Molecular Simulation

- Describes chemical systems at an atomic level of detail.
- Specifies a collection of atoms or molecules in a simulation cell interacting through a potential and evolving according to some simulation algorithm.
- Different methods can be used to obtain both thermodynamic and kinetic properties.

Simulation Algorithms

- Molecular Mechanics: Mechanical study of the properties of one or several molecules.
- Monte Carlo Simulation: Calculates various thermodynamic properties using stochastic moves of particles.
- Molecular Dynamics Simulation: Classical equations of motion are integrated in time.

What Is Molecular Dynamics?

- Computational technique used in a variety of disciplines like physics, chemistry, biology, material science in modeling real systems.
- Simulates the thermodynamic behavior of materials using their positions, velocities and forces.
- N particles interact by certain laws.
- Classical molecular dynamics – Newton's equations of motion.

FACTORS GOVERNING MD SIMULATION

- choice of the degrees of freedom
- force field parameters
- treatment of non-bonded interactions
- solvation effects
- boundary conditions
- treatment of temperature and pressure
- integration time step
- starting configuration

Potential Energy

- The force between particles is dependent on the distance r between the particles
- These forces can be defined in terms of the potential energy $\Phi(r)$ between the particles: $f(r) = -\nabla\Phi(r)$
- Can distinguish the three different interaction models by the potential energy used by each model

Three Interaction Models

- **Hooke's Law:**
  forces proportional to the displacements

- **Lennard-Jones Potential:**
  - strong repulsive force when particles are close
  - weak attractive force when particles are far apart

- **Hard-Sphere Interaction:**
  - no force when separated
  - large instantaneous repulsive force when they touch

Potential Energy Definitions

- Hooke's Law Potential: $\Phi(r) = \| r \|^2$
- Lennard-Jones Potential: $\Phi(r) = \frac{1}{\| r \|^{12}} - \frac{2}{\| r \|^6}$
- Hard-Sphere Potential: $\Phi(r) = \begin{cases} 0, & \| r \| > \sigma \\ \infty, & \| r \| \leq \sigma \end{cases}$

