Molecular dynamics (MD) simulations

◆ A deterministic method based on the solution of Newton's equation of motion

$$F_i = m_i\, a_i$$

for the ith particle; the acceleration at each step is calculated from the negative gradient of the overall potential, using

$$F_i = -\,grad\ V_i - = -\,\nabla\ V_i$$

$V_i = \sum_k$(energies of interactions between i and all other residues k located within a cutoff distance of R_c from i)

∇V_i = Gradient of potential?

- ◆ Derivative of V with respect to the position vector $r_i = (x_i, y_i, z_i)^T$ at each step

$$a_{xi} \sim -\partial V/\partial x_i$$
$$a_{yi} \sim -\partial V/\partial y_i$$
$$a_{zi} \sim -\partial V/\partial z_i$$

Interaction potentials include;

Non-Bonded Interaction Potentials

- ◆ Electrostatic interactions of the form $E_{ik}(es) = q_i q_k / r_{ik}$
- ◆ Van de Waals interactions $E_{ij}(vdW) = - a_{ik}/r_{ik}^6 + b_{ik}/r_{ik}^{12}$

Bonded Interaction Potentials

- ◆ Bond stretching $E_i(bs) = (k_{bs}/2) (l_i - l_i^0)^2$
- ◆ Bond angle distortion $E_i(bad) = (k_\theta/2) (\theta_i - \theta_i^0)^2$
- ◆ Bond torsional rotation $E_i(tor) = (k_\phi/2) f(\cos\phi_i)$

Example 1: gradient of vdW interaction with k, with respect to r_i

- $E_{ik}(vdW) = -a_{ik}/r_{ik}^6 + b_{ik}/r_{ik}^{12}$

- $r_{ik} = r_k - r_i$
  - $x_{ik} = x_k - x_i$
  - $y_{ik} = y_k - y_i$
  - $z_{ik} = z_k - z_i$
  - $r_{ik} = [\,(x_k - x_i)^2 + (y_k - y_i)^2 + (z_k - z_i)^2\,]^{1/2}$

- $\partial V/\partial x_i = \partial\,[-a_{ik}/r_{ik}^6 + b_{ik}/r_{ik}^{12}]\,/\,\partial x_i$

  where $r_{ik}^6 = [\,(x_k - x_i)^2 + (y_k - y_i)^2 + (z_k - z_i)^2\,]^3$

Example 2: gradient of bond stretching potential with respect to r_i

- $E_i(bs) = (k_{bs}/2)(l_i - l_i^0)^2$
- $l_i = r_{i+1} - r_i$
  - $l_{ix} = x_{i+1} - x_i$
  - $l_{iy} = y_{i+1} - y_i$
  - $l_{iz} = z_{i+1} - z_i$
  - $l_i = [(x_{i+1} - x_i)^2 + (y_{i+1} - y_i)^2 + (z_{i+1} - z_i)^2]^{1/2}$

$\partial E_i(bs)/\partial x_i = -m_i a_{ix}(bs)$ *(induced by deforming bond l_i)*

$\quad = (k_{bs}/2)\,\partial\{[(x_{i+1} - x_i)^2 + (y_{i+1} - y_i)^2 + (z_{i+1} - z_i)^2]^{1/2} - l_i^0\}^2/\partial x_i$

$\quad = k_{bs}(l_i - l_i^0)\,\partial\{[(x_{i+1} - x_i)^2 + (y_{i+1} - y_i)^2 + (z_{i+1} - z_i)^2]^{1/2} - l_i^0\}/\partial x_i$

$\quad = k_{bs}(l_i - l_i^0)(1/2)(l_i^{-1})\,\partial(x_{i+1} - x_i)^2/\partial x_i = -k_{bs}(1 - l_i^0/l_i)(x_{i+1} - x_i)$

The Verlet algorithm

Perhaps the most widely used method of integrating the equations of motion is that initially adopted by Verlet [1967] .The method is based on positions $r(t)$, accelerations $a(t)$, and the positions $r(t-\delta t)$ from the previous step.

