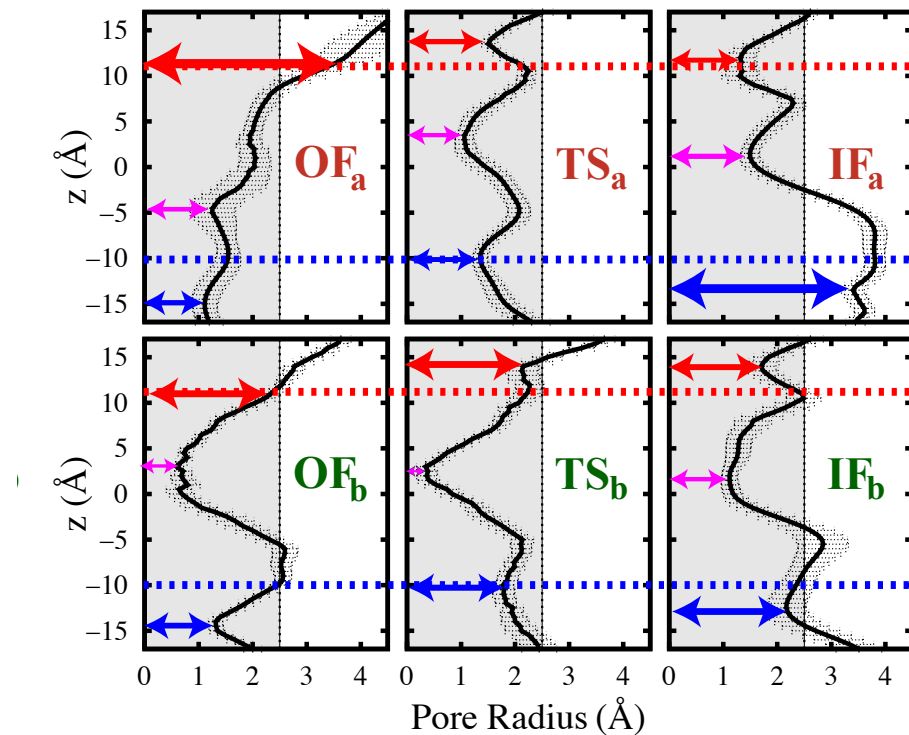
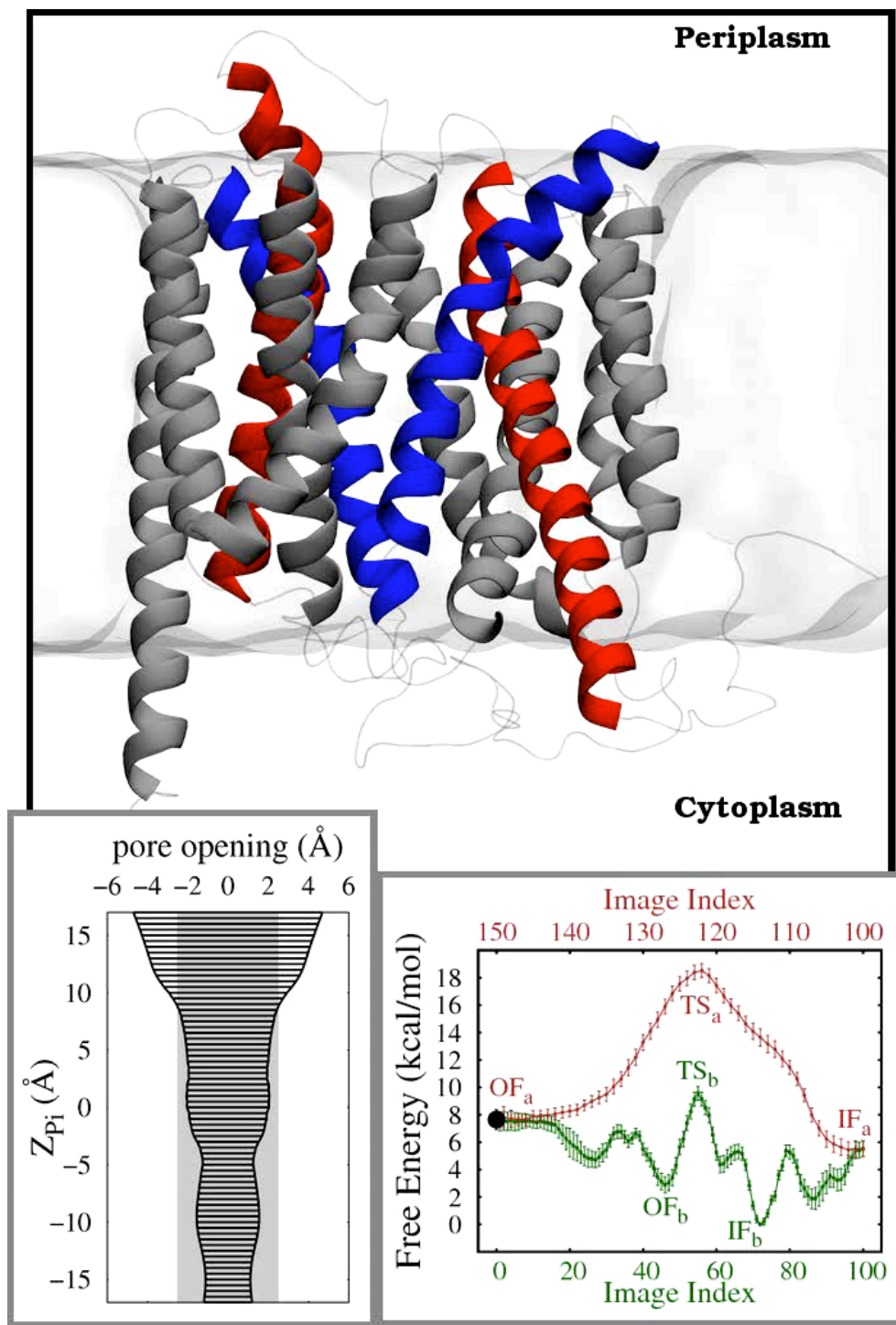


**Secondary  
Phosphate  
Antiporter**

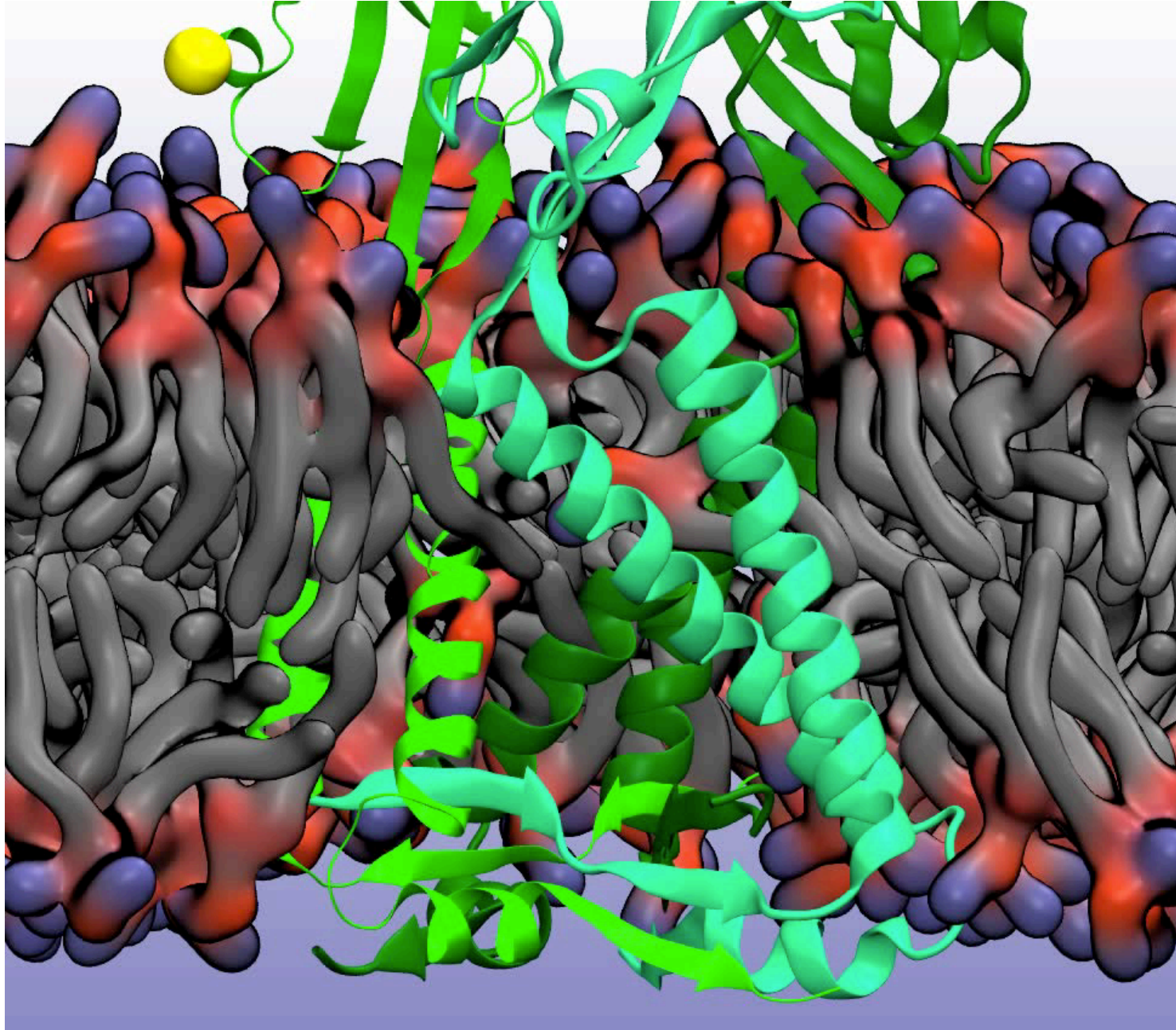
**NON-EQUILIBRIUM METHODS ARE REQUIRED.**