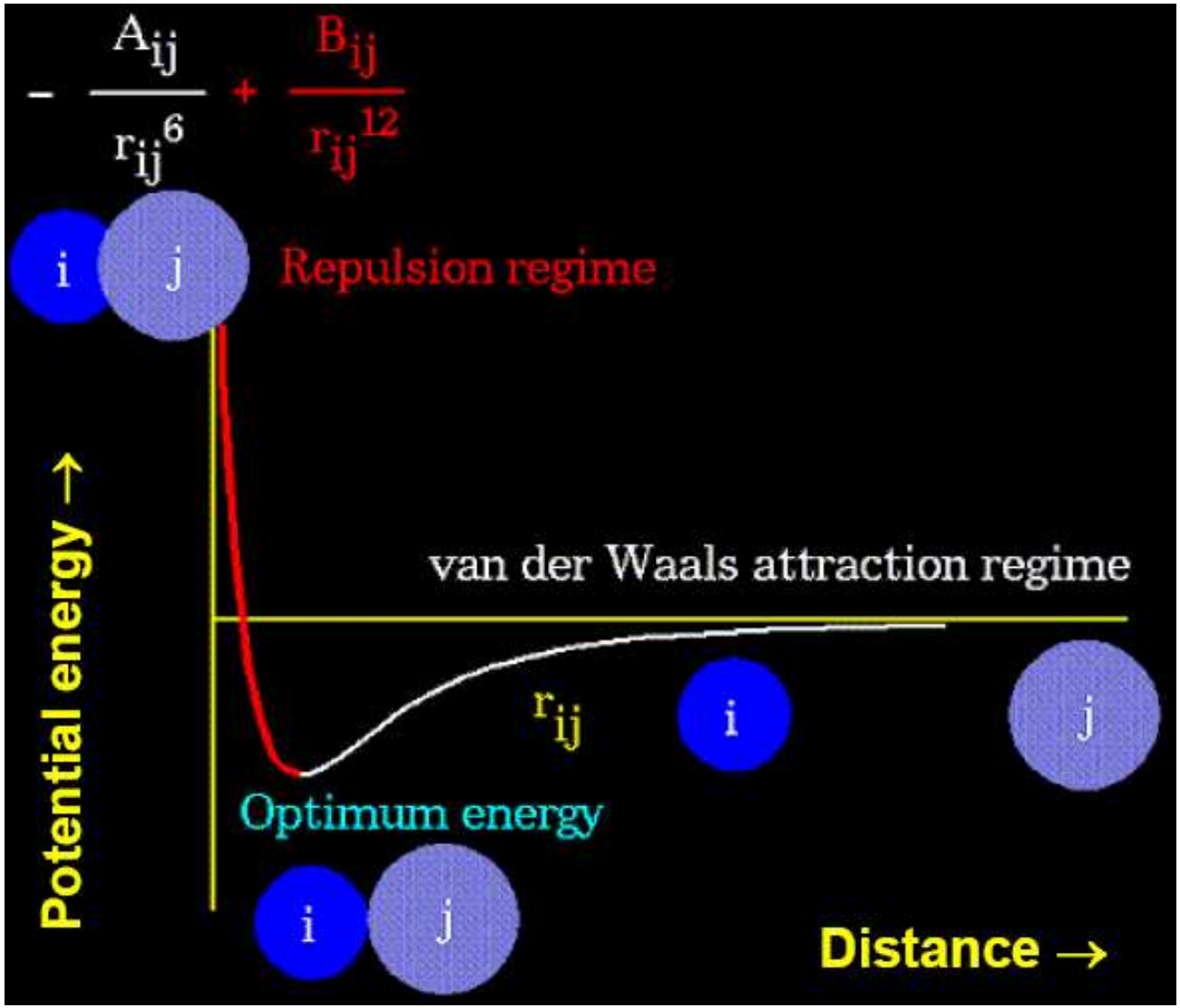
Physics of MD and MC

- Connection to classical statistical mechanics
  - Average values (NVT ensemble averages) of an observable A (e.g. P, E, C_V) can be computed as

$$\langle A \rangle = \frac{\int d\vec{r}^N d\vec{p}^N e^{-\beta H(\vec{r}^N, \vec{p}^N)} A(\vec{r}^N, \vec{p}^N)}{\int d\vec{r}^N d\vec{p}^N e^{-\beta H(\vec{r}^N, \vec{p}^N)}}$$

where H is the Hamiltonian and $\beta = 1/k_B T$

van der Waals Interactions



General Scheme of MD Simulation

- Predict the positions, velocities, accelerations at time $t + \delta t$ using their current values.
- Evaluate the forces and accelerations from the new positions using $\mathbf{a}_i = \frac{\mathbf{f}_i}{m_i}$.
- Correct the predicted positions, velocities and accelerations using new accelerations.
- Calculate any variable of interest such as energy, virial coefficients etc.

What Goes Into a MD Code?

Fortran 77 Fortran 90 C C++

Initialization

Force Calculation $\Rightarrow$ Lennard-Jones potential

Integration $\Rightarrow$ Verlet

Velocity Verlet

Leap frog

Force Calculation

MD with Lennard-Jones Potential

$$U_{LJ} = 4\varepsilon[(\frac{\sigma}{r})^{12} - (\frac{\sigma}{r})^{6}]$$

Lennard-Jones Force

$$F_{LJ} = -\frac{24\varepsilon}{r}[2(\frac{\sigma}{r})^{12} - (\frac{\sigma}{r})^{6}]$$

Verlet Algorithm

Direct solution of the second order differential equation

$$\mathbf{F} = m\frac{d^2\mathbf{r}}{dt^2}$$

Equations for generating the position coordinates

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

Correct except for errors $O(\delta t^4)$

Velocity Verlet Algorithm

A Verlet equivalent algorithm which yields position, velocity and acceleration at time *t*.

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

$$\mathbf{v}(t + \delta t) = \mathbf{v}(t) + \frac{1}{2} \delta t [\mathbf{a}(t) + \mathbf{a}(t + \delta t)]$$

Minimizes round-off error.

Leap Frog Algorithm

Modifications of the basic Verlet scheme.

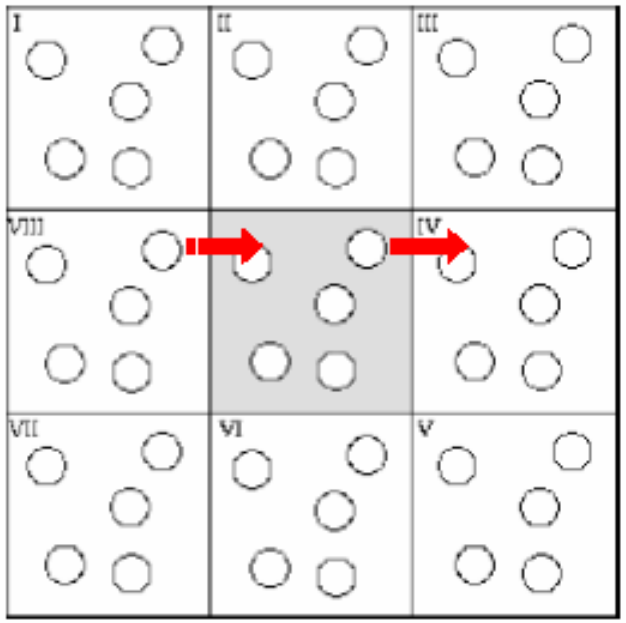
Velocities calculated at time $t + \frac{1}{2}\delta t$ are used to calculate the position $\mathbf{r}$ at time $t + \delta t$

$$\mathbf{r}(t + \delta t) = \mathbf{r}(t) + \delta t \mathbf{v}(t + \frac{1}{2}\delta t)$$

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

Periodic Boundary Condition

- For explicit representation of the solvent
- The boundaries of the system must be represented
- Permits the modeling of very large systems



