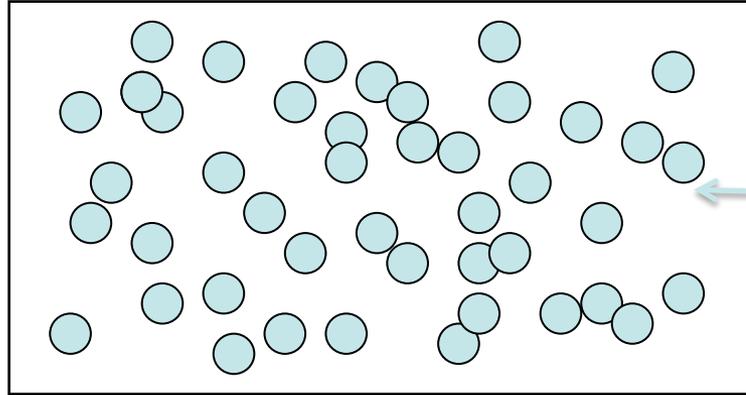


The Very Basics of Molecular Dynamics



What is Molecular Dynamics?

$V(\{R(t)\})$



?

$$F(t) = M \ddot{R}(t) = -\nabla V(\{R(t)\})$$

?

Numerical Integration (?)

Trajectory: Positions and Velocities over time

?

Ingredients to conduct an MD simulation

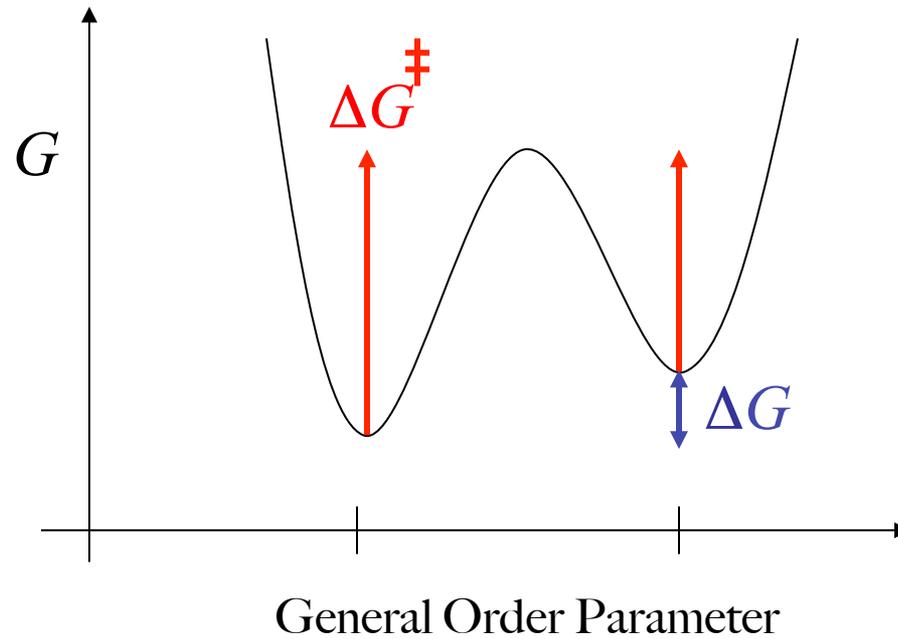
- 1) Must need a way to integrate the differential equation above to get positions and velocities in time
- 2) Need a potential to get the forces
- 3) Must generate initial velocities and/or thermostat or keep the system at a particular

Classical Statistical Mechanics, Thermodynamics, Classical Mechanics

What we can learn from MD simulations?

- Atomic and molecule distribution functions
- Phase diagrams
- Transport coefficients (viscosity, diffusion, thermal conductivity,...)
- Solvation energy and free energy
- Binding energy and free energy
- *Microscopic insight*

The free energy (vs potential energy) landscape



ΔG^\ddagger activation free energy \rightarrow rate

ΔG free energy difference between isomers \rightarrow equilibrium constant

$$k_{rate} \propto \exp\left(-\frac{\Delta G_{act}}{k_B T}\right)$$

Sampling problems in Molecular Dynamics

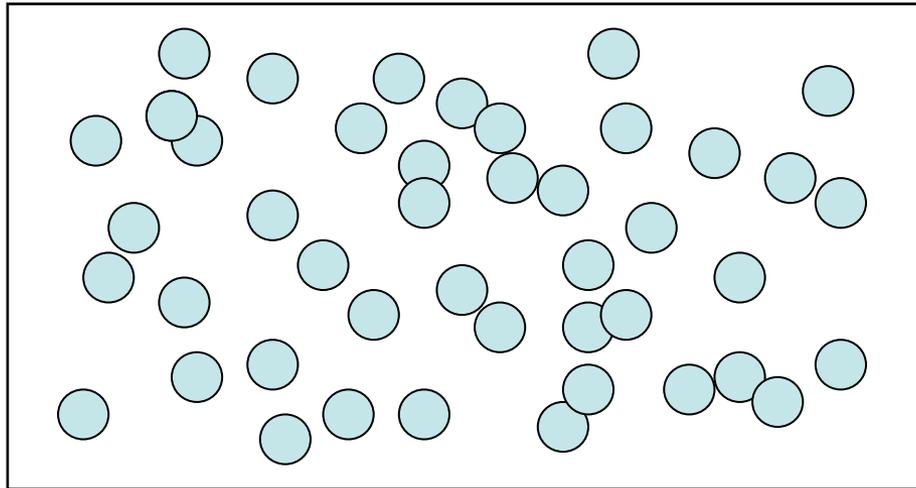
Static properties

- Monte Carlo
- Molecular dynamics (particles have kinetic energy)

Dynamic properties

- Molecular dynamics

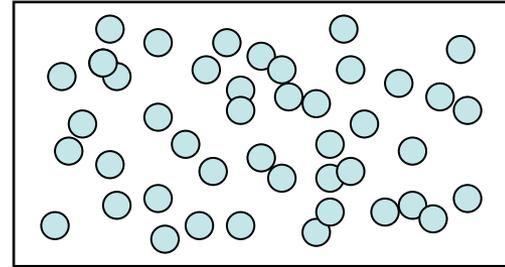
Main ideas (I):



Many-particle systems rapidly lose memory of their initial conditions, and reach *equilibrium*, characterized by a handful of variables (T, P, N, V, \dots)

Main ideas (2):

isolated, energy-conserving system:



At equilibrium, every combination of momenta and positions

$$\mathbf{p}_1, \mathbf{p}_2, \mathbf{p}_3, \dots, \mathbf{p}_N, \mathbf{r}_1, \mathbf{r}_2, \mathbf{r}_3, \dots, \mathbf{r}_N$$

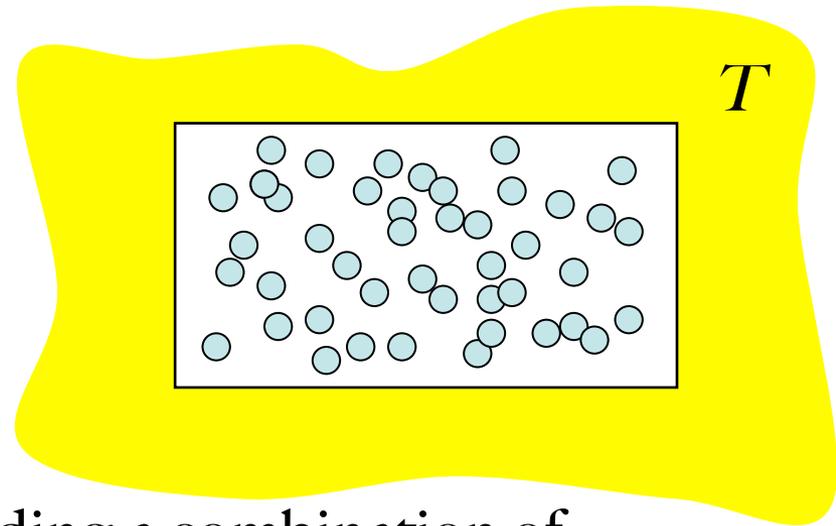
allowed by energy conservation

$$\frac{\mathbf{p}_1^2}{2m_1} + \frac{\mathbf{p}_2^2}{2m_2} + \frac{\mathbf{p}_3^2}{2m_3} + \dots + \frac{\mathbf{p}_N^2}{2m_N} + V(\mathbf{r}_1, \mathbf{r}_2, \mathbf{r}_3, \dots, \mathbf{r}_N) = E$$

is equally likely.

Main ideas (3):

system in contact with heat bath
at temperature T .



At equilibrium, probability of finding a combination of
momenta and positions

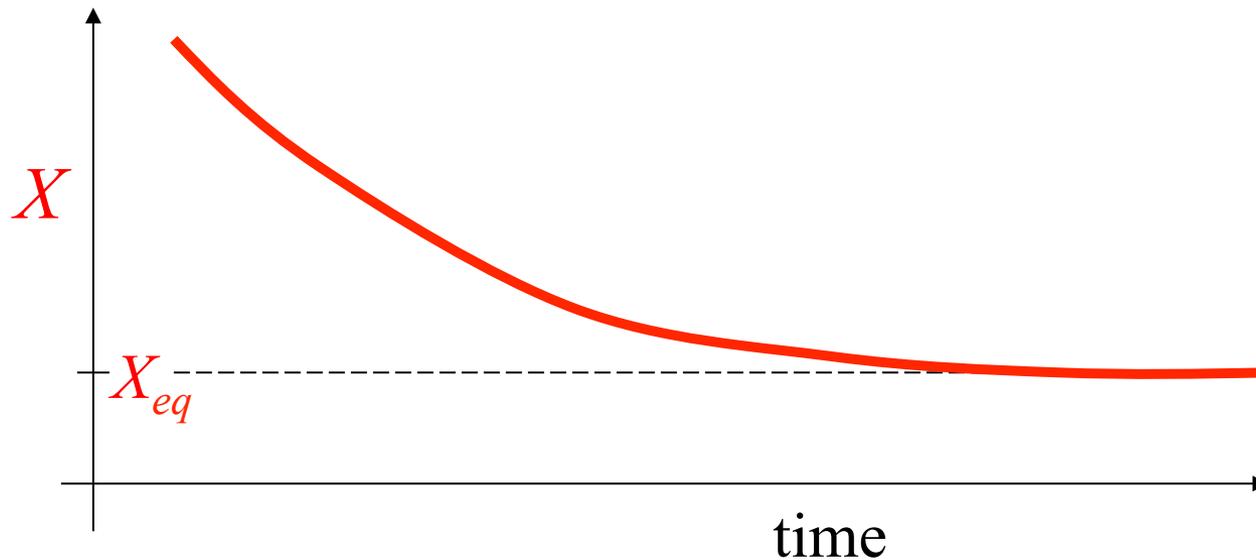
$$\mathbf{p}_1, \mathbf{p}_2, \mathbf{p}_3, \dots, \mathbf{p}_N, \mathbf{r}_1, \mathbf{r}_2, \mathbf{r}_3, \dots, \mathbf{r}_N$$

is proportional to Boltzmann factor,

$$P(\mathbf{p}_1, \mathbf{p}_2, \mathbf{p}_3, \dots, \mathbf{p}_N, \mathbf{r}_1, \mathbf{r}_2, \mathbf{r}_3, \dots, \mathbf{r}_N)$$

$$\propto \exp \left[-\beta \left(\frac{\mathbf{p}_1^2}{2m_1} + \frac{\mathbf{p}_2^2}{2m_2} + \frac{\mathbf{p}_3^2}{2m_3} + \dots + \frac{\mathbf{p}_N^2}{2m_N} + V(\mathbf{r}_1, \mathbf{r}_2, \mathbf{r}_3, \dots, \mathbf{r}_N) \right) \right] \quad \left(\beta = \frac{1}{k_B T} \right)$$

Behavior of Macroscopic Variables



X irreversibly approaches an equilibrium value X_{eq} .

X_{eq} can be predicted from handful of other macroscopic variables (pressure, temperature, composition) $\sim 10^{23}$ coord's. not required!

Once equilibrium attained, system never changes or reverses itself.