# IF $\leftrightarrow$ OF transition induced by imposing rotational change on helices

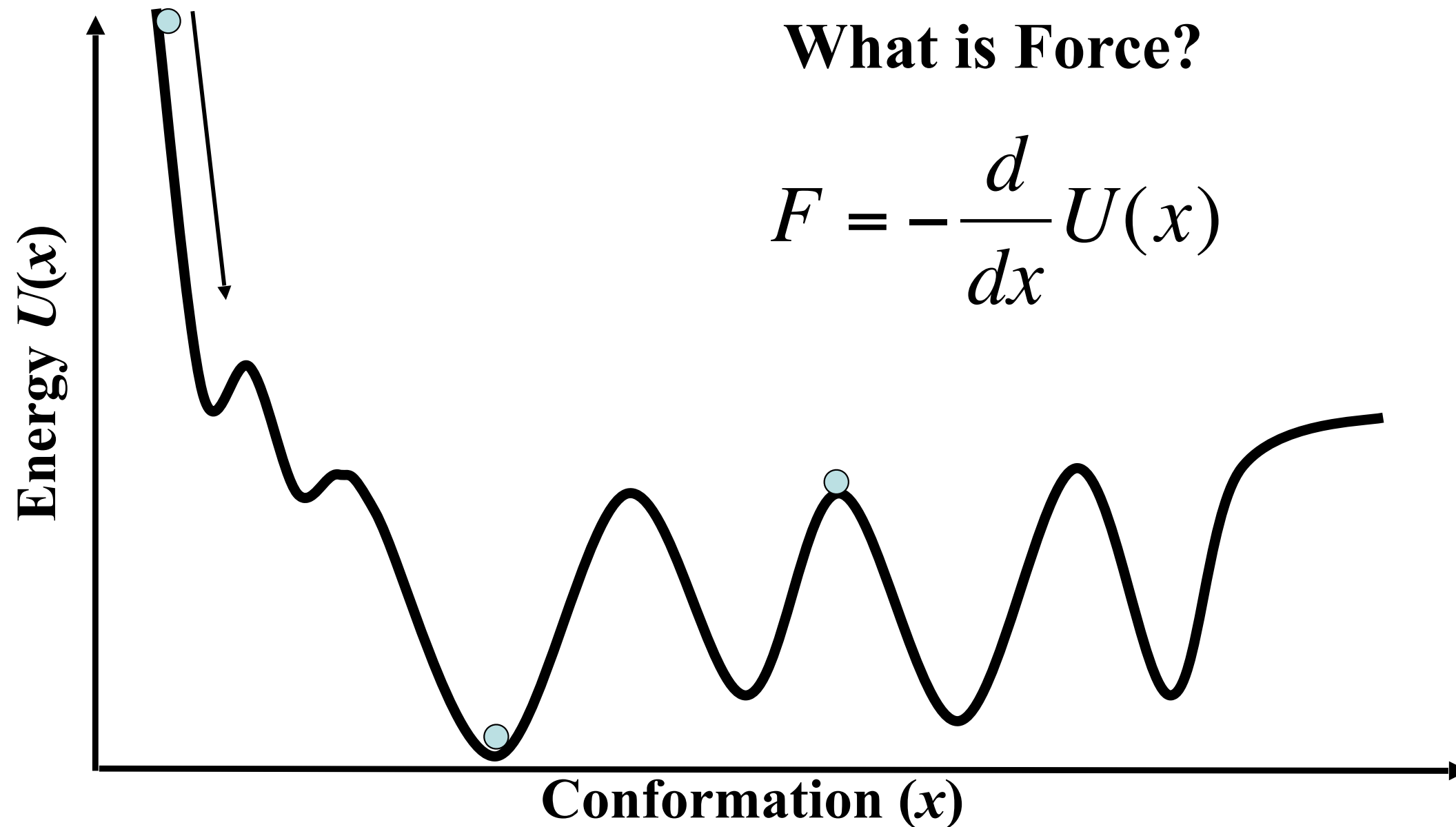




# Lipid Protein Interaction



# Potential Energy (hyper)Surface





# Classical Molecular Dynamics

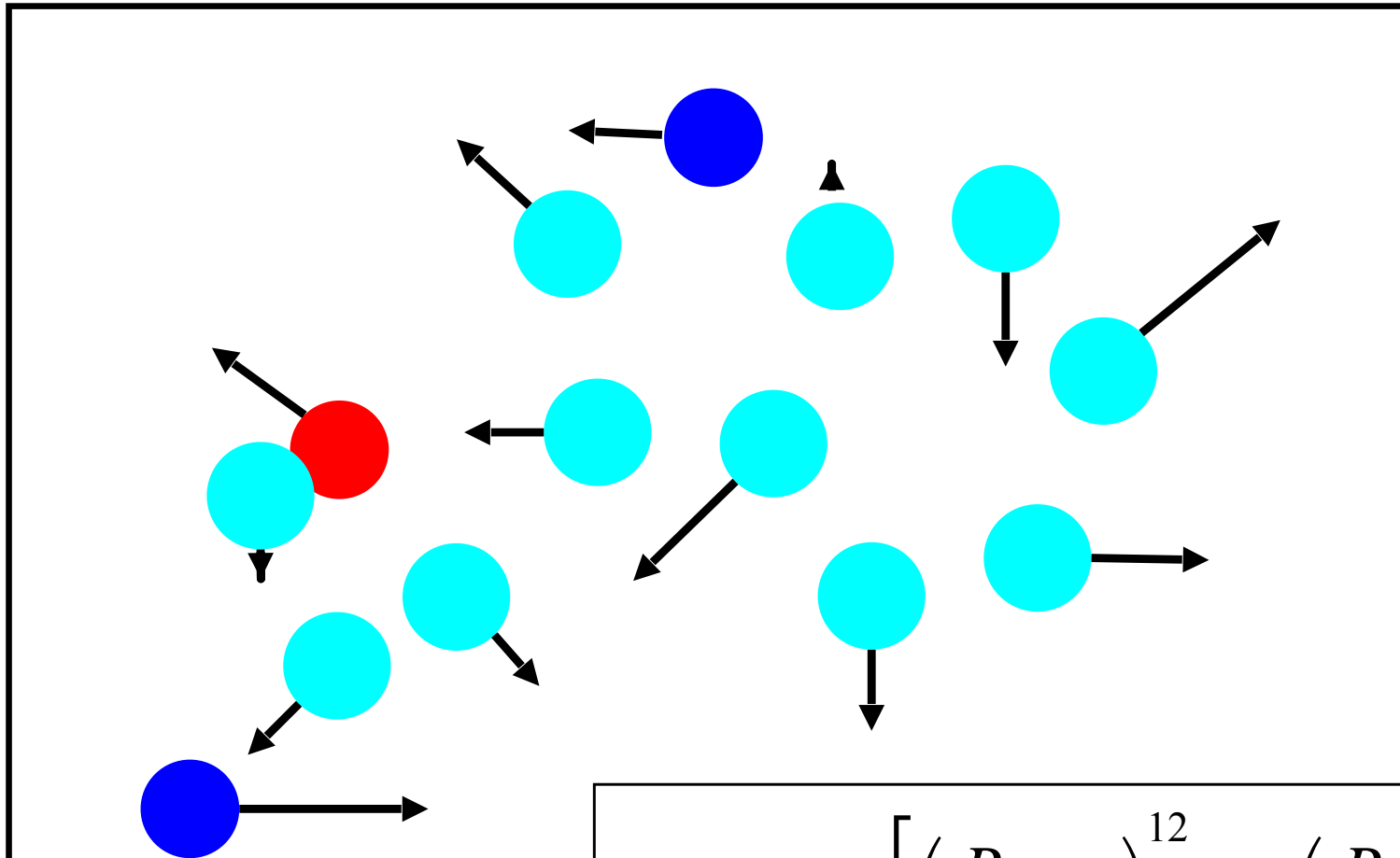
$$\mathbf{r}(t + \delta t) = \mathbf{r}(t) + \mathbf{v}(t)\delta t$$