The equation for advancing the positions reads as

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

There are several points to note about this equation. It will be seen that the velocities do not appear at all. They have been eliminated by addition of the equations obtained by Taylor expansion about $r(t)$:
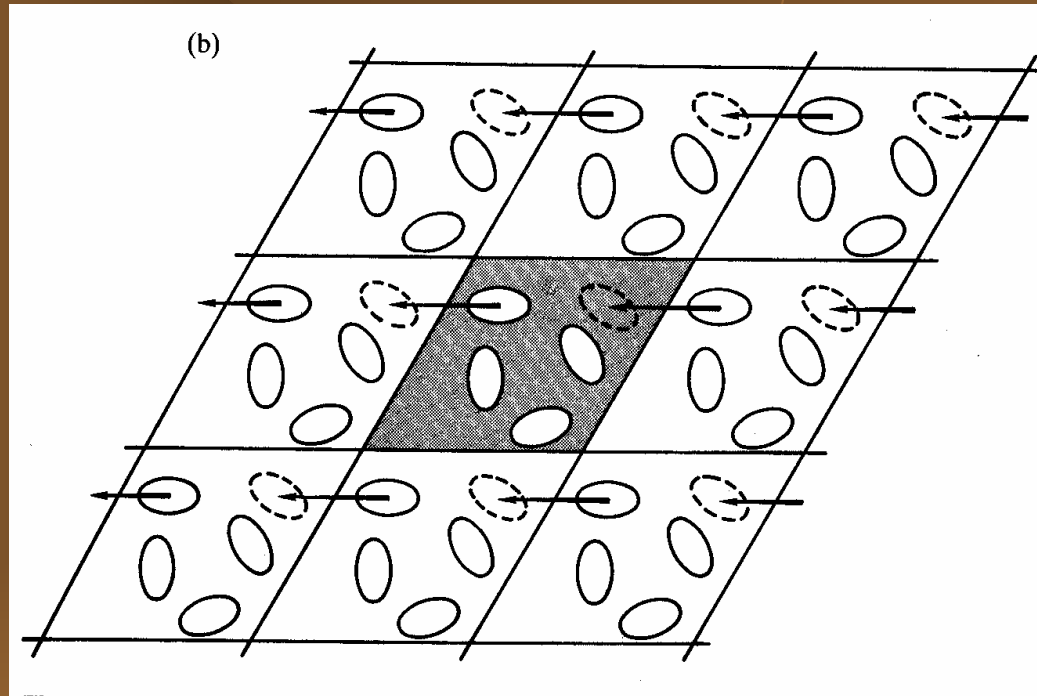
$$r(t+\delta t) = r(t) + \delta t\, v(t) + (1/2) \delta t^2\, a(t)+ \dots$$

$$r(t-\delta t) = r(t) - \delta t\, v(t) + (1/2) \delta t^2\, a(t)-$$

The velocities are not needed to compute the trajectories, but they are useful for estimating the kinetic energy (and hence the total energy). They may be obtained from the formula

$$v(t)= [r(t+\delta t)-r(t-\delta t)]/2\delta t$$

Periodic boundary conditions

Initial velocities (v_i)

using the Boltzmann distribution at the given temperature

$$v_i = (m_i/2\pi kT)^{1/2} \exp(- m_i v_i^2/2kT)$$

How to generate MD trajectories?

- Known initial conformation, i.e. $r_i(0)$ for all atom i
- Assign $v_i(0)$, based on Boltzmann distribution at given T
- Calculate $r_i(\delta t) = r_i(0) + \delta t\, v_i(0)$
- Using new $r_i(\delta t)$ evaluate the total potential V_i on atom I
- Calculate negative gradient of V_i to find $a_i(\delta t) = -\nabla V_i / m_i$
- Start Verlet algorithm using $r_i(0)$, $r_i(\delta t)$ and $a_i(\delta t)$
- Repeat for all atoms (including solvent, if any)
- Repeat the last three steps for $\sim 10^6$ successive times (MD steps)

Limitations of MD simulations

- Full atomic representation → noise
- Empirical force fields → limited by the accuracy of the potentials
- Time steps constrained by the fastest motion (bond stretching of the order of femptoseconds
- Inefficient sampling of the complete space of conformations
- Limited to small proteins (100s of residues) and short times (subnanoseconds)