Ergodic hypothesis allows us to dispense with time average.

$$A_{Time} = \lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T dt A(p(t), x(t))$$

What we can get from an MD simulation

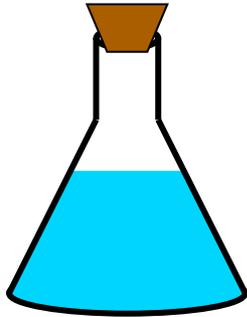
$$\langle A(\mathbf{p}^N, \mathbf{r}^N) \rangle_{ensemble} = \frac{1}{\Omega} \int d\mathbf{p}^N d\mathbf{r}^N A(\mathbf{p}^N, \mathbf{r}^N) \delta(H(\mathbf{p}^N, \mathbf{r}^N) - E)$$

Ensemble Average: Experimental measurement

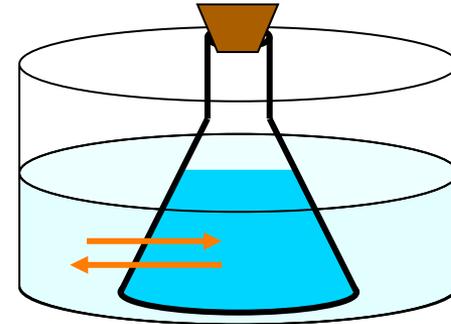
$$A_{time} \approx \langle A(\mathbf{p}^N, \mathbf{r}^N) \rangle_{ensemble}$$

Common Experimental Conditions

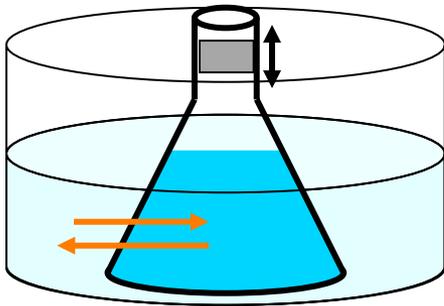
isolated system (N, V, E)



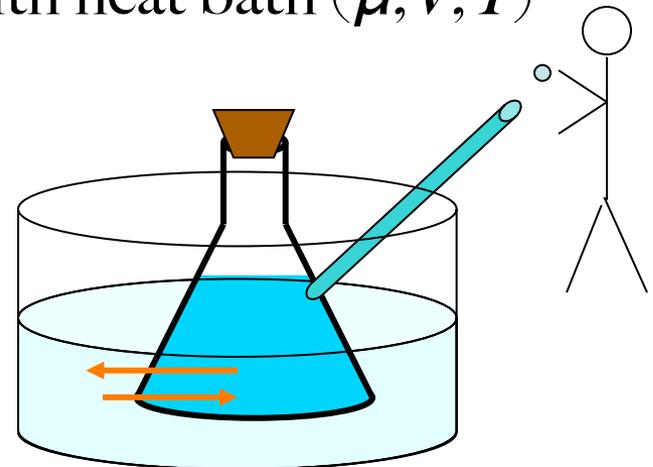
closed system in contact with heat bath (N, V, T)



closed system in contact with heat bath and volume reservoir (N, P, T)

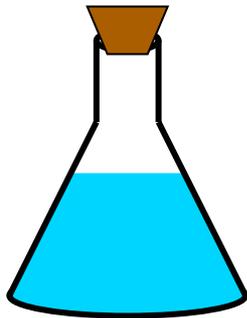


open system in contact with heat bath (μ, V, T)



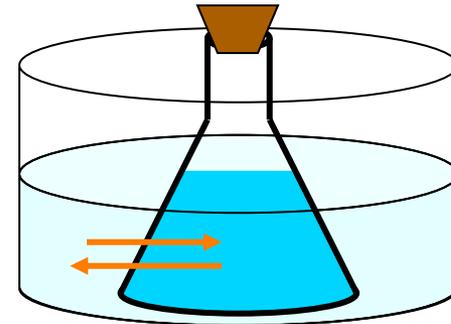
Molecular Dynamics Ensembles

isolated system (N, V, E)



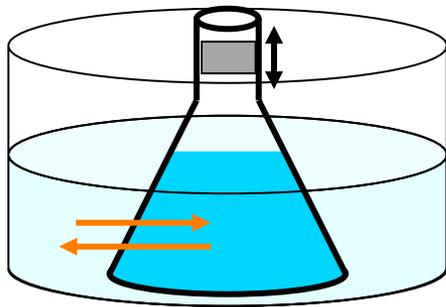
microcanonical ensemble

closed system in contact with heat bath (N, V, T)



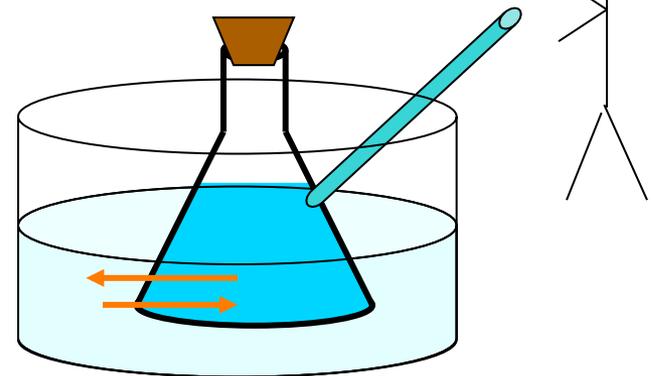
canonical ensemble

closed system in contact with heat bath and volume reservoir (N, P, T)



Isothermal-isobaric ensemble

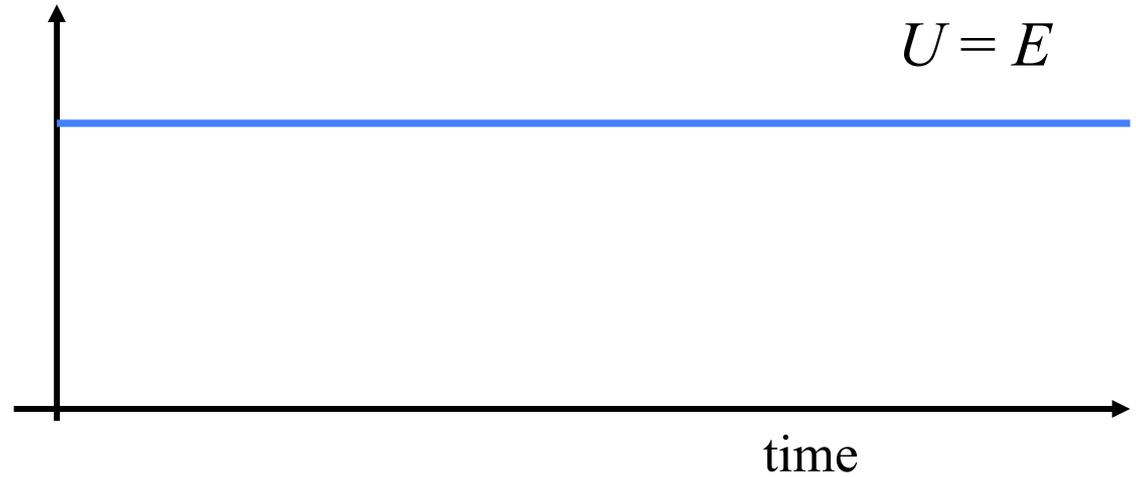
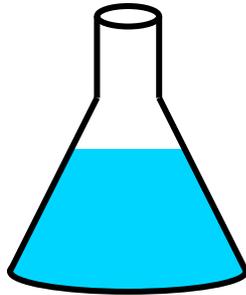
open system in contact with heat bath (μ, V, T)



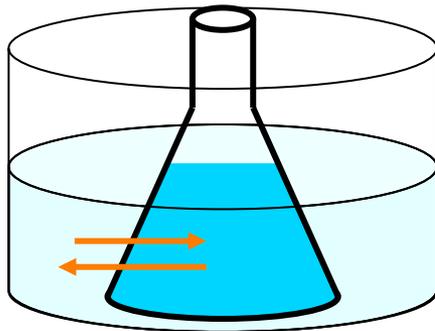
Grand-Canonical Ensemble

Isolated System vs System and Heat Bath

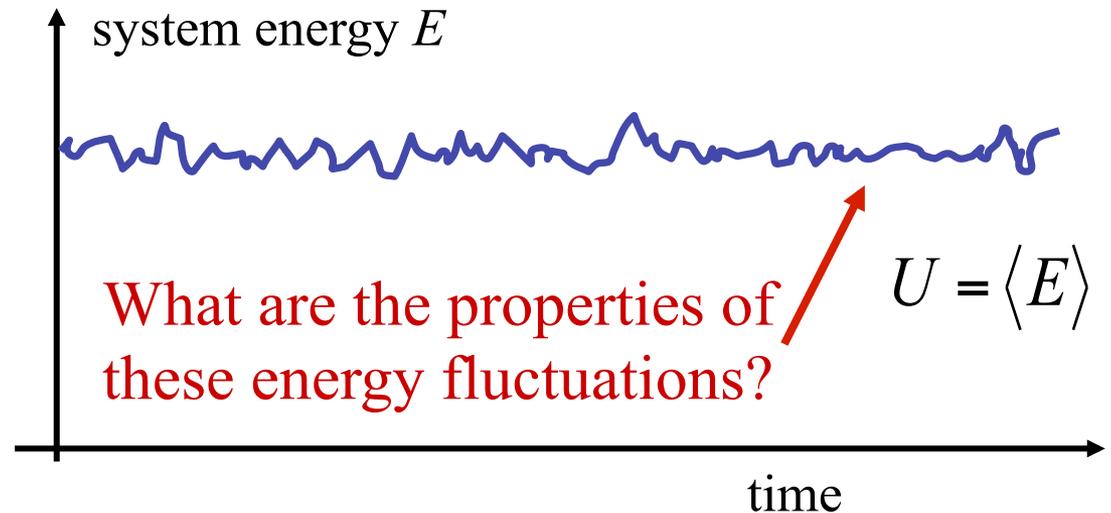
isolated system



system maintained at a temperature T



energy exchange between system and surroundings

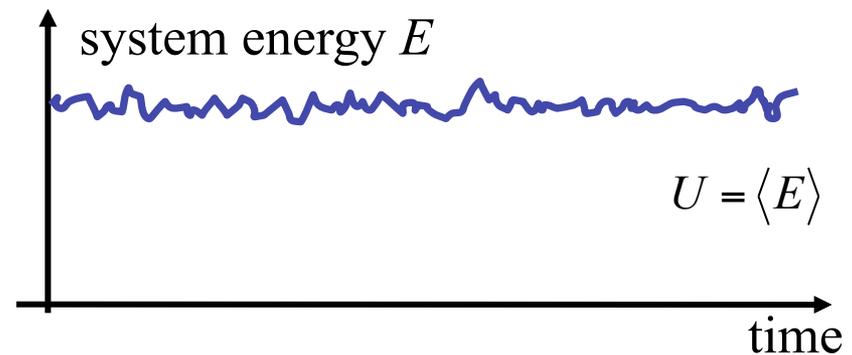
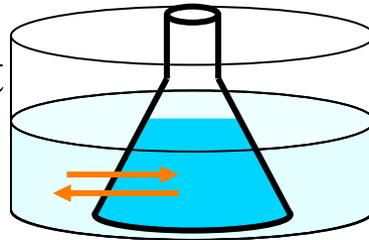


What are the properties of these energy fluctuations?

$$U = \langle E \rangle$$

Properties of an object in contact with heat bath

system maintained at a temperature T



THE ANSWER:

$$[\text{probability that the system is found in microstate } j] = P_j \propto \exp\left[-\frac{E_j}{k_B T}\right]$$

If there are $\Omega(E)$ microstates with the same energy E ,

$$[\text{probability of finding the system with energy } E] = P(E) \propto \sum_{j=1}^{\Omega(E)} \exp\left[-\frac{E_j}{k_B T}\right]$$
$$\propto \Omega(E) \exp\left[-\frac{E}{k_B T}\right]$$

All $\Omega(E)$ microstates have the same energy $E_j = E$.