$$\mathbf{v}(t + \delta t) = \mathbf{v}(t) + \mathbf{a}(t)\delta t$$

$$\mathbf{a}(t) = \mathbf{F}(t) / m$$

$$\mathbf{F} = -\frac{d}{dr}U(\mathbf{r})$$

# Classical Molecular Dynamics



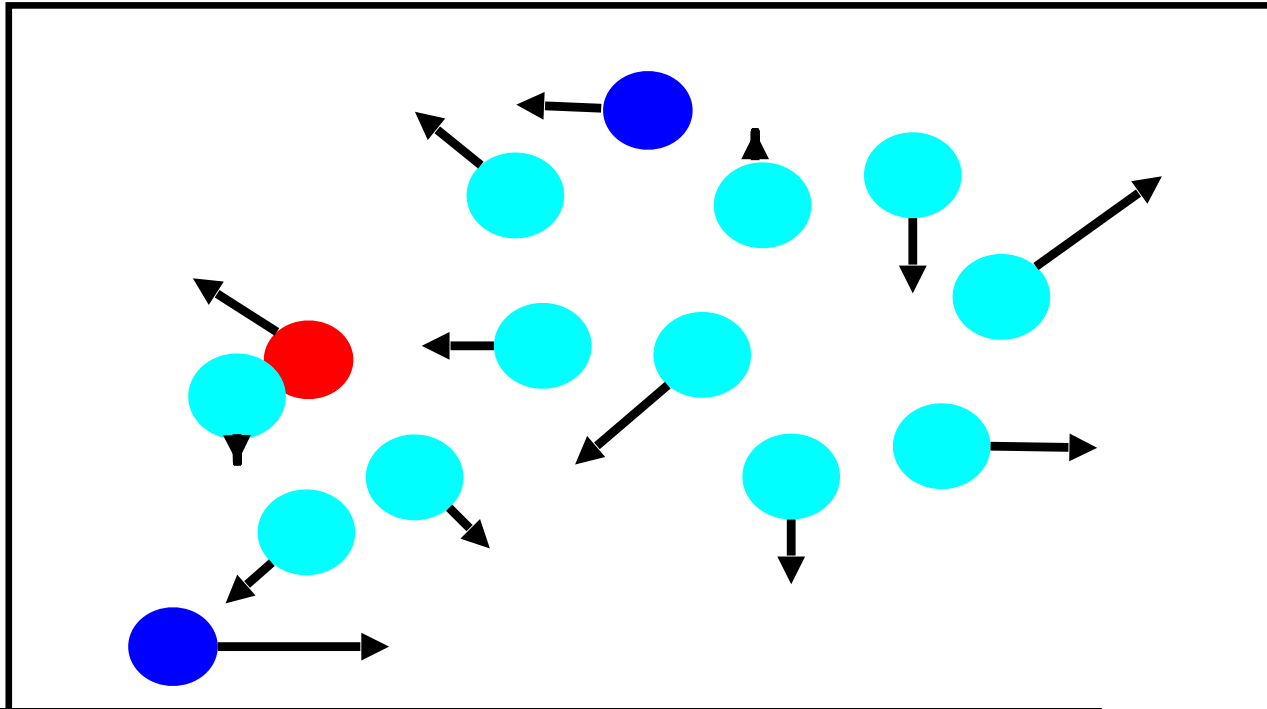
$$U(r) = \frac{1}{4\pi\epsilon_0} \frac{q_i q_j}{r_{ij}}$$

Coulomb interaction

$$U(r) = \epsilon_{ij} \left[ \left( \frac{R_{\min,ij}}{r_{ij}} \right)^{12} - 2 \left( \frac{R_{\min,ij}}{r_{ij}} \right)^6 \right]$$

