

Molecular Dynamics Simulations

Molecular dynamics (MD): force fields

$\vec{F}_i = -\nabla_i U_{pot}$

potential energy

$$U_{pot} = \sum_{bonds} \frac{1}{2} k_b \cdot (r - r_0)^2 + \sum_{angles} \frac{1}{2} k_\theta (\theta - \theta_0)^2 + \sum_{dihedrals} K_\phi \cdot (1 + \cos(n \cdot \phi - \delta)) + \sum_{improper\ dihedrals} \frac{1}{2} k_\xi (\xi - \xi_0)^2 + \sum_{atom\ pairs} \left[\frac{1}{4 \cdot \pi \cdot \epsilon_0} \frac{q_i q_j}{r_{ij}} + \frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^6} \right]$$

bonded

nonbonded

Molecular dynamics (MD): algorithms

all algorithms are based on Taylor expansions of atomic positions around a given time

$$\mathbf{r}_i(t + \Delta t) = \mathbf{r}_i(t) + \Delta t \frac{d\mathbf{r}_i(t)}{dt} + \frac{\Delta t^2}{2} \frac{d^2\mathbf{r}_i(t)}{dt^2} + \dots$$

this gives a discretization suitable for integration of the equations of motion

$$\mathbf{F}_i = m_i \mathbf{a}_i \quad (\mathbf{F}_i = -\nabla_i U_{pot})$$

analytical derivatives
in cartesian coordinates

Verlet/Leap Frog algorithm

$$\mathbf{v}_i \left(t + \frac{\Delta t}{2} \right) = \mathbf{v}_i \left(t - \frac{\Delta t}{2} \right) + \frac{\mathbf{F}_i}{m_i} \Delta t$$

$$\mathbf{r}_i(t + \Delta t) = \mathbf{r}_i(t) + \mathbf{v}_i \left(t + \frac{\Delta t}{2} \right) \Delta t$$

Molecular dynamics (MD): algorithms

Verlet/Leap Frog algorithm

$$\mathbf{v}_{n+1/2} = \mathbf{v}_{n-1/2} + \mathbf{a}_n \Delta t$$

$$\mathbf{r}_{n+1} = \mathbf{r}_n + \mathbf{v}_{n+1/2} \Delta t$$

initial conditions

from X-ray, homology modelling, docking etc.

from T=0 or from Maxwell distribution

temperature control

$$f(v_i) = \left(\frac{m}{2\pi kT} \right)^{1/2} e^{-\frac{mv_i^2}{2kT}}$$

$$\mathbf{v}_{n+1/2} \rightarrow \mathbf{v}_{n+1/2} \left[1 + \frac{\Delta t}{2\tau} \left(\frac{T_{target}}{T_{n+1/2}} - 1 \right) \right]$$

$$\Delta T(t) = \Delta T(0) e^{-t/\tau}$$

Molecular dynamics (MD): algorithms

Verlet/Leap Frog algorithm

$$v_{n+1/2} = v_{n-1/2} + a_n \Delta t$$

$$r_{n+1} = r_n + v_{n+1/2} \Delta t$$

computation scheme

$$a_n = -\nabla_i U_{pot} / m_i$$

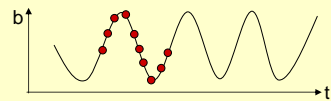
$$v_{n+1/2} = v_{n-1/2} + a_n \Delta t$$

$$v_{n+1/2} = v_{n+1/2} \lambda(T)$$

$$r_{n+1} = r_n + v_{n+1/2} \Delta t$$

accuracy \leftrightarrow Δt

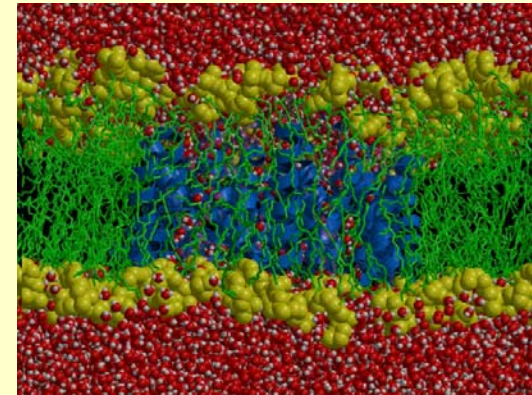
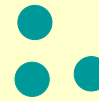
Δt is determined by the highest frequencies of the system, typically X-H vibrations