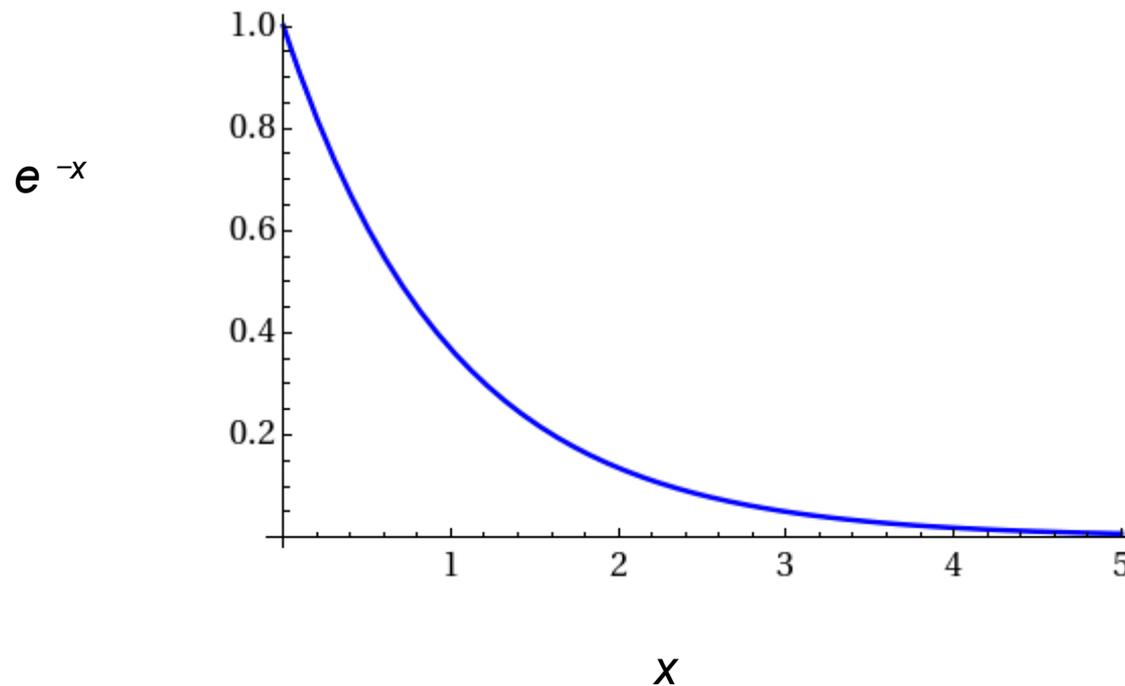
Normalize canonical partition function

$$P_j \propto \exp[-\beta E_j]$$

$$P_j = \frac{e^{-\beta E_j}}{Q} \quad Q(N, V, T) = \sum_j e^{-\beta E_j}$$
$$= \sum_E \Omega(E) e^{-\beta E}$$

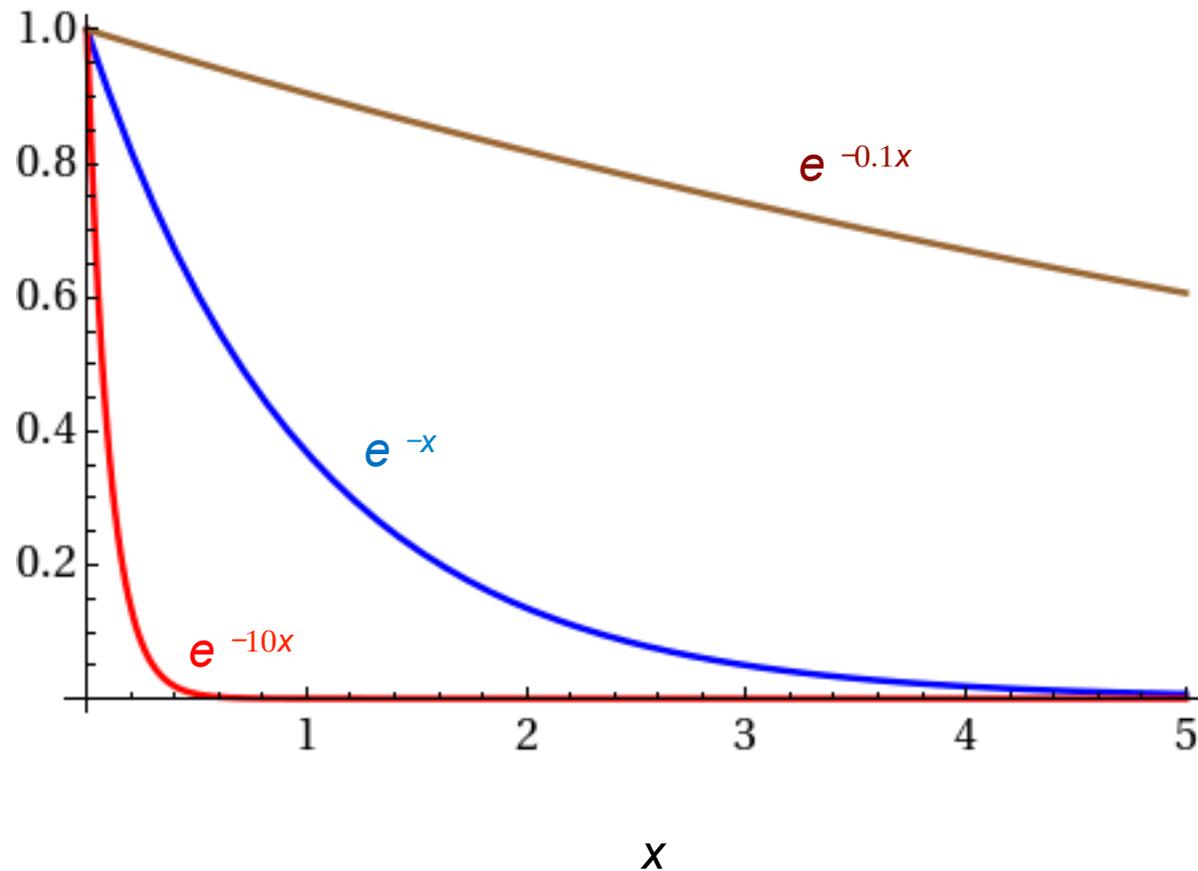
Q is the *canonical partition function*.

The Boltzmann Factor: exponential function



How would the Boltzmann factor look for different temperatures, lets say 20K vs 300K?

The Boltzmann Factor: exponential function



Relative Fluctuations for Ideal Atomic Gas

$$\frac{\sigma_E}{\langle E \rangle} \propto \frac{1}{\sqrt{N}}$$

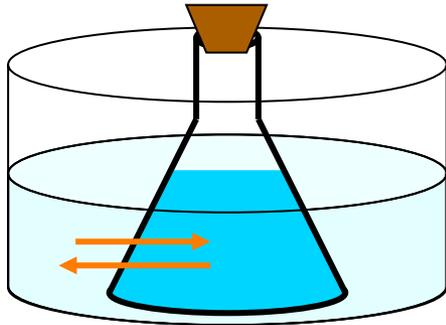
Ideal atomic gas example:

$$\langle E \rangle = \frac{3N}{2\beta} \quad \sigma_E^2 = - \left(\frac{\partial \langle E \rangle}{\partial \beta} \right)_{N,V} = - \left(\frac{\partial}{\partial \beta} \left(\frac{3N}{2\beta} \right) \right)_{N,V} = \frac{3N}{2\beta^2}$$

$$\sigma_E = \sqrt{\frac{3N}{2\beta^2}} \quad \frac{\sigma_E}{\langle E \rangle} = \left(\frac{\sqrt{\frac{3N}{2\beta^2}}}{\frac{3N}{2\beta}} \right) \propto \frac{1}{\sqrt{N}}$$

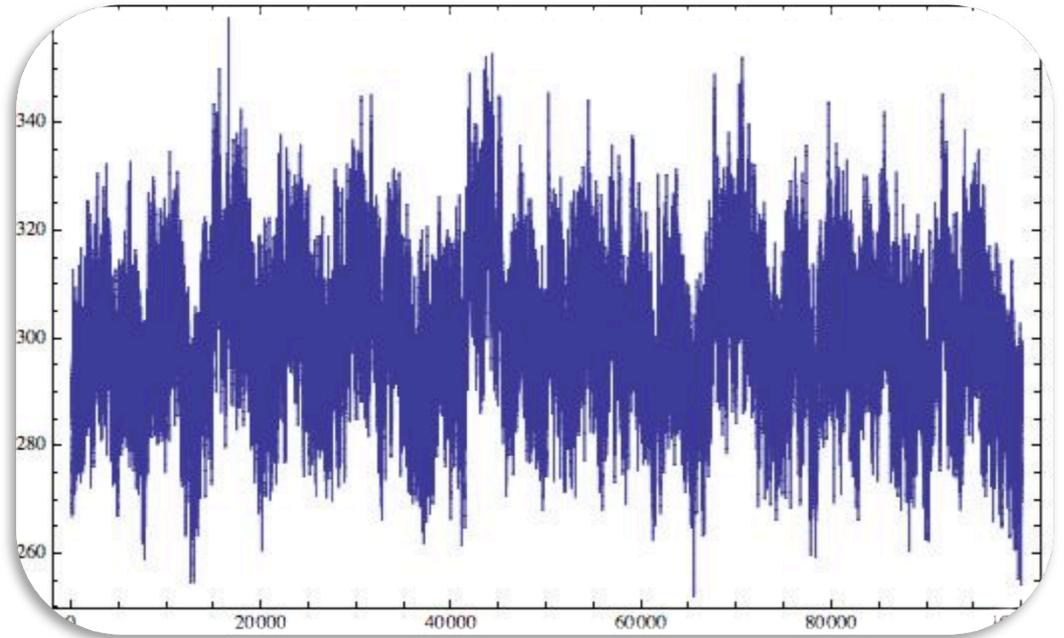
How about the temperature?

closed system in contact with
heat bath (N, V, T)



canonical ensemble

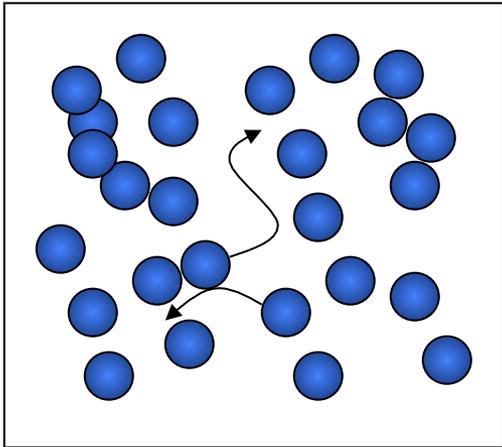
$$\frac{\sigma_T}{\langle T \rangle} \propto \frac{1}{\sqrt{N_f}}$$



In the NVT ensemble it is the average temperature that is conserved:
instantaneous temperature fluctuates

Classical Statistical Mechanics: I

Classical stat. mech. for N particles in 3-dimensions



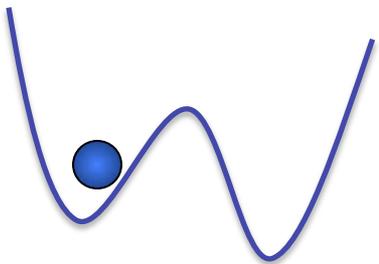
$$P(\mathbf{r}^N, \mathbf{p}^N) \propto \exp \left[-\beta \left(\sum_{i=1}^N \frac{\mathbf{p}_i^2}{2m_i} + V(\mathbf{r}^N) \right) \right]$$

$$\beta = \frac{1}{k_B T}$$

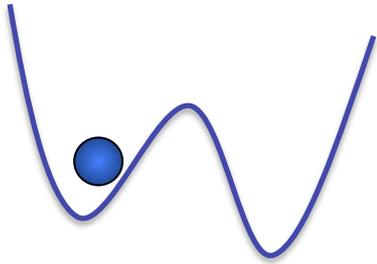
$$\mathbf{r}^N \Leftrightarrow \mathbf{r}_1, \mathbf{r}_2, \mathbf{r}_3, \dots, \mathbf{r}_N$$

$$\mathbf{p}^N \Leftrightarrow \mathbf{p}_1, \mathbf{p}_2, \mathbf{p}_3, \dots, \mathbf{p}_N$$

Classical statistical mechanics for 1 particles in 1-dimension



$$P(x, p) \propto \exp \left[-\beta \left(\frac{p^2}{2m} + V(x) \right) \right]$$



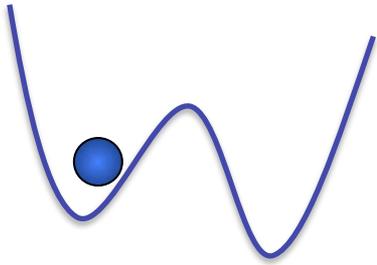
$$P(x, p) \propto \exp\left[-\beta\left(\frac{p^2}{2m} + V(x)\right)\right]$$

$$\beta = \frac{1}{k_B T}$$

Normalization: $\int_{-\infty}^{\infty} dx \int_{-\infty}^{\infty} dp P(x, p) = 1$

$$P(x, p) = \frac{1}{C} \exp\left[-\beta\left(\frac{p^2}{2m} + V(x)\right)\right]$$

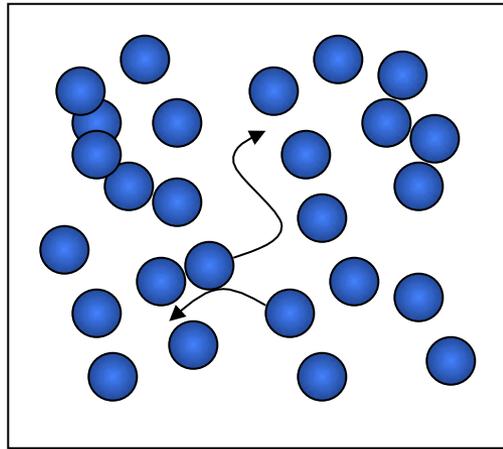
$$C = \int_{-\infty}^{\infty} dx \int_{-\infty}^{\infty} dp \exp\left[-\beta\left(\frac{p^2}{2m} + V(x)\right)\right]$$



$$\begin{aligned} C &= \int_{-\infty}^{\infty} dx \int_{-\infty}^{\infty} dp \exp \left[-\beta \left(\frac{p^2}{2m} + V(x) \right) \right] \\ &= \int_{-\infty}^{\infty} dx \exp[-\beta V(x)] \times \int_{-\infty}^{\infty} dp \exp \left[-\beta \frac{p^2}{2m} \right] \\ &= C_x \times C_p \end{aligned}$$

Probability factors

$$\begin{aligned} P(x, p) &= \frac{1}{C} \exp \left[-\beta \left(\frac{p^2}{2m} + V(x) \right) \right] = \frac{\exp[-\beta V(x)]}{C_x} \times \frac{\exp \left[-\beta \frac{p^2}{2m} \right]}{C_p} \\ &= P(x) \times P(p) \end{aligned}$$



Probability
distribution factors.