van der Waals interaction

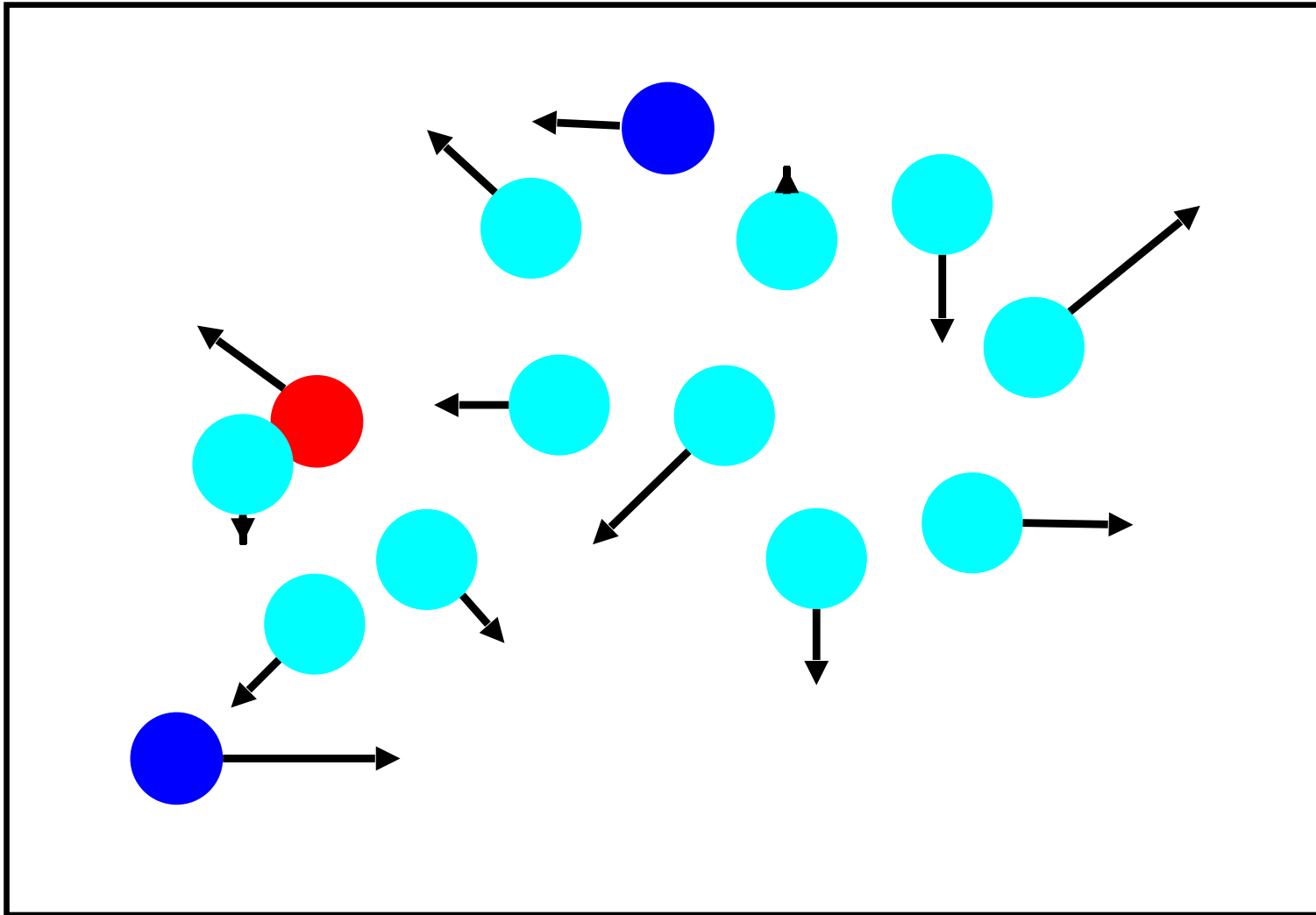
# Classical Molecular Dynamics



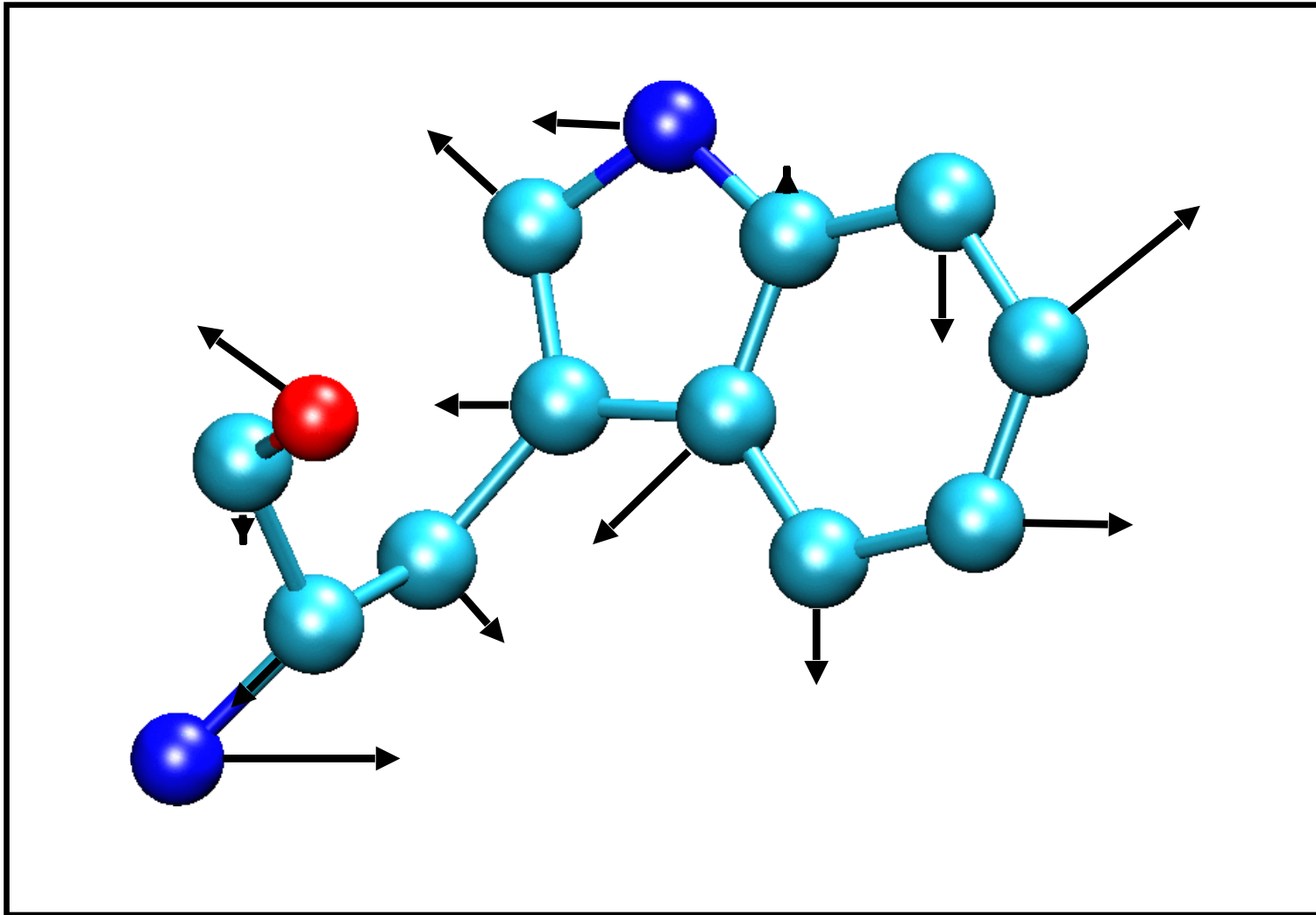
$$U(\mathbf{r}) = \frac{1}{4\pi\epsilon_0} \frac{q_i q_j}{r_{ij}} + \epsilon_{ij} \left[ \left( \frac{R_{\min,ij}}{r_{ij}} \right)^{12} - 2 \left( \frac{R_{\min,ij}}{r_{ij}} \right)^6 \right]$$

$$\mathbf{F}(\mathbf{r}) = \left( -\frac{1}{4\pi\epsilon_0} \frac{q_i q_j}{r_{ij}^2} - 12 \frac{\epsilon_{ij}}{|r_{ij}|} \left[ \left( \frac{R_{\min,ij}}{r_{ij}} \right)^{12} - \left( \frac{R_{\min,ij}}{r_{ij}} \right)^6 \right] \right) \hat{\mathbf{r}}_{ij}$$

# Classical Molecular Dynamics



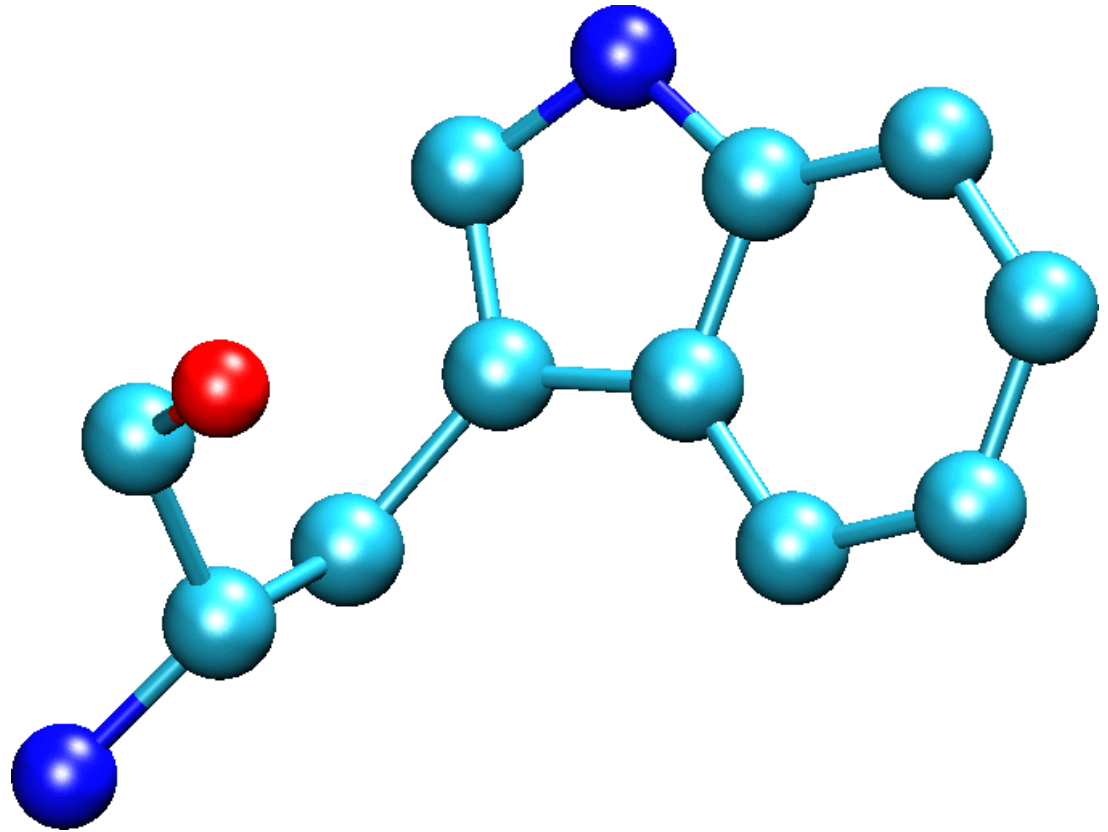
# Classical Molecular Dynamics



Bond definitions, atom types, atom names, parameters, ....

# What is a Force Field?

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 electrostatic interactions between atoms, one uses a **force field**.

The **force field** is a collection of equations and associated constants designed to reproduce molecular geometry and selected properties of tested structures.

# Energy Functions

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

$U_{\text{bond}}$  = oscillations about the equilibrium bond length

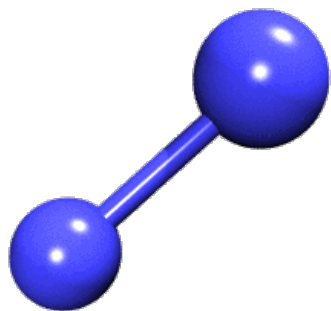
$U_{\text{angle}}$  = oscillations of 3 atoms about an equilibrium bond angle

$U_{\text{dihedral}}$  = torsional rotation of 4 atoms about a central bond

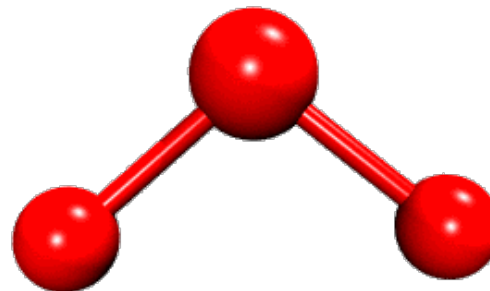
$U_{\text{nonbond}}$  = non-bonded energy terms (electrostatics and Lenard-Jones)