5-10 sampling points/period \Rightarrow
 $\Delta t \sim 1 \times 10^{-15} s$

Molecular dynamics (MD): what happens

\rightarrow trajectories \rightarrow thermodynamic averages



Molecular dynamics (MD): boundary conditions

three basic approaches:

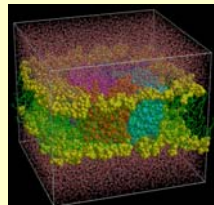
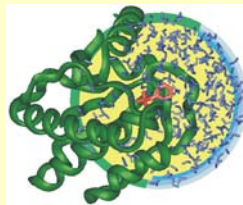
dielectric continuum

finite aperiodic

infinite periodic



$$U_{el} = \frac{q_i q_j}{r \epsilon(\mathbf{r})}$$



energetics? structure? dynamics?

Molecular dynamics (MD): boundary conditions

macroscopic vs. microscopic solvation:

macroscopic

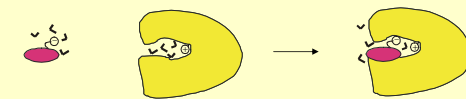
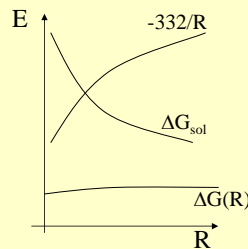
$$\Delta G(R) = 332 Q_1 Q_2 / \epsilon R$$

$\epsilon=80$



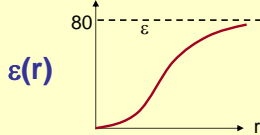
E

microscopic



Molecular dynamics (MD): boundary conditions

dielectric continuum models



$\epsilon(r)$

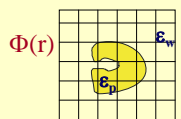
80

ϵ

r

e.g., Mehler & Eichele, 1984

Poisson-Boltzmann



$\Phi(r)$

E_w

q_p

Generalized Born

$$\Delta G_{sol} = -166 \left(1 - \frac{1}{\epsilon} \right) \sum_{i,j} \frac{q_i q_j}{\sqrt{r_{ij}^2 - \alpha_i \alpha_j e^{-r_{ij}^2 / (4\alpha_i \alpha_j)^{1/2}}}}$$

can be combined with Langevin dynamics:

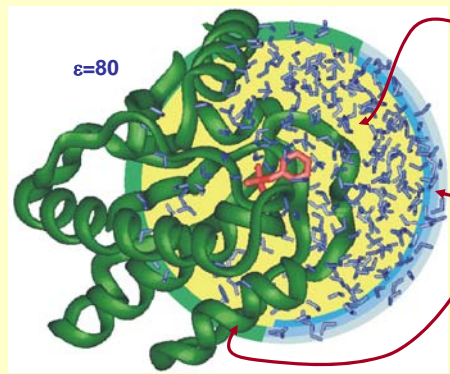
$$m\ddot{a} = \vec{F}(t) - m\gamma\dot{v}(t) + \vec{R}(t)$$

hydrophobic effects? e.g., surface area relationships

$$\Delta G_{Hyphobic} \propto \gamma A_S$$

Molecular dynamics (MD): boundary conditions

finite aperiod models – usually spherical



$\epsilon=80$

full MD

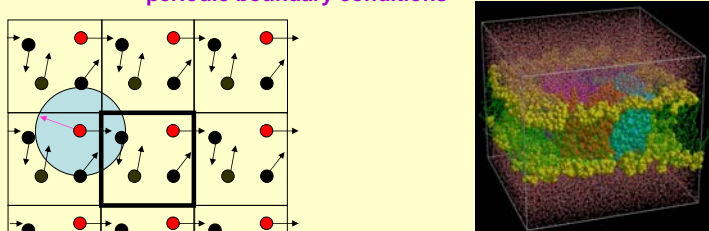
restrained MD

$$U_{pot} = \sum_{bonds} \frac{1}{2} k_b \cdot (r - r_0)^2 + \sum_{angles} \frac{1}{2} k_a \cdot (\theta - \theta_0)^2 + \sum_{dihedrals} K_p \cdot (1 + \cos(n \cdot \phi - \delta)) + \sum_{improper\ dihedrals} \frac{1}{2} k_\phi \cdot (\xi - \xi_0)^2 + \sum_{atom\ pairs} \frac{q_i q_j}{r_{ij}} + \frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^6} + U_{restraints}$$