Classical statistical mechanics

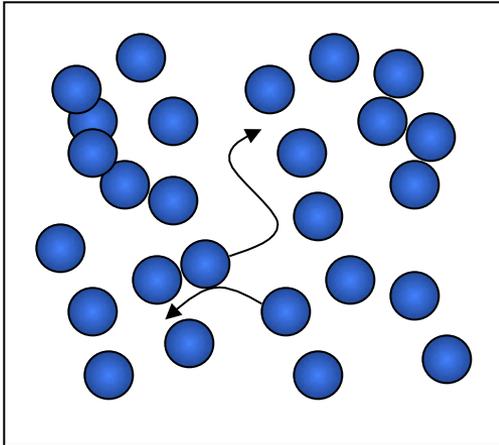
$$P(\mathbf{r}^N, \mathbf{p}^N) \propto \exp \left[-\beta \left(\sum_{i=1}^N \frac{\mathbf{p}_i^2}{2m_i} + V(\mathbf{r}^N) \right) \right]$$

$$P(\mathbf{r}^N, \mathbf{p}^N) \propto \exp \left[-\beta \sum_{i=1}^N \frac{\mathbf{p}_i^2}{2m_i} \right] \exp \left[-\beta V(\mathbf{r}^N) \right]$$

$$P(\mathbf{r}^N, \mathbf{p}^N) = P(\mathbf{r}^N)P(\mathbf{p}^N)$$

In classical statistical mechanics, momentum and configurational fluctuations are strictly uncorrelated (statistically independent).

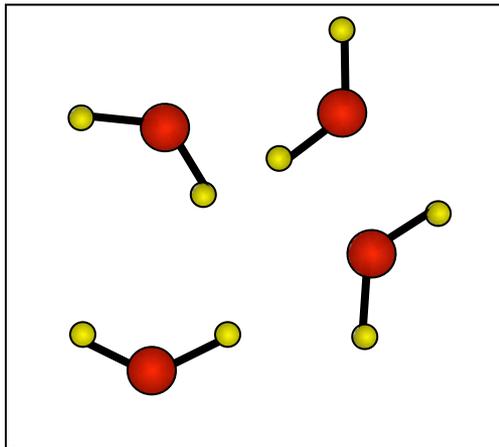
H₂O and D₂O (what would change?)



Classical statistical mechanics

$$P(\mathbf{r}^N, \mathbf{p}^N) \propto \exp\left[-\beta \sum_{i=1}^N \frac{\mathbf{p}_i^2}{2m_i}\right] \exp[-\beta V(\mathbf{r}^N)]$$

$$P(\mathbf{r}^N, \mathbf{p}^N) = P(\mathbf{r}^N)P(\mathbf{p}^N)$$



Compare simulations of H₂O and D₂O.

In classical stat. mech., is there a difference in their boiling or freezing point?

Is there a difference in their configurational distribution functions?

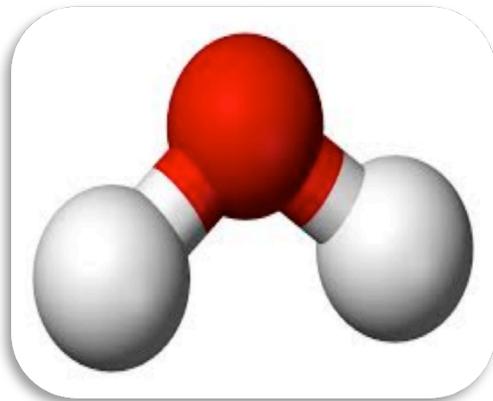
When does classical stat. mech break down?

Question: When is the classical limit a good approximation?

Answer: Limit of large mass/high temperature (?)

Nuclear quantum effects are important when

$$\frac{\bar{h}\omega}{k_B T} > 1$$



Zero point energy of O-H stretch of water is more than 0.2 eV!

Where do we get the forces?

Ingredients to conduct an MD simulation

$$P(\mathbf{r}^N, \mathbf{p}^N) \propto \exp\left[-\beta\left(\sum_{i=1}^N \frac{\mathbf{p}_i^2}{2m_i} + V(\mathbf{r}^N)\right)\right]$$

$$F(t) = M \ddot{R}(t) = -\nabla V(\{R(t)\})$$

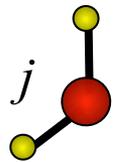
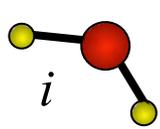
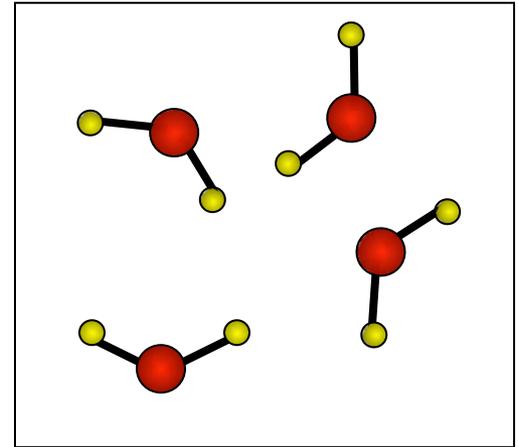
I need an algorithm that allows me to generate positions and velocities in time that will be subject to the above rules:

- 1) Must need a way to integrate the differential equation above to get positions and velocities in time
- 2) Need a potential to get the forces
- 3) Must generate initial velocities (How?)

What are empirical potentials?

Function devised to approximate Born-Oppenheimer energy as a function of nuclear positions.

Empirical potentials often deduced from potential between a pair of molecules...



$$v(\mathbf{r}_i, \omega_i; \mathbf{r}_j, \omega_j)$$

center of mass coord's

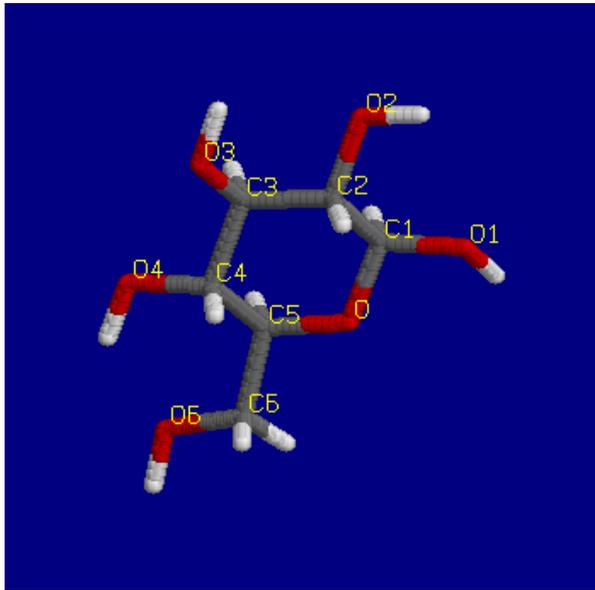
angular coord's

... and then assuming full N -molecule potential is sum of pairwise interactions.

$$V(\mathbf{r}^N) = \sum_{i < j} v(\mathbf{r}_i, \omega_i; \mathbf{r}_j, \omega_j)$$

Recent interest in high-quality parameterizations, including 3-body, 4-body,..interactions until convergence.

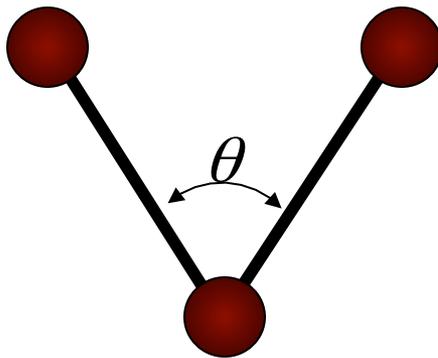
Intramolecular (bonded) potentials



Harmonic distance interaction between neighboring atoms:



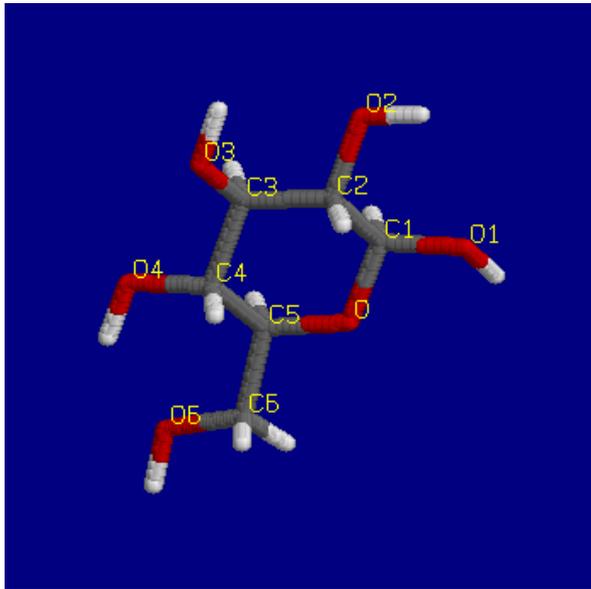
$$v_{harm}(r_{ij}) = \frac{k}{2} (r_{ij} - r_{ij}^0)^2$$



Harmonic angle potentials:

$$v_{ang}(\theta) = \frac{k}{2} (\theta - \theta^0)^2$$

Intramolecular (bonded) potentials

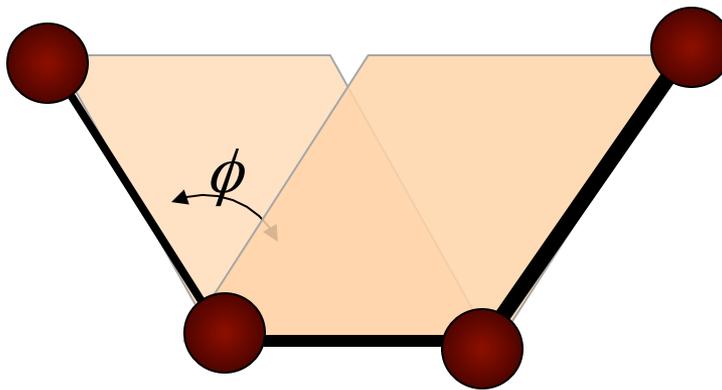


Harmonic dihedral angle potential:

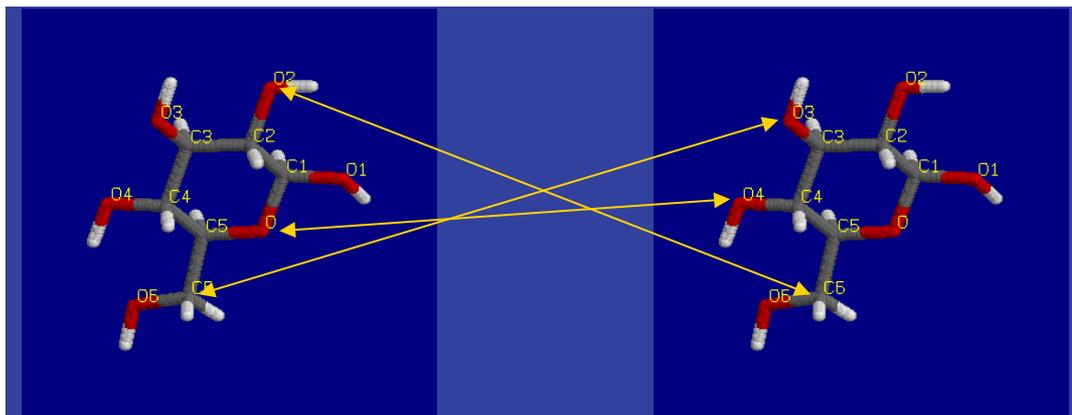
$$v_{harm}(\phi) = \frac{k}{2} (\phi - \phi^0)^2$$