# Energy Terms Described in the CHARMm Force Field

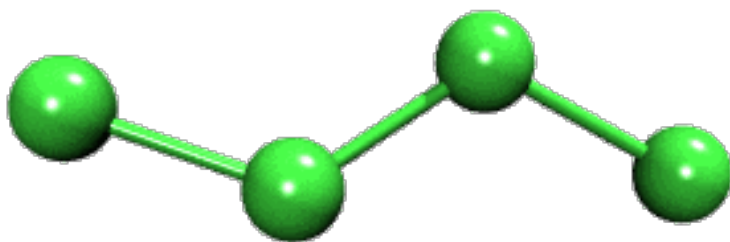
Bond



Angle



Dihedral



Improper

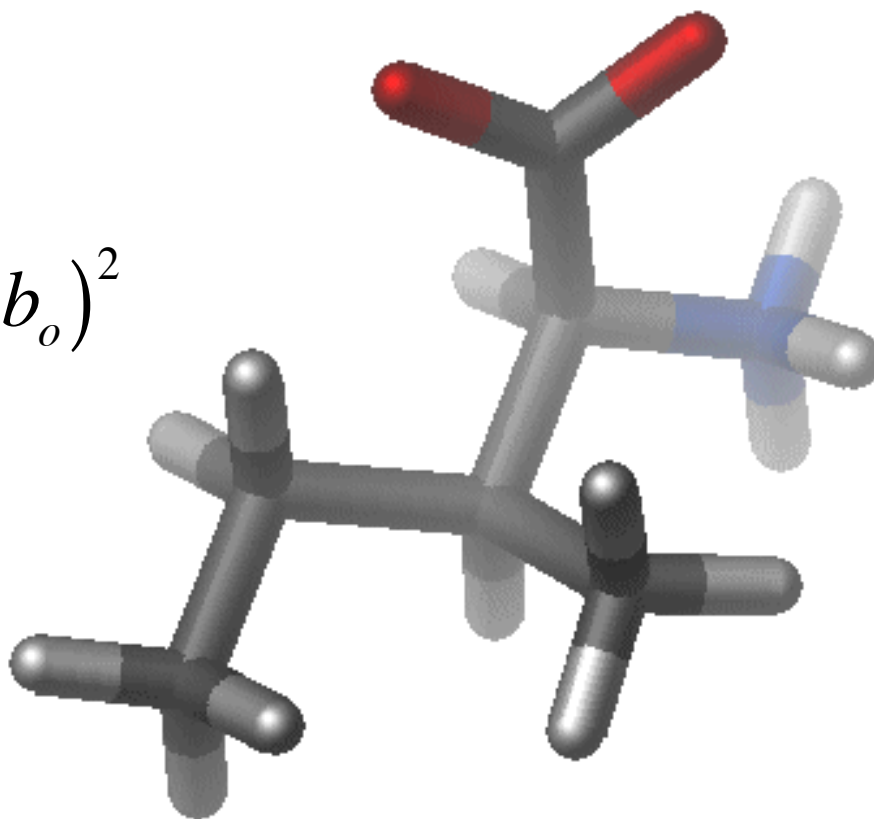




# Interactions between bonded atoms

$$V_{angle} = K_{\theta} (\theta - \theta_o)^2$$

$$V_{bond} = K_b (b - b_o)^2$$



$$V_{dihedral} = K_{\phi} (1 + \cos(n\phi - \delta))$$

# Classical Dynamics

*F=ma at 300K*

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

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 2<sup>nd</sup>-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.

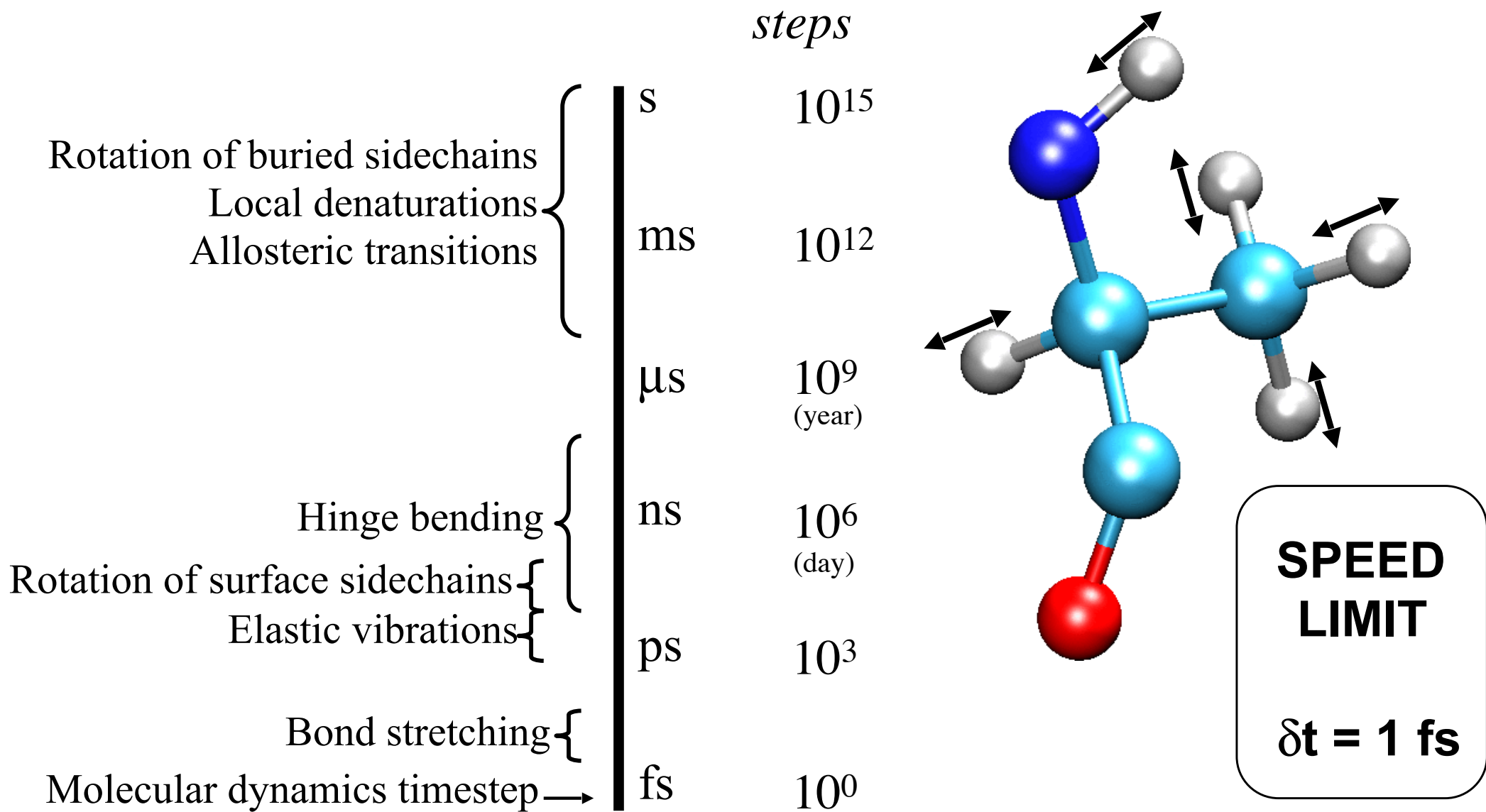
Maintain appropriate temperature by adjusting velocities.