Two-dimensional Periodic system

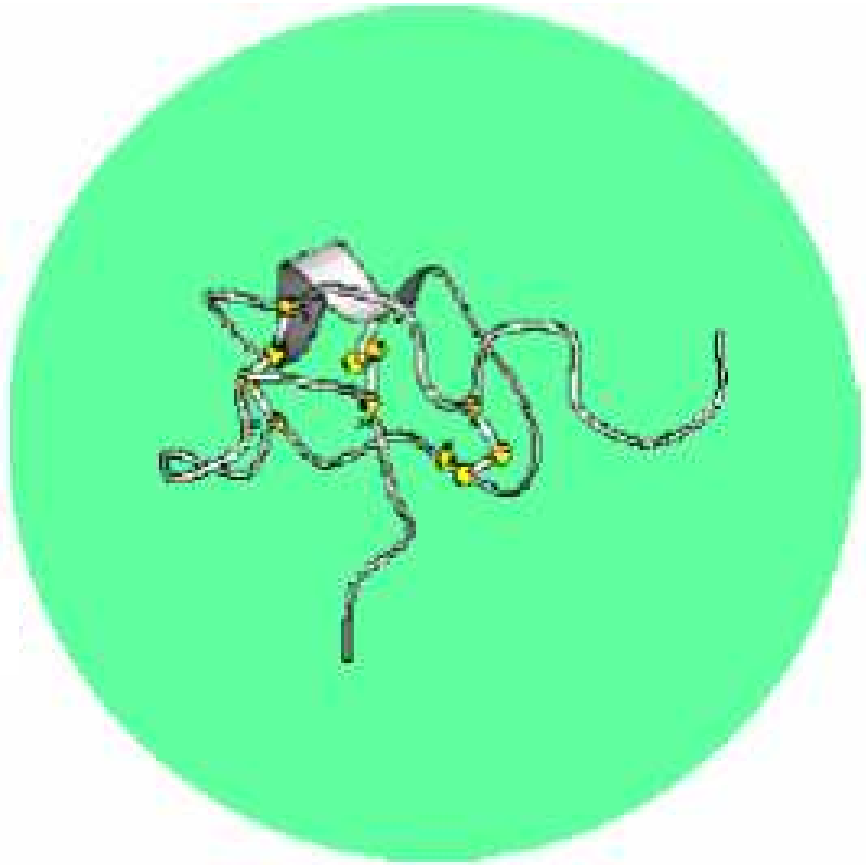
Treatment of Solvent

- Implicit: the macromolecule interacts with itself

$$E_{elec}(r) = \frac{q_i q_j}{\varepsilon r^2}$$

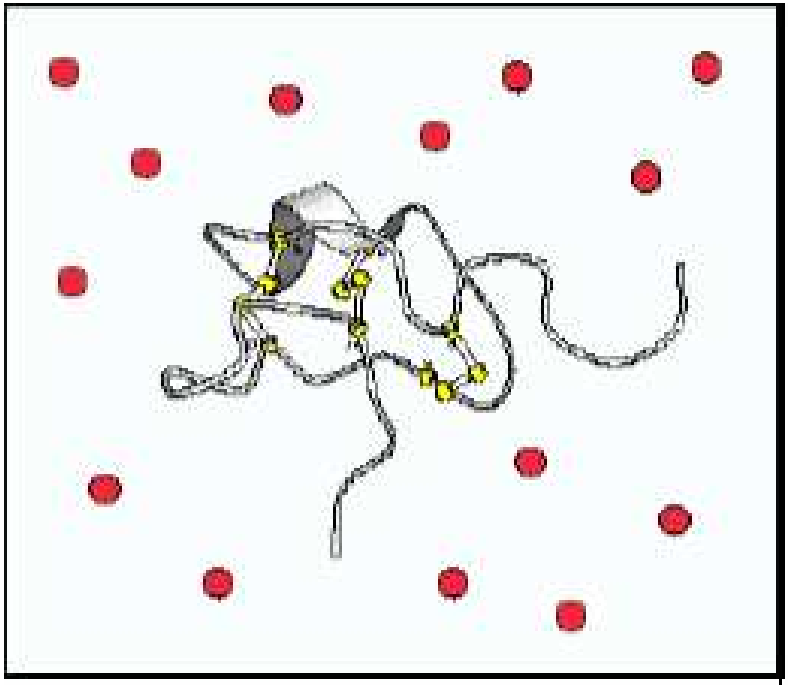
- Solvent effects are contained in the dielectric constant

ε



Treatment of Solvent

- Explicit representation the macromolecule is surrounded by water, ions with which it interacts.
- Specific non-bonded interactions are calculated.



$$\sum_{i,j}\{4\varepsilon[(\frac{\sigma_{ij}}{r_{ij}})^{12}-(\frac{\sigma_{ij}}{r_{ij}})^{6}]+\frac{q_i q_j}{r_{ij}}\}$$

Protocol for MD Simulation

- Initial Coordinates

X-ray diffraction or NMR coordinates from Protein Data Bank

Coordinates obtained from Homology Modeling

- Treatment of Non-bonded Interactions
- Treatment of Solvent

Implicit: Choice of dielectric constant

Explicit: Solvation protocol

- Periodic Boundary Condition