Periodic dihedral angle potential:

$$v_{harm}(\phi) = \cos[n(\phi - \phi^0)]$$



Bonded vs Non-bonded Interactions

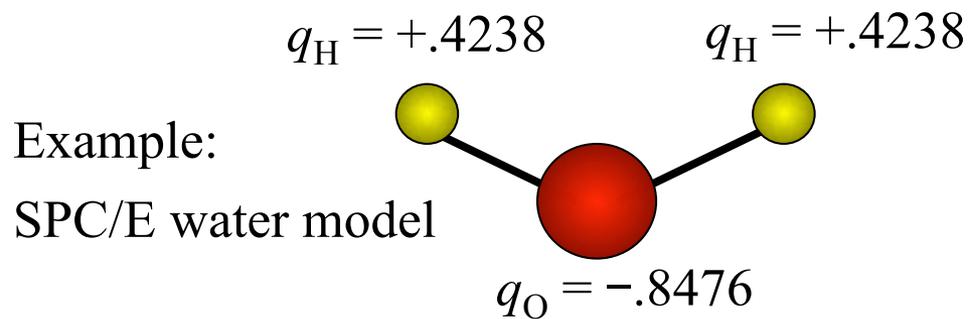


$$V(r^N) = \sum_{i,j} 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \sum_{i,j} \frac{q_i q_j}{r_{ij}}$$

Lennard Jones potential

Electrostatics

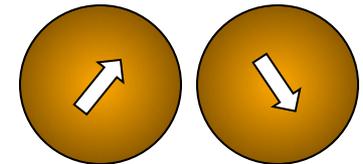
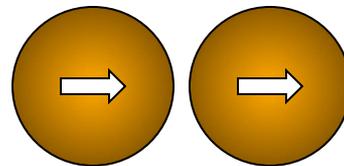
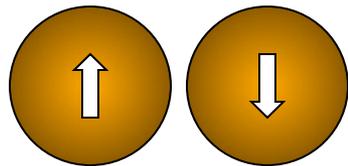
Molecular charge distribution usually represented by distribution of point charges.



$$v_{e-s} = \sum_{\substack{\text{sites } a \text{ on} \\ \text{first molecule}}} \sum_{\substack{\text{sites } b \text{ on} \\ \text{second molecule}}} \frac{q_a q_b}{|\mathbf{r}_a - \mathbf{r}_b|}$$

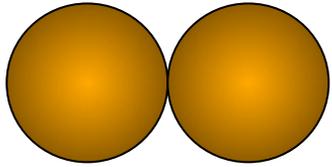
London dispersion forces

Quantum mechanical motion of electrons in different atoms or molecules is correlated.



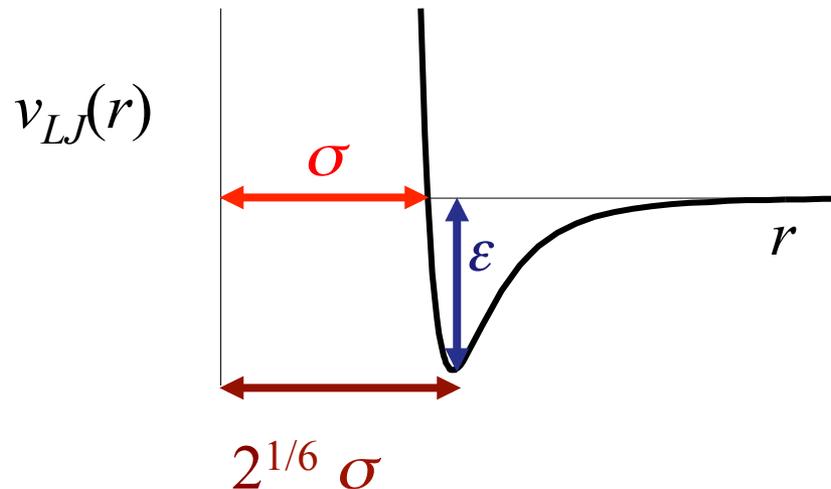
Correlation of instantaneous polarizations leads to $(\text{distance})^{-6}$ attraction.

Lennard-Jones Potential



Common (traditional) 2-parameter potential to describe overlap repulsion and London dispersion forces.

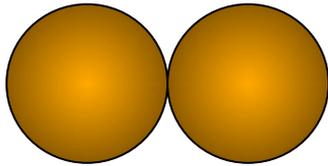
$$v_{LJ}(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right]$$



Actually, repulsive part of potential better described by an exponential: Ae^{-br}

(“Buckingham” or “exp-6” potentials)

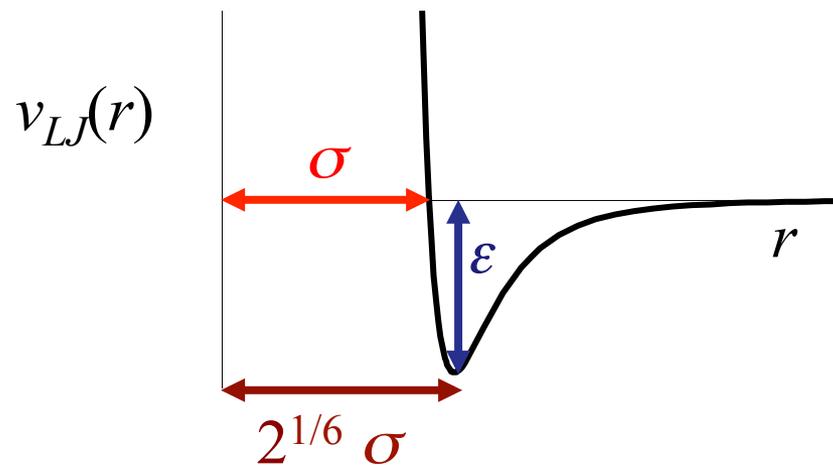
Other ways to specify Lennard-Jones Potential



$$v_{LJ}(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right]$$

$$v_{LJ}(r) = \frac{C_{12}}{r^{12}} - \frac{C_6}{r^6}$$

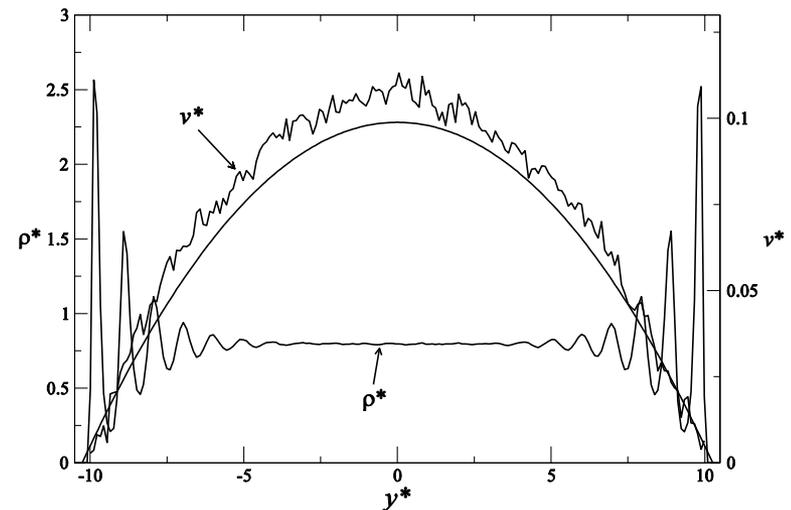
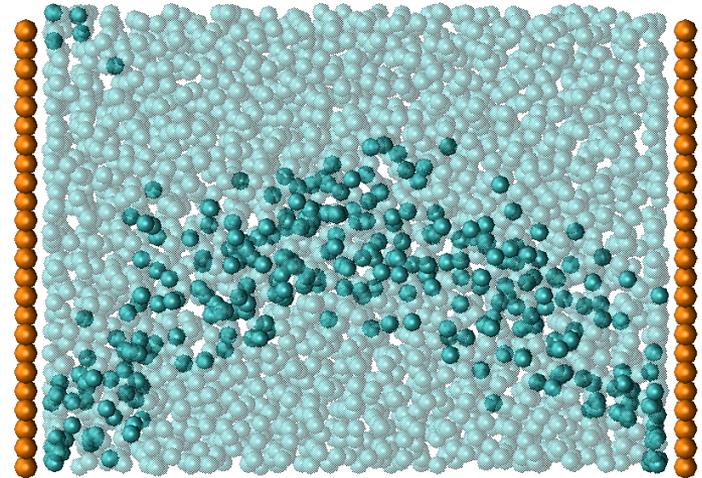
$$v_{LJ}(r) = \frac{A}{r^{12}} + \frac{B}{r^6}$$



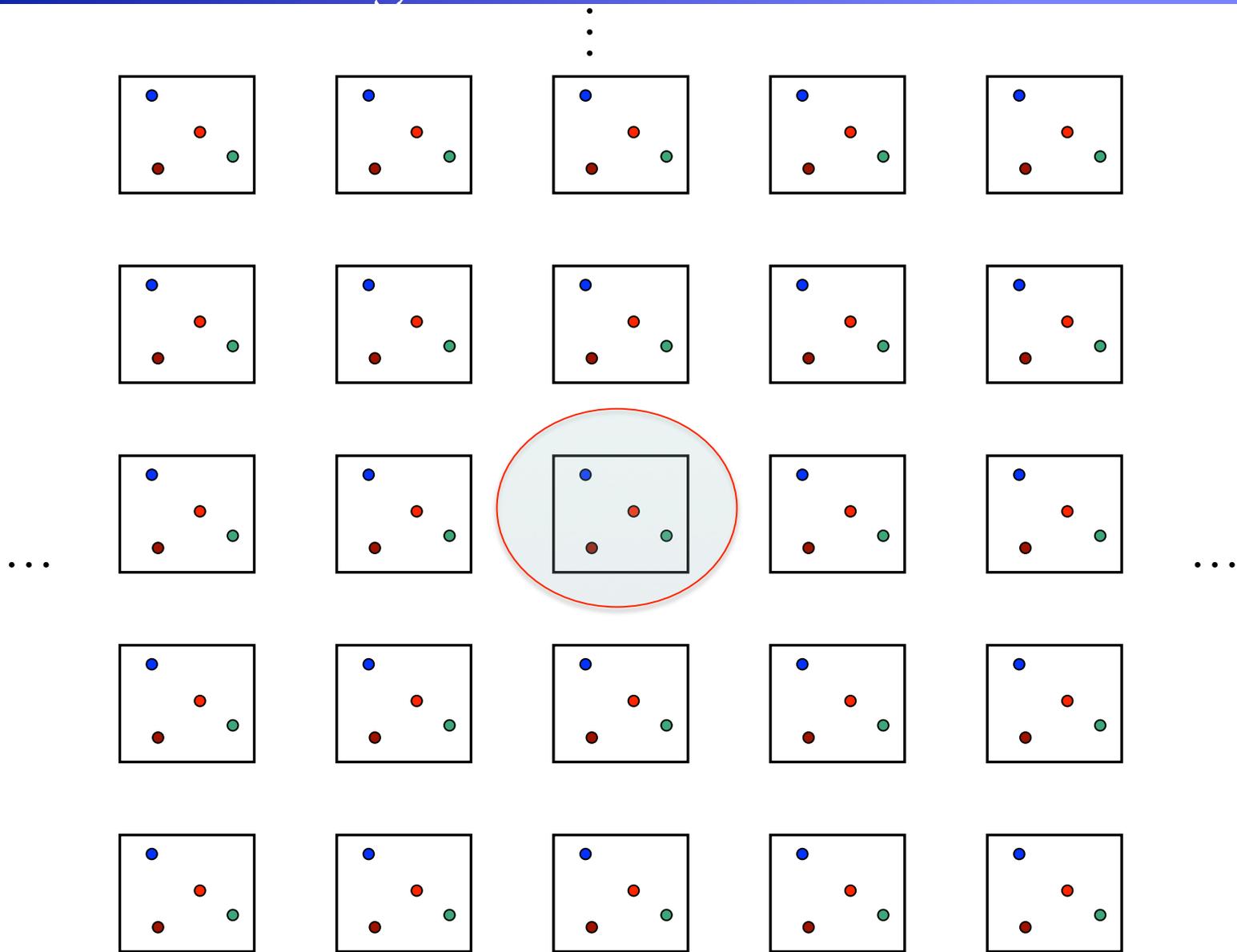
PBC, Minimum Image, Ewald

The need for periodic boundary conditions

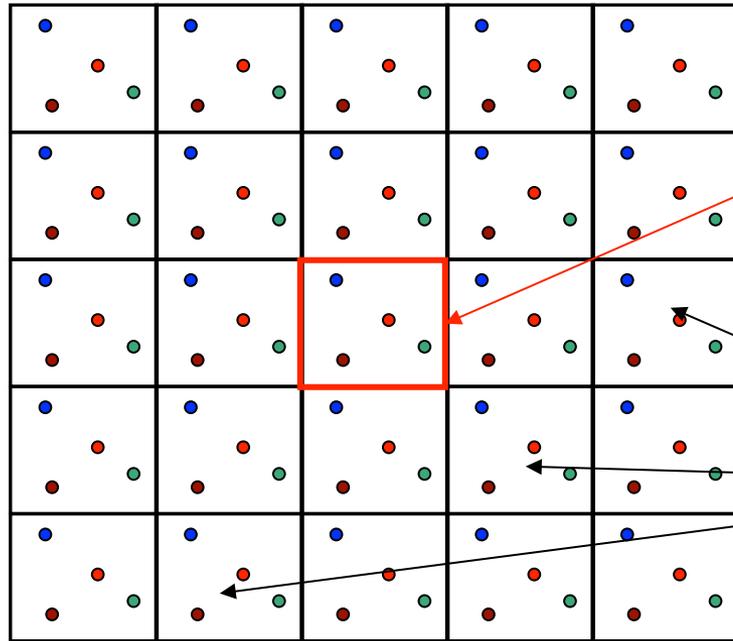
Fluid can be strongly perturbed by wall out to ~ 5 molecular diameters.