# Langevin Dynamics

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

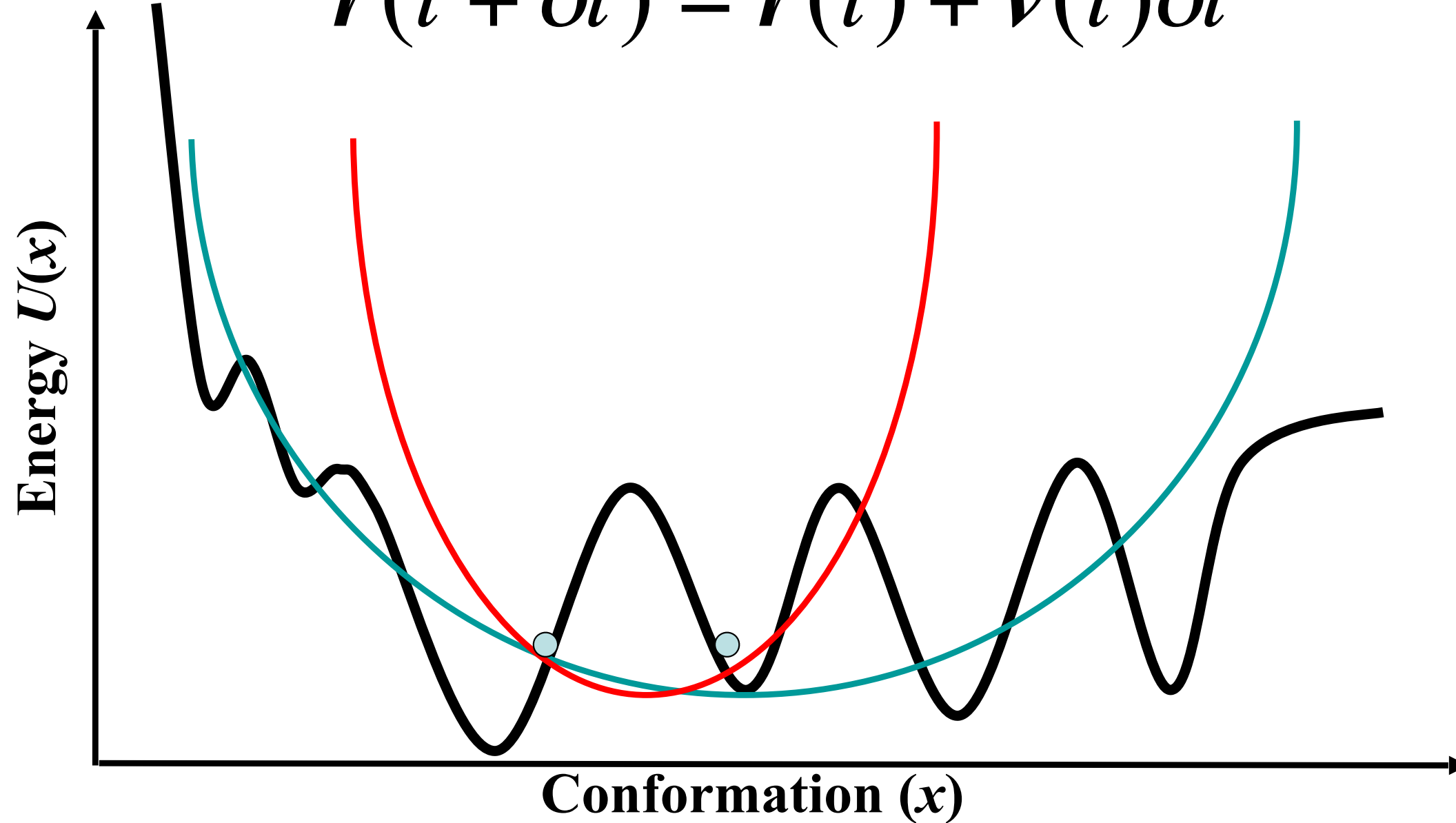
$$m \ddot{\vec{r}} = \vec{F}(\vec{r}) - \gamma m \dot{\vec{r}} + \vec{R}(t)$$

# The most serious bottleneck



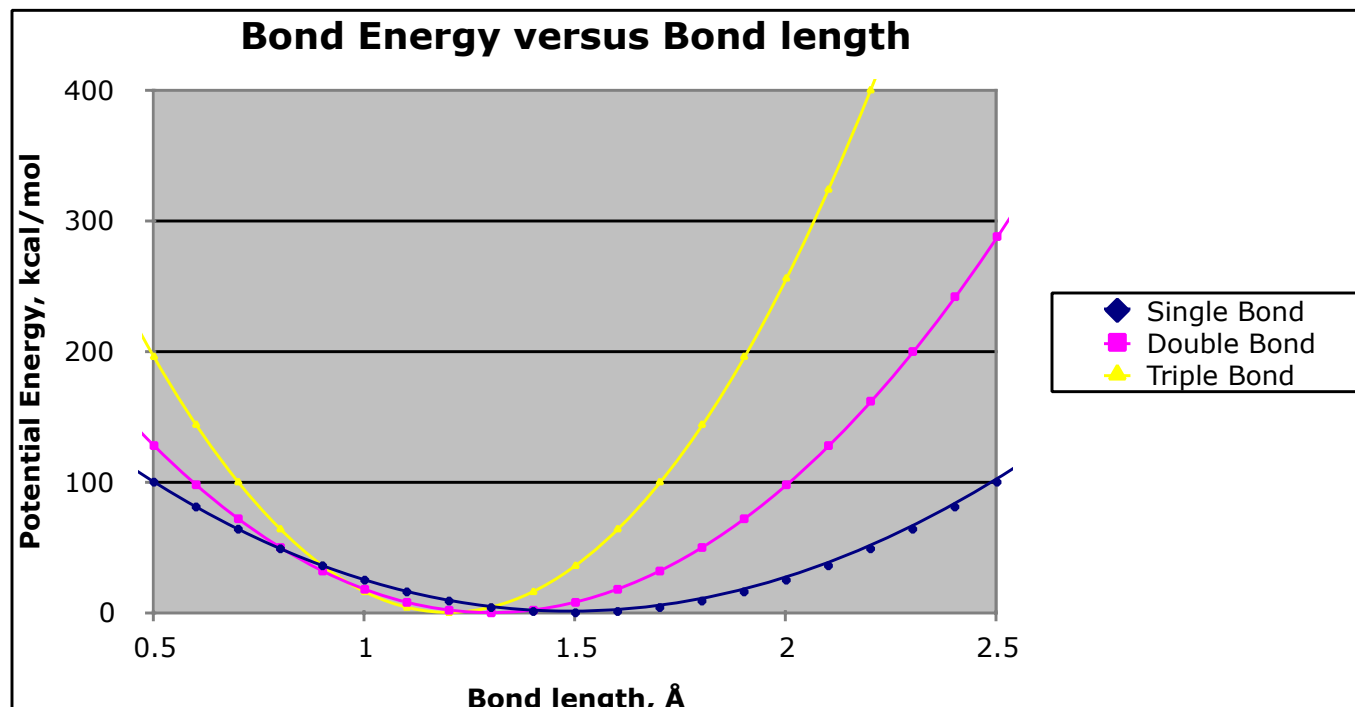
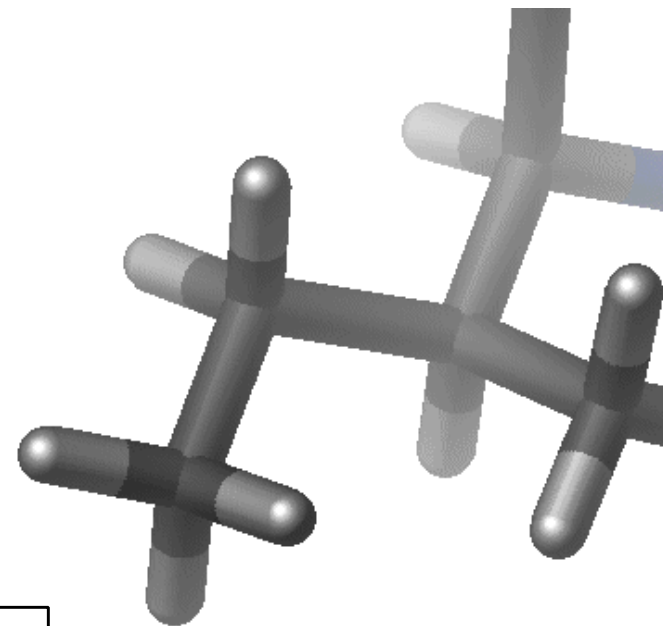
# Potential Energy (hyper)Surface