Periodic Boundary Conditions (PBC)



Periodic Boundary Conditions



“simulation cell, primary cell, ...”

“periodic replicas”

for simplicity, cubic simulation cell of volume L^3 :

position of particle i
in replica indexed
by $\mathbf{n} = (n_x, n_y, n_z)$

$$= \mathbf{r}_{i,\mathbf{n}} = \mathbf{r}_i + \mathbf{n} L$$

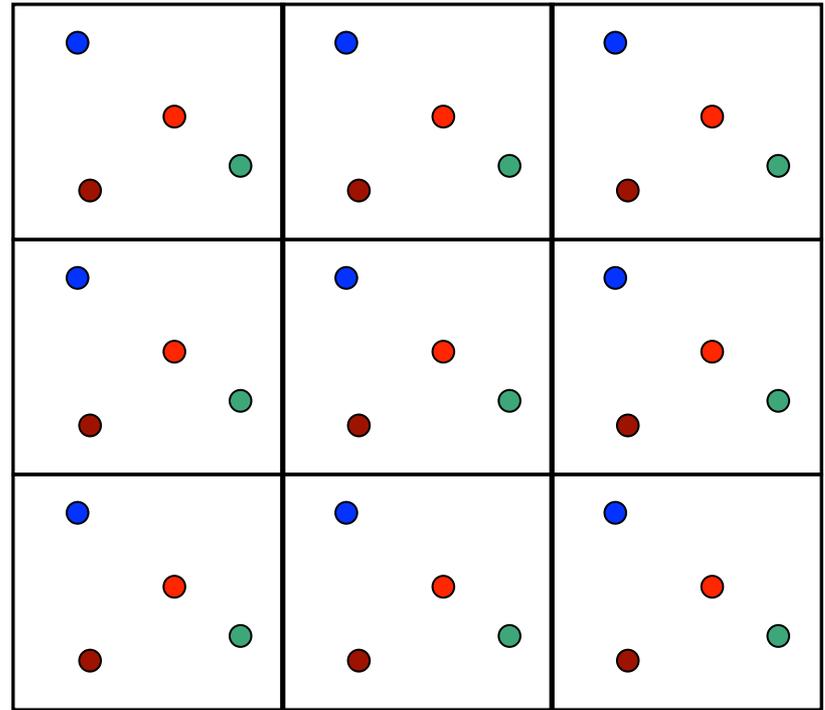
position of i in
primary cell

$\mathbf{n} = (0,0,0)$ indexes
the primary cell

Minimum Image Convention

When
potential decays rapidly with
distance

neglect all \mathbf{n} except the one for
which $|\mathbf{r}_i - \mathbf{r}_j + \mathbf{n}L|$ is smallest.



$$E_{cell} = \lim_{N_{cell} \rightarrow \infty} \frac{1}{2} \sum_{\mathbf{n}}^{N_{cell}} \sum_{i,j}^N v(\mathbf{r}_i - \mathbf{r}_j + \mathbf{n}L) \approx \sum_{i < j}^N \text{Min}_{\mathbf{n}} v(\mathbf{r}_i - \mathbf{r}_j + \mathbf{n}L)$$

omit $i=j$ when $\mathbf{n} = \mathbf{0}$.

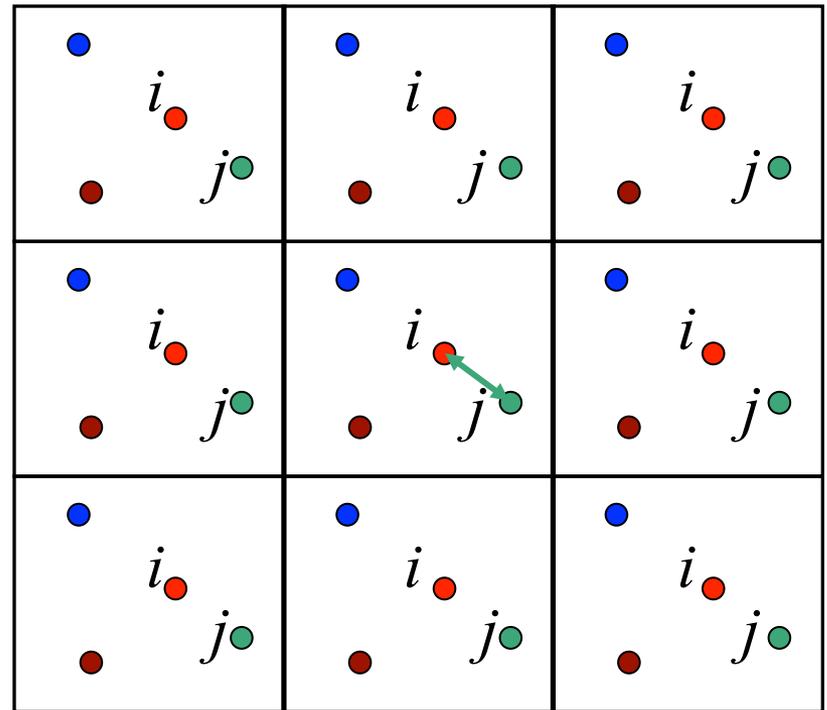
“Min” refers to $\mathbf{r}_i - \mathbf{r}_j + \mathbf{n}L$

Minimum Image Convention

$$E_{cell} \approx \sum_{i < j}^N \text{Min}_{\mathbf{n}} v(\mathbf{r}_i - \mathbf{r}_j + \mathbf{n}L)$$

Neglect all \mathbf{n} except the one for which $|\mathbf{r}_i - \mathbf{r}_j + \mathbf{n}L|$ is smallest.

The minimum image between particles i and j in the drawing are within the same cell.

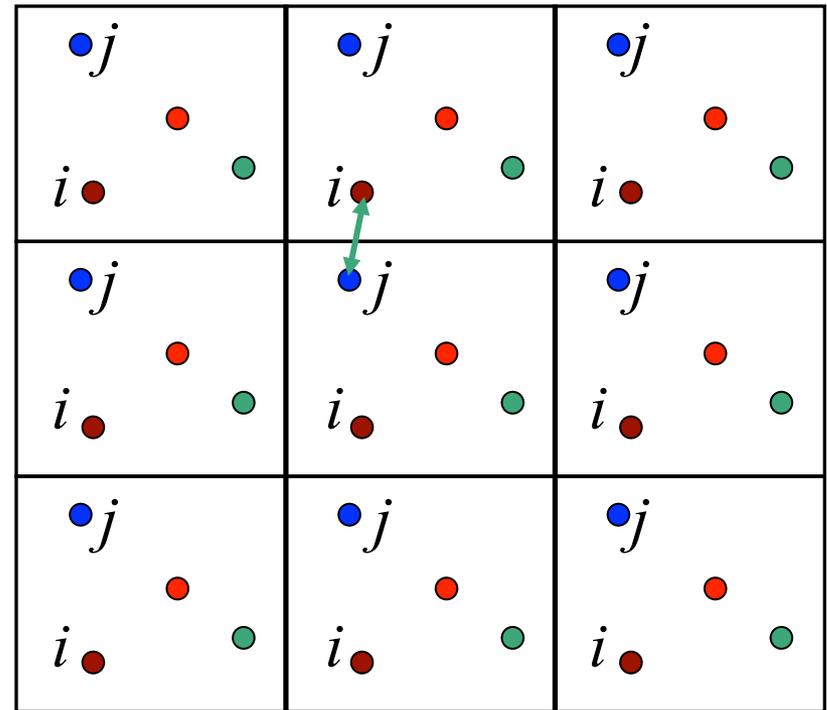


Minimum Image Convention

$$E_{cell} \approx \sum_{i < j}^N \text{Min}_{\mathbf{n}} v(\mathbf{r}_i - \mathbf{r}_j + \mathbf{n}L)$$

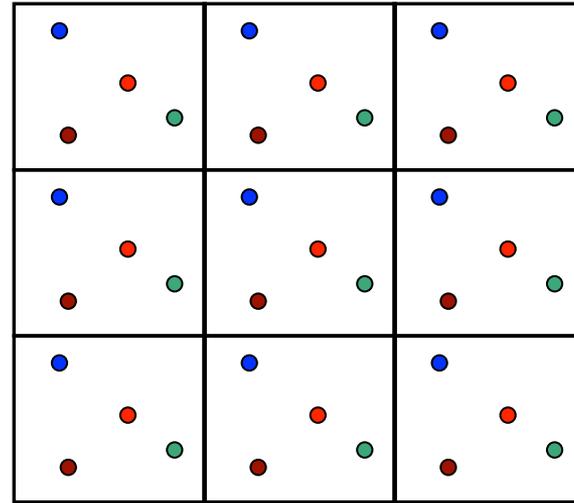
Neglect all \mathbf{n} except the one for which $|\mathbf{r}_i - \mathbf{r}_j + \mathbf{n}L|$ is smallest.

The minimum image between particles i and j in the drawing are across two different cells.



How to implement Minimum Image

$$E_{cell} \approx \sum_{i < j}^N \text{Min}_n v(\mathbf{r}_i - \mathbf{r}_j + \mathbf{n}L)$$



Place coordinate within primary cell,
so that $-L_x/2 < x_i \leq L_x/2$

$$x(i) = x(i) - \text{nint}(x(i)/L_x) * L_x$$

nearest integer function

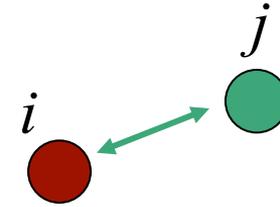
Minimum image distance between particles i and j .

$$x_{ij} = x(i) - x(j)$$

$$x_{ij} = x_{ij} - \text{nint}(x_{ij}/L_x) * L_x$$

Calculating force between two particles

We'll need this soon ...



Suppose there is an interaction $v(|\mathbf{r}_i - \mathbf{r}_j|)$ between particles i and j .

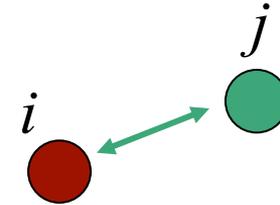
Calculate the force on particle i from this interaction

Exercise

$$f_{x,i} = ?$$

Calculating force between two particles

We'll need this soon ...



Suppose there is an interaction $v(|\mathbf{r}_i - \mathbf{r}_j|)$ between particles *i* and *j*.

Calculate the force on particle *i* from this interaction

$$f_{x,i} = -\frac{\partial}{\partial x_i} v(|\mathbf{r}_i - \mathbf{r}_j|) = -v'(|\mathbf{r}_i - \mathbf{r}_j|) \frac{\partial}{\partial x_i} |\mathbf{r}_i - \mathbf{r}_j|$$

$$\frac{\partial}{\partial x_i} |\mathbf{r}_i - \mathbf{r}_j| = \frac{x_i - x_j}{|\mathbf{r}_i - \mathbf{r}_j|}$$

If $v(|\mathbf{r}_i - \mathbf{r}_j|)$, then $f_{x,i} = -v'(|\mathbf{r}_i - \mathbf{r}_j|) \frac{x_i - x_j}{|\mathbf{r}_i - \mathbf{r}_j|}$.

Ewald Sum for Electrostatics

$$E_{cell} = \lim_{N_{cell} \rightarrow \infty} \frac{1}{2} \sum_{\mathbf{n}}^{N_{cell}} \sum_{i,j}^N v(\mathbf{r}_i - \mathbf{r}_j + \mathbf{n}L)$$

omit $i=j$ when $\mathbf{n} = \mathbf{0}$.

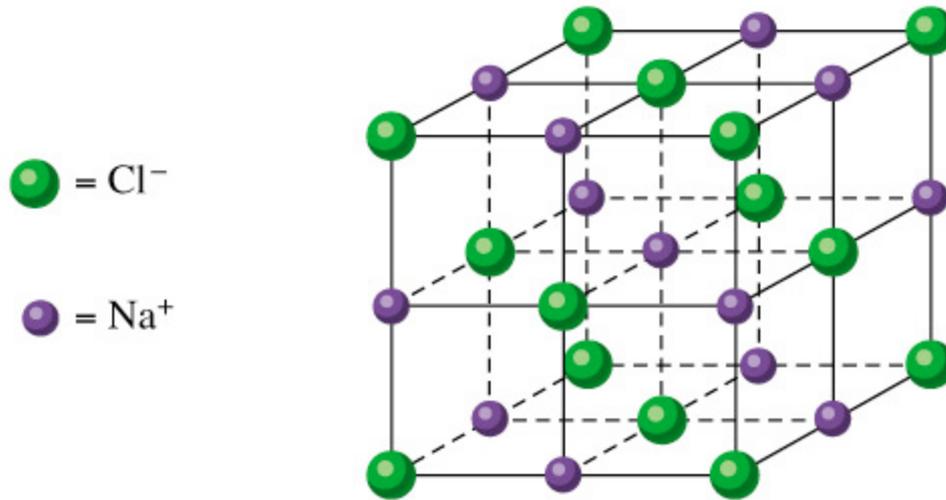
When potential is long range (Coulomb,...), the full sum must be calculated.

Full sum is softly slowly (and conditionally) convergent.

Ewald method:

Original slowly convergent sum \rightarrow two rapidly convergent sums.

Coulomb Sums are Conditionally Convergent



Coulomb sum with only like
 or unlike charges $\sim 4\pi \int_{r_0}^{\infty} dr r^2 \frac{1}{r}$
 does not converge.

$$E_{cell} = \lim_{N_{cell} \rightarrow \infty} \frac{1}{2} \sum_{\mathbf{n}}^{N_{cell}} \sum_{i,j}^N v(\mathbf{r}_i - \mathbf{r}_j + \mathbf{n}L)$$

$$= \lim_{N_{cell} \rightarrow \infty} \frac{1}{2} \sum_{\mathbf{n}}^{N_{cell}} \left[\sum_{i \in \text{Na}^+, j \in \text{Na}^+}^N v(\mathbf{r}_i - \mathbf{r}_j + \mathbf{n}L) + \sum_{i \in \text{Na}^+, j \in \text{Cl}^-}^N v(\mathbf{r}_i - \mathbf{r}_j + \mathbf{n}L) + \dots \right]$$

$$= \infty - \infty + \infty - \infty = ??$$

Ewald Sum

deLeeuw, Perram, Smith, *Proc.RoySoc.Lond.* **A373**:27 (1980)

Introduce integral representation for r^{-1} .

$$\frac{1}{r} = \frac{1}{\sqrt{\pi}} \int_0^{\infty} dt t^{-1/2} e^{-tr^2}$$

Break this integral into two parts.

$$\frac{1}{r} = \underbrace{\frac{1}{\sqrt{\pi}} \int_0^{\alpha^2} dt t^{-1/2} e^{-tr^2}}_{\text{long-range}} + \underbrace{\frac{1}{\sqrt{\pi}} \int_{\alpha^2}^{\infty} dt t^{-1/2} e^{-tr^2}}_{\text{short-range}}$$

long-range

short-range

α will be chosen for numerical convenience.

Ewald Method

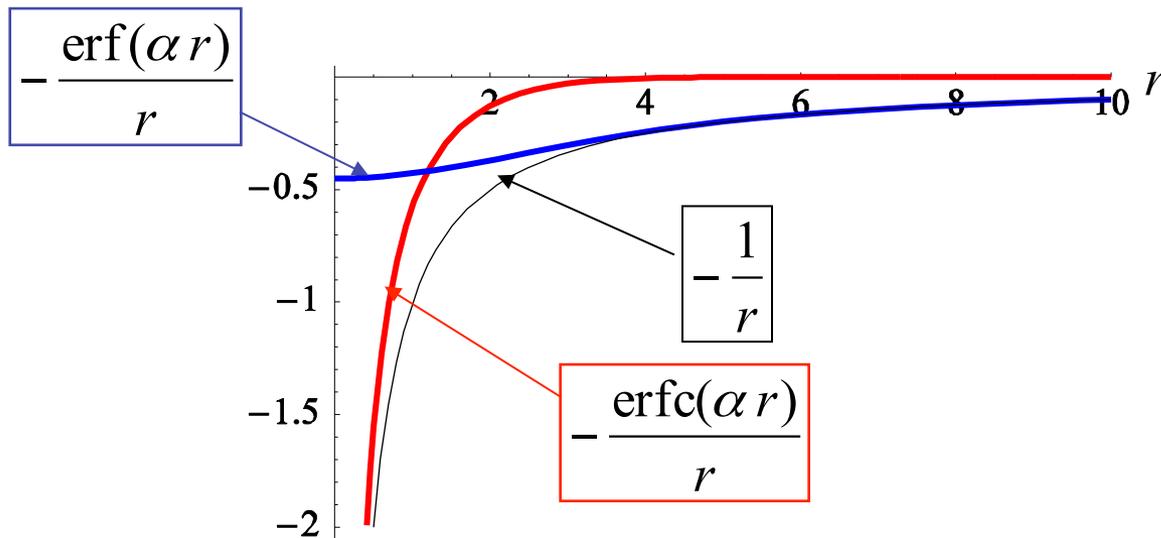
$$\frac{1}{r} = \underbrace{\frac{1}{\sqrt{\pi}} \int_0^{\alpha^2} dt t^{-1/2} e^{-tr^2}}_{\text{long-range}} + \underbrace{\frac{1}{\sqrt{\pi}} \int_{\alpha^2}^{\infty} dt t^{-1/2} e^{-tr^2}}_{\text{short-range}}$$

$$\frac{\text{erf}(\alpha r)}{r}$$

long-range

$$\frac{1 - \text{erf}(\alpha r)}{r} = \frac{\text{erfc}(\alpha r)}{r}$$

short-range



Ewald Method: Hidden Assumptions

$$E_{cell} = E_{real} + E_{self} + E_{recip}$$

$$E_{real} = \lim_{N_{cell} \rightarrow \infty} \frac{1}{2} \sum_{\mathbf{n}}^{N_{cell}} \sum_{i,j}^N q_i q_j \frac{\text{erfc}(\alpha |\mathbf{r}_i - \mathbf{r}_j + \mathbf{n}L|)}{|\mathbf{r}_i - \mathbf{r}_j + \mathbf{n}L|} \quad E_{self} = -\frac{\alpha}{\sqrt{\pi}} \sum_{i=1}^N q_i^2$$

$$E_{recip} = \frac{1}{2\pi L^3} \sum_{i,j}^N q_i q_j \sum_{\mathbf{m} \neq 0}^{\infty} \left(\frac{\mathbf{m}}{L}\right)^{-2} \exp\left[-\left(\frac{\pi \mathbf{m}}{\alpha L}\right)^2\right] \exp\left[2\pi i \mathbf{m} \cdot (\mathbf{r}_i - \mathbf{r}_j) / L\right] \\ - \frac{2}{3} \frac{\pi}{L^3} \left(\sum_{i=1}^N q_i \mathbf{r}_i\right)^2$$

Hidden assumptions: • $\sum_{i=1}^N q_i = 0$

Integrators & Thermostats

“Molecular dynamics” means solve Newton’s equations of motion for many atoms or molecules.

$$m_i \frac{d^2}{dt^2} \mathbf{r}_i = - \frac{\partial}{\partial \mathbf{r}_i} V(\mathbf{r}^N)$$

“Usual” MD is microcanonical simulation

Variants for constant T or P are common.

MD Integration: Verlet Algorithm

L. Verlet, *Phys. Rev.* **159**:98 (1967)

$$\left. \begin{aligned} \mathbf{r}^N(t + \Delta t) &= \mathbf{r}^N(t) + \Delta t \mathbf{v}^N(t) + \frac{1}{2} \Delta t^2 \mathbf{a}^N(t) + \dots \\ \mathbf{r}^N(t - \Delta t) &= \mathbf{r}^N(t) - \Delta t \mathbf{v}^N(t) + \frac{1}{2} \Delta t^2 \mathbf{a}^N(t) + \dots \end{aligned} \right\} \begin{array}{l} \text{Forwards and} \\ \text{backwards Taylor} \\ \text{expansions} \end{array}$$

$$\mathbf{r}^N(t + \Delta t) + \mathbf{r}^N(t - \Delta t) = 2\mathbf{r}^N(t) + \Delta t^2 \mathbf{a}^N(t) + \dots \quad \leftarrow \text{ADD 2 eq.'s}$$

Verlet algorithm (1st version)

$$\mathbf{r}^N(t + \Delta t) = 2\mathbf{r}^N(t) - \mathbf{r}^N(t - \Delta t) + \Delta t^2 \mathbf{a}^N(t) + \dots$$

- Configuration at two time points needed to start .

Verlet Algorithm

L. Verlet, *Phys. Rev.* **159**:98 (1967)

$$\mathbf{r}^N(t + \Delta t) = \mathbf{r}^N(t) + \Delta t \mathbf{v}^N(t) + \frac{1}{2} \Delta t^2 \mathbf{a}^N(t) + \dots$$

$$\mathbf{r}^N(t - \Delta t) = \mathbf{r}^N(t) - \Delta t \mathbf{v}^N(t) + \frac{1}{2} \Delta t^2 \mathbf{a}^N(t) + \dots$$

Forwards and
backwards Taylor
expansions

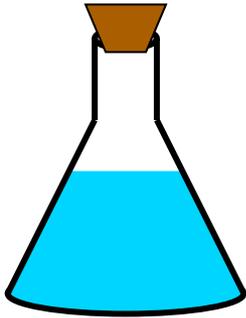
$$\mathbf{r}^N(t + \Delta t) - \mathbf{r}^N(t - \Delta t) = 2\Delta t \mathbf{v}^N(t) + \dots$$

← SUBTRACT
2 eq.'s

• Velocity:
$$\mathbf{v}^N(t) = \frac{\mathbf{r}^N(t + \Delta t) - \mathbf{r}^N(t - \Delta t)}{2\Delta t}$$

Molecular Dynamics Ensembles

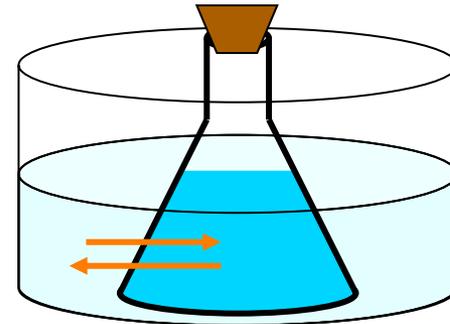
isolated system (N, V, E)



microcanonical ensemble

Potential + Kinetic Energy

closed system in contact with
heat bath (N, V, T)



canonical ensemble

Different conserved quantities

Constant Temperature MD: Nose Thermostat

Extend Hamiltonian to include “heat bath” variable s .

Nosé, *J.Chem.Phys.* **81**:511 (1984), *Mol.Phys.* **52**:255 (1984)

STATIS file:
conserved quantity

$$H(\mathbf{p}^N, \mathbf{r}^N, s, p_s) = \frac{1}{2} \sum_{j=1}^N \frac{\mathbf{p}_j^2}{m_j s^2} + V(\mathbf{r}^N) + \frac{p_s^2}{2M} + \frac{g+1}{\beta} \ln s$$

(Choice of the constant g made later.)