$$\mathbf{r}(t + \delta t) = \mathbf{r}(t) + \mathbf{v}(t)\delta t$$



$$V_{bond} = K_b (b - b_o)^2$$

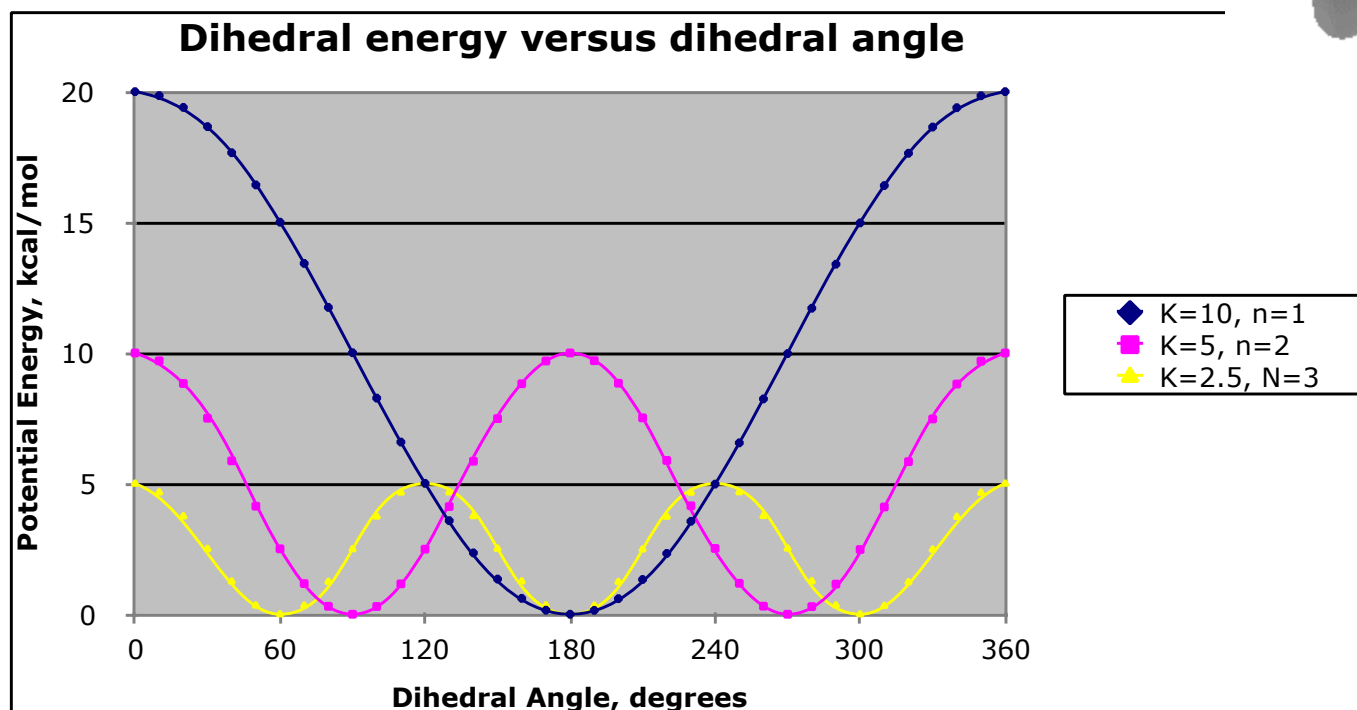
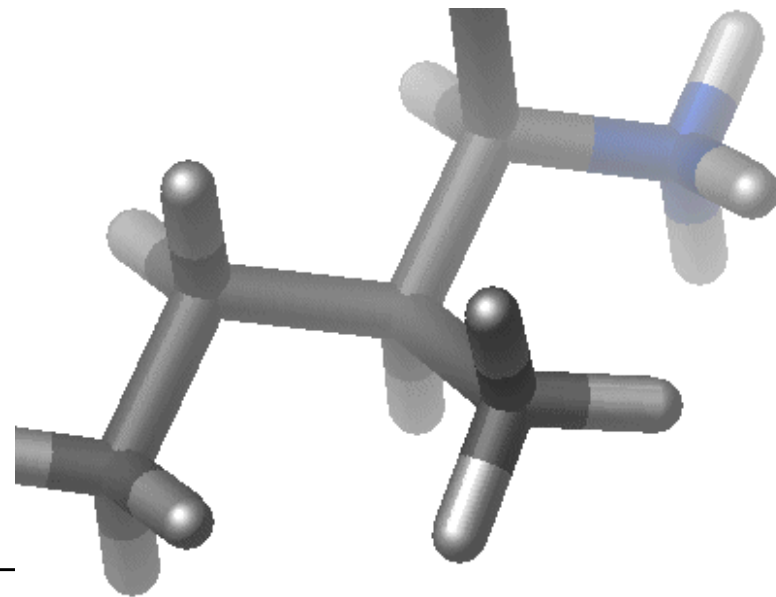
Chemical type	$K_{bond}$	$b_o$
C-C	100 kcal/mole/Å <sup>2</sup>	1.5 Å
C=C	200 kcal/mole/Å <sup>2</sup>	1.3 Å
C≡C	400 kcal/mole/Å <sup>2</sup>	1.2 Å



*Bond angles* and *improper* terms have similar quadratic forms, but with softer spring constants. The force constants can be obtained from vibrational analysis of the molecule (experimentally or theoretically).