MD average from this Hamiltonian.

$$\langle A(\mathbf{p}^N, \mathbf{r}^N) \rangle = \frac{1}{\Omega} \int d\mathbf{p}^N d\mathbf{r}^N dp_s ds A(\mathbf{p}^N, \mathbf{r}^N) \delta(H(\mathbf{p}^N, \mathbf{r}^N, s, p_s) - E)$$

$$\Omega = \int d\mathbf{p}^N d\mathbf{r}^N dp_s ds \delta(H(\mathbf{p}^N, \mathbf{r}^N, s, p_s) - E)$$

Constant Temperature MD: Nose Thermostat

Microcanonical molecular dynamics with the Hamiltonian,

$$H(\mathbf{p}^N, \mathbf{r}^N, s, p_s) = \sum_{j=1}^N \frac{\mathbf{p}_j^2}{2m_j s^2} + V(\mathbf{r}^N) + \frac{p_s^2}{2M} + \frac{g+1}{\beta} \ln s, \quad g = 3N$$

leads to a *canonical* distribution with respect to another Hamiltonian,

$$H_0 = \sum_{j=1}^N \frac{\mathbf{p}'_j{}^2}{2m_j} + V(\mathbf{r}^N), \quad \text{where } \mathbf{p}'_j = \frac{\mathbf{p}_j}{s}.$$

Nose *Mol. Phys.*, 52:255 (1984); *J. Chem. Phys.*, 81:511 (1984).

Nose Thermostat: Equations of Motion

$$H(\mathbf{p}^N, \mathbf{r}^N, s, p_s) = \sum_{j=1}^N \frac{\mathbf{p}_j^2}{2m_j s^2} + V(\mathbf{r}^N) + \frac{p_s^2}{2M} + \frac{g+1}{\beta} \ln s,$$

The Nosé Hamiltonian leads to the following equations of motion

$$\dot{\mathbf{r}}_j = \frac{\partial H}{\partial \mathbf{p}_j} = \frac{\mathbf{p}_j}{m_j s^2}$$

$$\dot{\mathbf{p}}_j = -\frac{\partial H}{\partial \mathbf{r}_j} = -\frac{\partial V}{\partial \mathbf{r}_j}$$

$$\dot{s} = \frac{\partial H}{\partial p_s} = \frac{p_s}{M}$$

$$\dot{p}_s = -\frac{\partial H}{\partial s} = -\sum_{j=1}^N \frac{\mathbf{p}_j^2}{m_j s^3} + \frac{g+1}{\beta s}$$

Nose-Hoover Thermostat: Equations of Motion

$$H(\mathbf{p}^N, \mathbf{r}^N, s, p_s) = \sum_{j=1}^N \frac{\mathbf{p}_j^2}{2m_j s^2} + V(\mathbf{r}^N) + \frac{p_s^2}{2M} + \frac{g+1}{\beta} \ln s,$$

Hoover showed rescaling to a new time variable $dt = s dt'$, leads to:

$$\frac{d\mathbf{r}_j}{dt'} = \frac{d\mathbf{r}_j}{dt} \frac{dt}{dt'} = \frac{\mathbf{p}_j}{m_j s^2} s = \frac{\mathbf{p}_j}{m_j s} = \frac{\mathbf{p}'_j}{m_j} \quad \text{where } \mathbf{p}'_j = \frac{\mathbf{p}_j}{s}.$$

$$\frac{d\mathbf{p}'_j}{dt'} = \frac{d(\mathbf{p}_j / s)}{dt} \frac{dt}{dt'} = \frac{d(\mathbf{p}_j / s)}{dt} s = -\frac{\partial V(\mathbf{r}^N)}{\partial \mathbf{r}_j} - \frac{\mathbf{p}_j}{s} \frac{ds}{dt} = -\frac{\partial V(\mathbf{r}^N)}{\partial \mathbf{r}_j} - \zeta \mathbf{p}'_j$$

where $\zeta = \frac{ds}{dt} = \frac{1}{s} \frac{ds}{dt'}$ is a type of friction coefficient.

Friction: CONTROL file Nose-Hoover time constant

Nose-Hoover Thermostat

Hoover, *Phys.Rev.* **A31**:1695 (1985)

$$dt = s dt'$$

$$\mathbf{p}'_j = \frac{\mathbf{p}_j}{s}$$

$$\frac{d\mathbf{r}_j}{dt'} = \frac{\mathbf{p}'_j}{m_j}$$

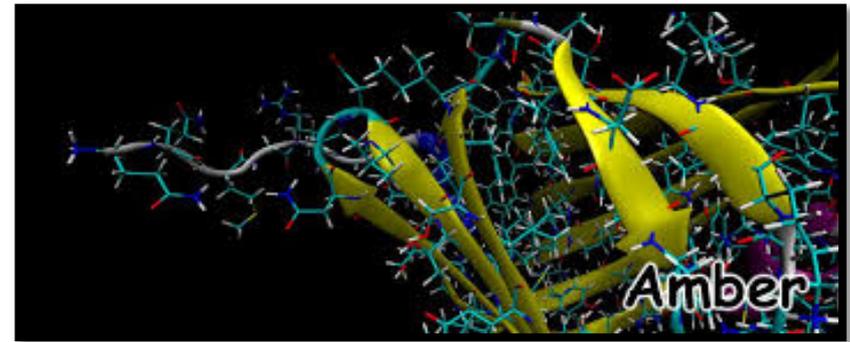
$$\frac{d\mathbf{p}'_j}{dt'} = -\frac{\partial V(\mathbf{r}^N)}{\partial \mathbf{r}_j} - \zeta \mathbf{p}'_j$$

$$\frac{d\zeta}{dt'} = \frac{1}{M} \left(\sum_{j=1}^N \frac{\mathbf{p}'_j{}^2}{m_j} - \frac{g+1}{\beta} \right), \quad g = 3N$$

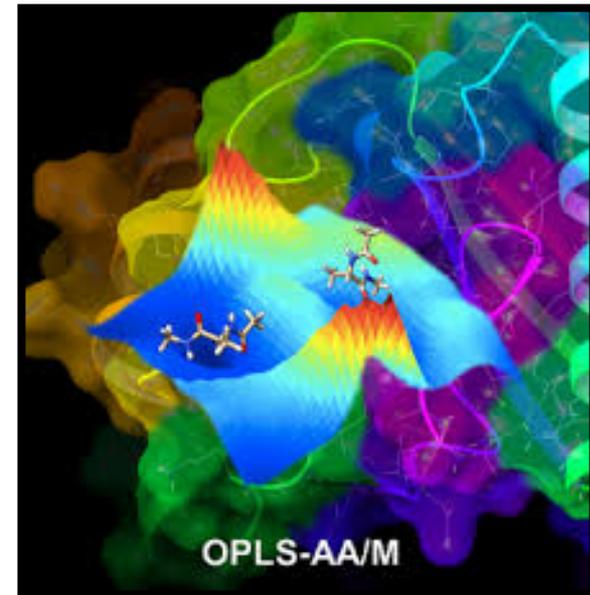
ζ changes according to difference between $K.E.$ and $3Nk_B T/2$.

Some Practical Issues of Force Fields

Force Fields for Bio-Molecular Simulations



GROMOS



Wisdom is that FF should not be mixed

FF fitting: experimental observables vs ab initio data

SPC and SPC/E: GROMOS

TIP₃P: CHARMM and AMBER

TIP₄P/TIP₅P/TIP₄P-EW: OPLS

Challenge of Current Water Models

TABLE III. Melting properties of ice I_h at $p=1$ bar for different models. T_m and T_c , melting and critical temperatures; ρ_l and ρ_{Ih} , coexistence densities of liquid water and ice; H_l and H_{Ih} , enthalpies of liquid and ice (we have not included the $3RT$ term arising from the translational and rotational kinetic terms); ΔH , melting enthalpy; dp/dT , slope of the coexistence curve. Numbers in parenthesis for the TIP4P model are the estimated errors for TIP4P. The errors for the other models are of the same order of magnitude. Unless otherwise stated, the quantities have been calculated in this work.

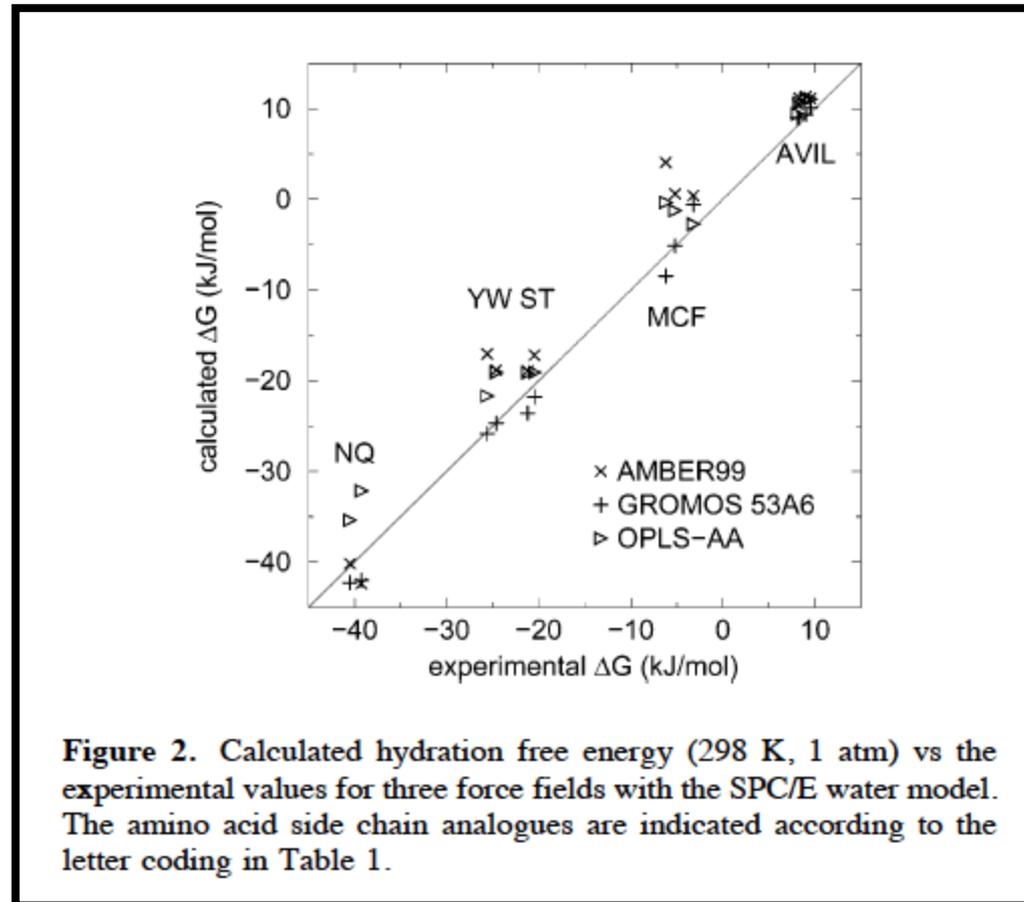
Model	SPC	SPC/E	TIP4P	TIP4P/Ew	TIP5P	TIP5P ^a	TIP3P	Expt.
T_m (K)	190.5	215	232.(5)	245.5	273.9	270	145.6	273.15
T_c (K) ^b	593.8	638.6	588.2	...	521.3	521.3		647.1
T_m/T_c	0.321	0.337	0.394	...	0.525	0.517		0.422
ρ_l (g/cm ³)	0.991	1.011	1.002(6)	0.992	0.987	1.000	1.017	0.999
ρ_{Ih} (g/cm ³)	0.934	0.950	0.940(2)	0.936	0.967	0.982	0.947	0.917
H_l (Kcal/mol)	-11.64	-12.49	-10.98	-12.02	-10.33	...	-11.69	...
H_{Ih} (Kcal/mol)	-12.22	-13.23	-12.03	-13.07	-12.08	...	-11.99	...
ΔH (Kcal/mol)	0.62	0.74	1.05(5)	1.05	1.75	1.73	0.3	1.44
dp/dT (bar/K)	-115	-126	-160(20)	-164	-708	-714	-66	-135

^aFrom Ref. 51.

^bFrom Ref. 22 (SPC, SPC/E), Ref. 23 (TIP4P), Refs. 87 and 99 (TIP5P).

How Good/Bad Are the Force Fields?

Hydration Free Energies



The Case of Folded vs Disordered Proteins

Developing a molecular dynamics force field for both folded and disordered protein states

Paul Robustelli^a, Stefano Piana^{a,1}, and David E. Shaw^{a,b,1}

^aD. E. Shaw Research, New York, NY 10036; and ^bDepartment of Biochemistry and Molecular Biophysics, Columbia University, New York, NY 10032

Edited by Michael L. Klein, Temple University, Philadelphia, PA, and approved April 16, 2018 (received for review January 19, 2018)