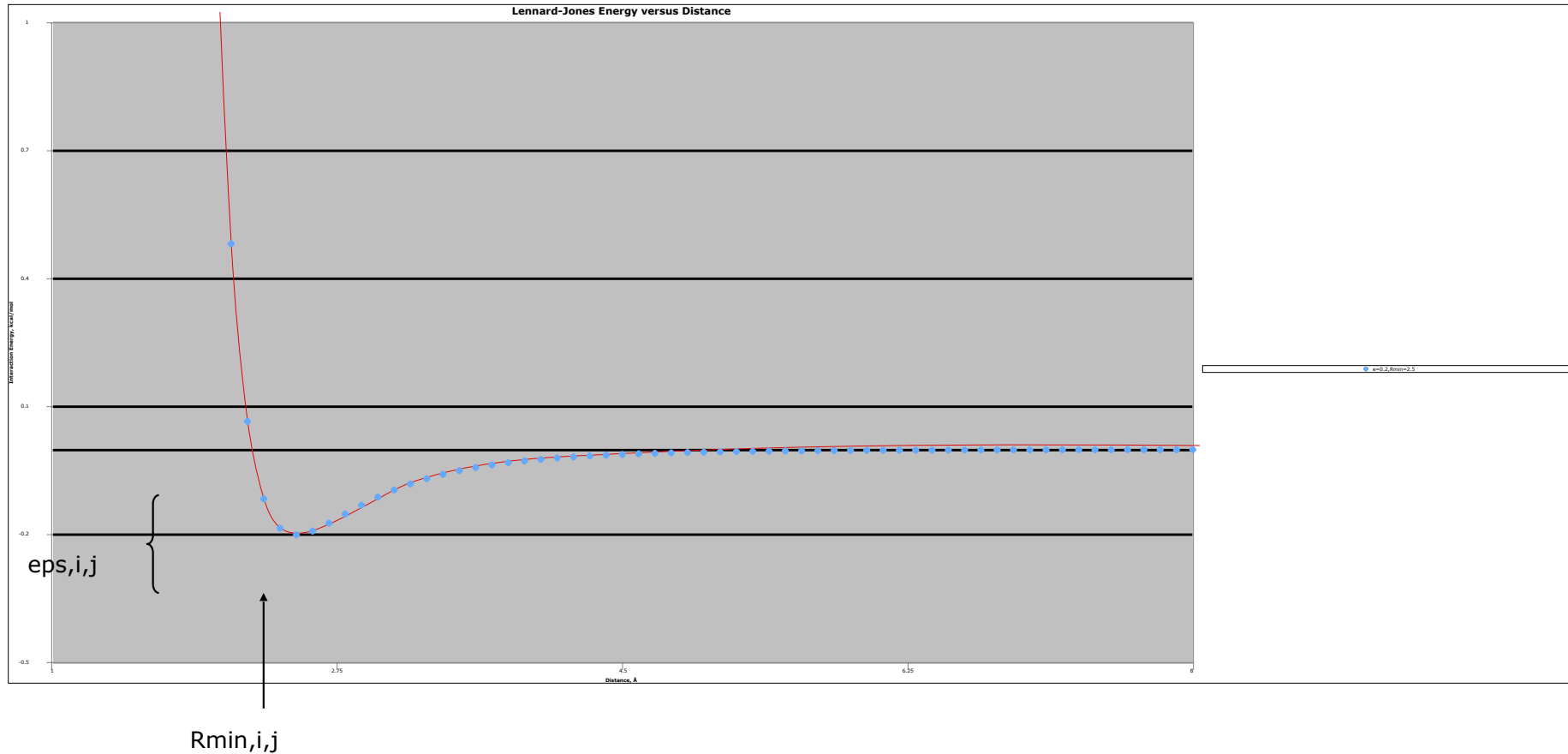
# Dihedral Potential

$$V_{dihedral} = K_{\phi} (1 + \cos(n\phi - \delta))$$



$$\delta = 0^\circ$$

# van der Waals interaction

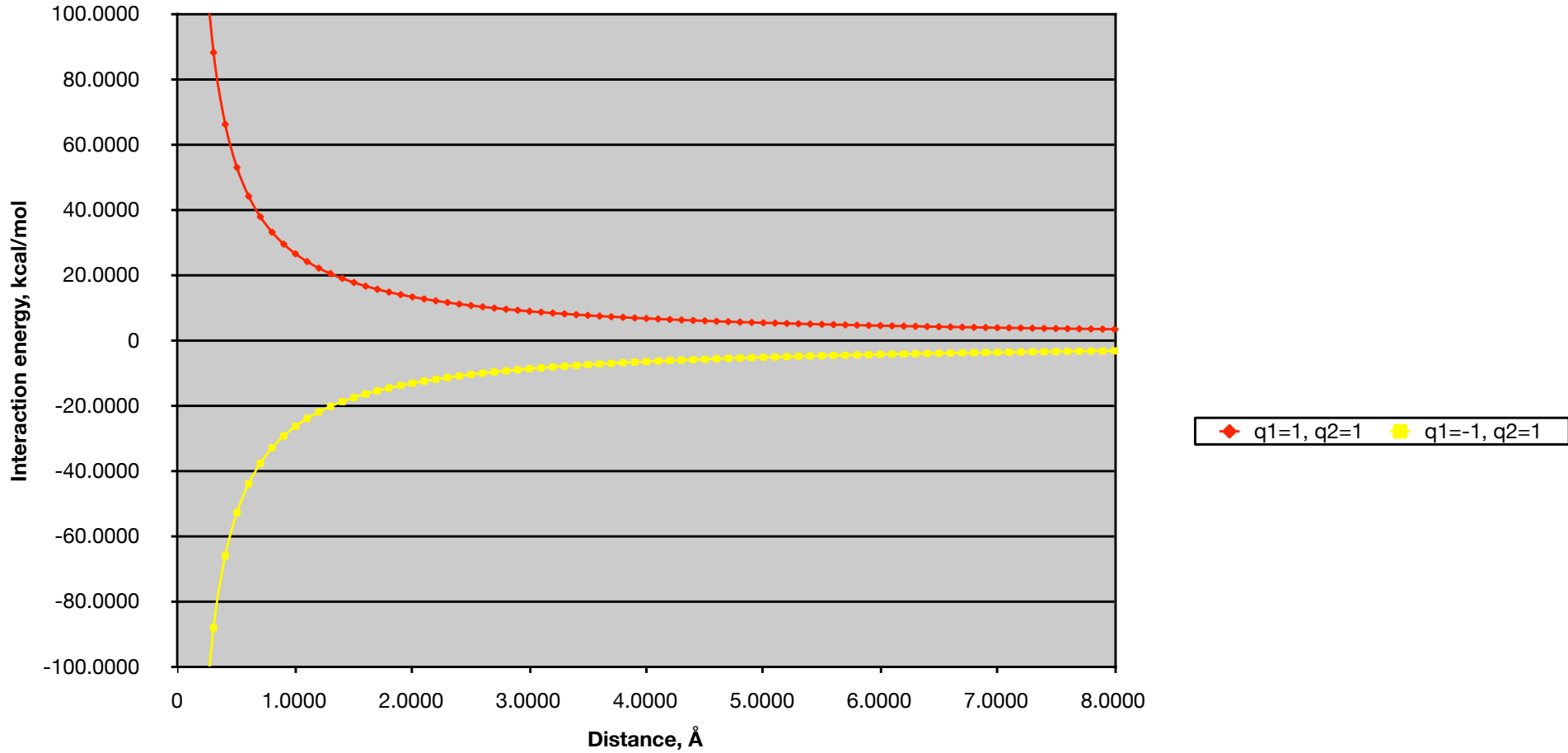


$$\epsilon_{ij} \left[ \left( \frac{R_{min,ij}}{r_{ij}} \right)^{12} - 2 \left( \frac{R_{min,ij}}{r_{ij}} \right)^6 \right]$$

Short range



### Electrostatic Energy versus Distance



Note that the effect is long range.

From MacKerell

# 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

# Preparing Your System for MD Solvation

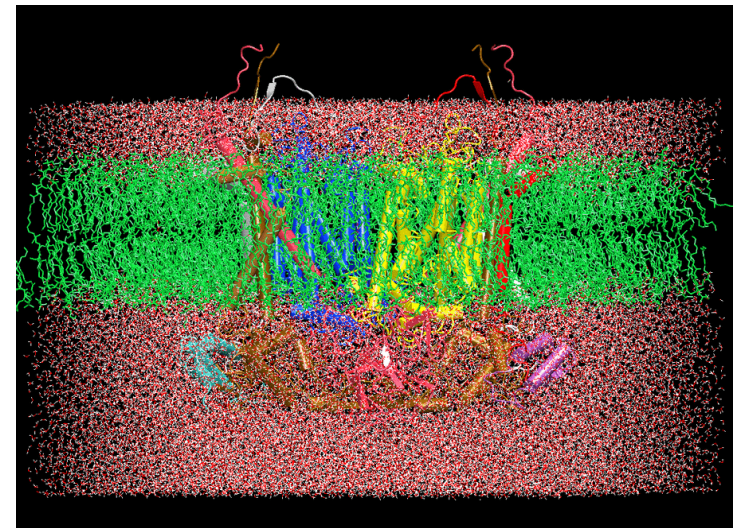
Biological activity is the result of interactions between molecules and occurs at the interfaces between molecules (protein-protein, protein-DNA, protein-solvent, DNA-solvent, etc).

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



# Classical Molecular Dynamics

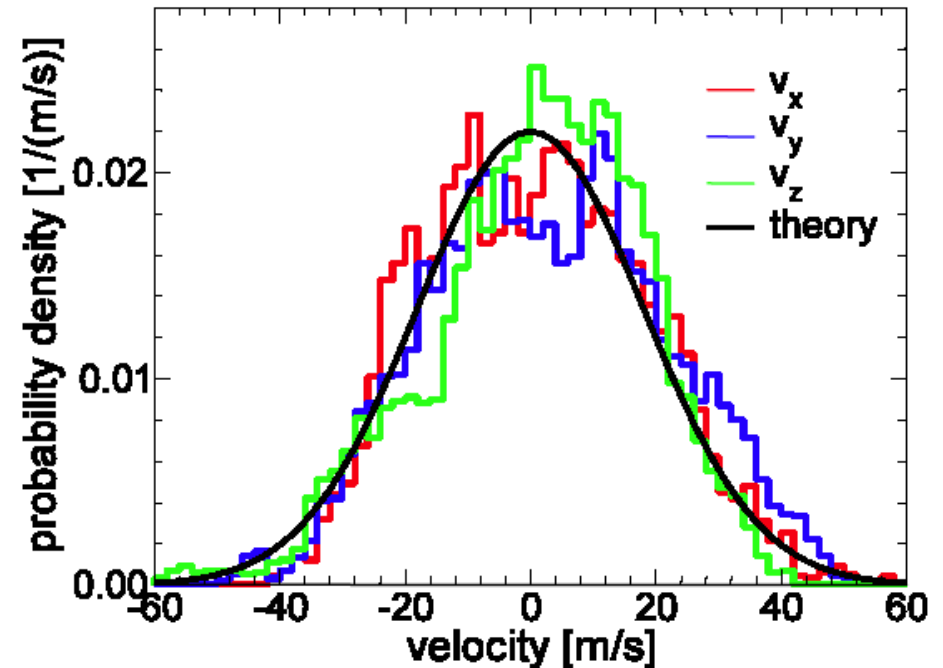
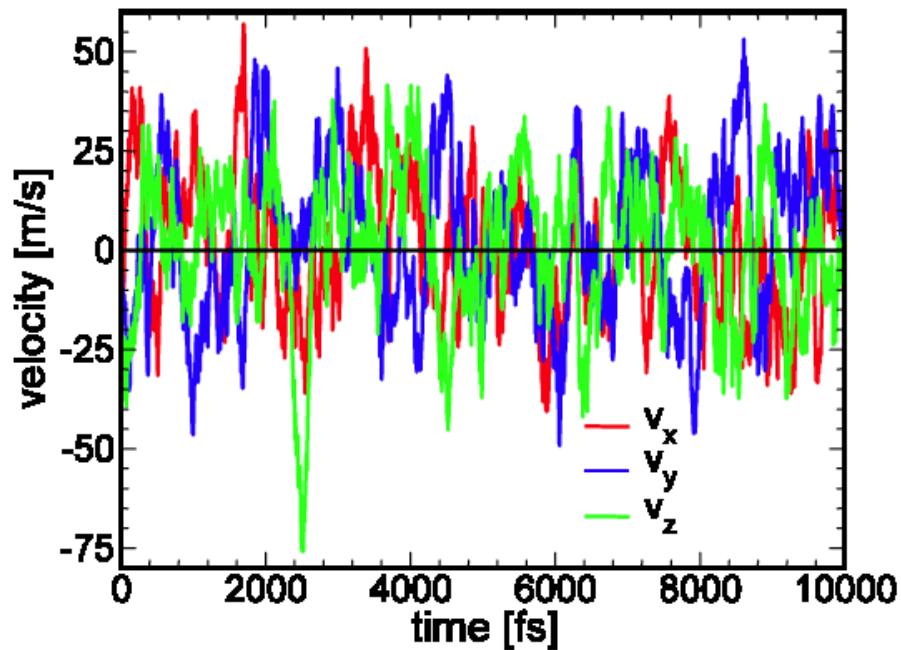
$$\mathbf{r}(t + \delta t) = \mathbf{r}(t) + \mathbf{v}(t)\delta t$$

$$\mathbf{v}(t + \delta t) = \mathbf{v}(t) + \mathbf{a}(t)\delta t$$

$$\mathbf{a}(t) = \mathbf{F}(t) / m$$

$$\mathbf{F} = -\frac{d}{dr}U(\mathbf{r})$$

# Maxwell Distribution of Atomic Velocities



$$p(v_\sigma) = \sqrt{\frac{m}{2\pi k_B T}} \exp\left[-\frac{mv_\sigma^2}{2k_B T}\right]$$

$$\sigma = x, y, z$$