fast and no artificial symmetry imposed

Molecular dynamics (MD): boundary conditions

periodic boundary conditions

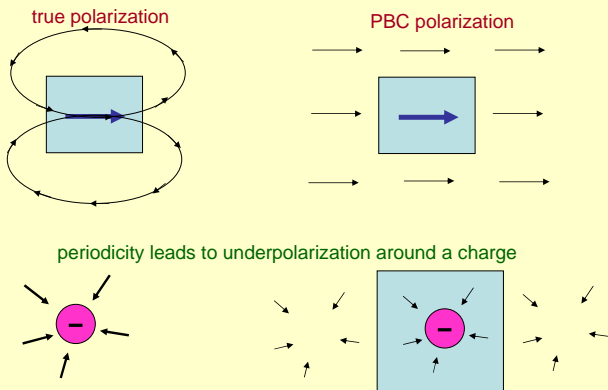


infinite no. of nonbonded interactions \Rightarrow use cutoff or lattice (Ewald summation)

Cube **Truncated octahedron** **Hexagonal prism** **Rhombic dodecahedron**

Molecular dynamics (MD): boundary conditions

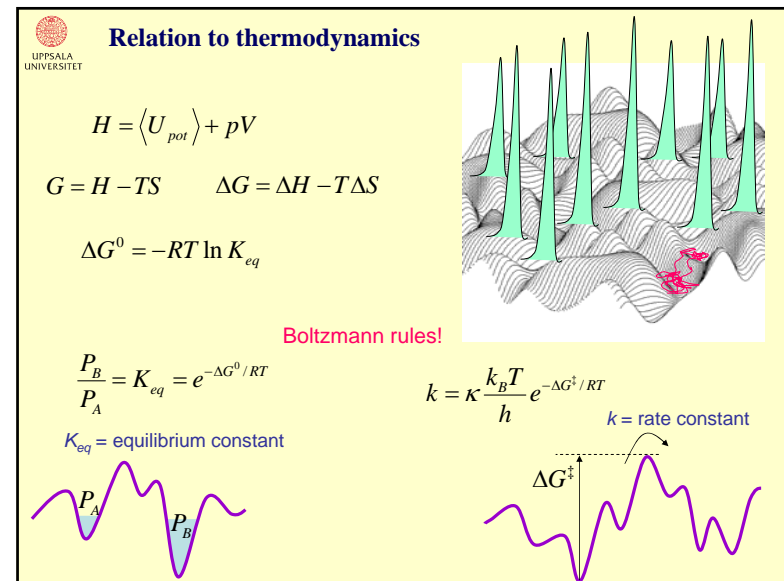
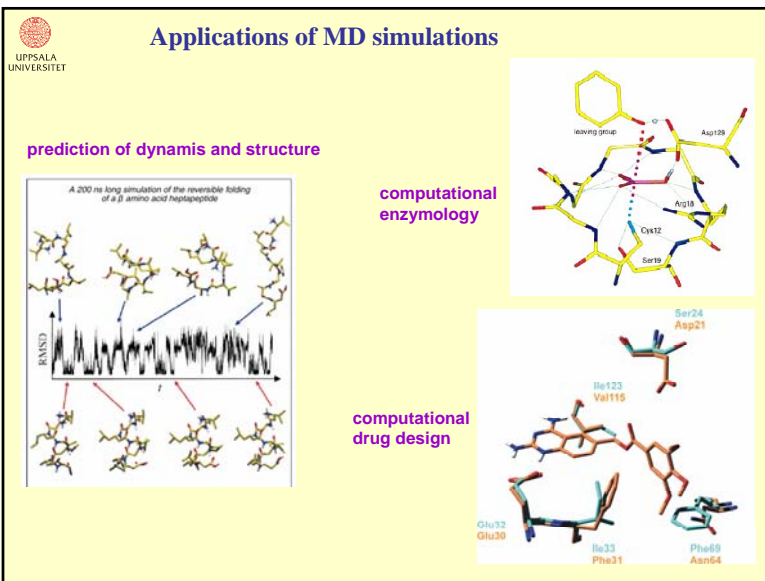
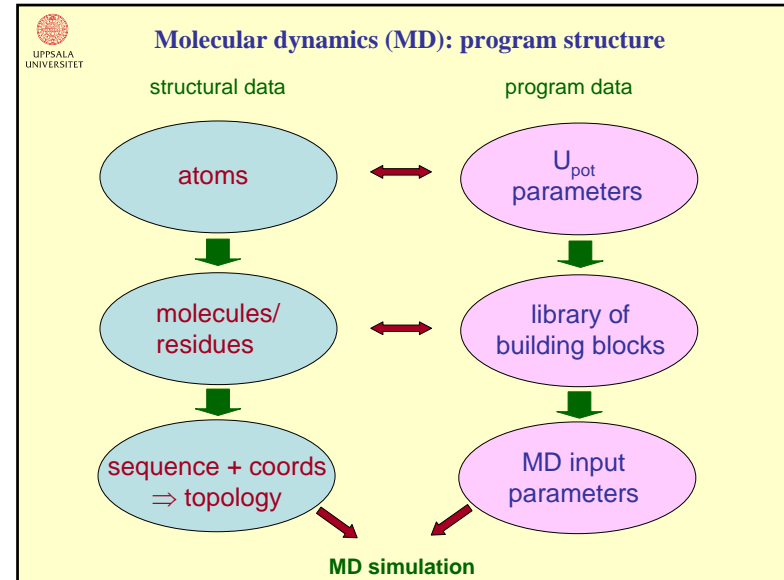
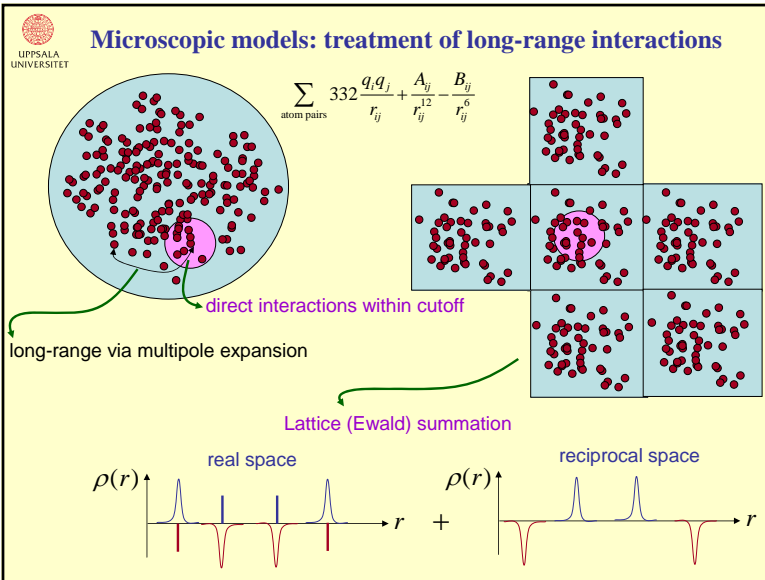
periodic boundary conditions – problems with artificial symmetry



true polarization

PBC polarization

periodicity leads to underpolarization around a charge



Free Energy Perturbation (FEP) and Thermodynamic Integration (TI) Methods

We consider two systems, A and B, described by potentials U_A and U_B

$$F = -kT \ln Q = -kT \ln \left(\int \dots \int e^{-U_{pot}/kT} d\vec{r}_1 \dots d\vec{r}_N \right) \prod_j \Lambda_j^{3N_j}$$

Z, the configuration integral

$$\Delta F = -kT \ln \frac{Q_B}{Q_A} = -kT \ln \frac{Z_B}{Z_A} = -kT \ln \frac{\int e^{-U_B/kT} d\Gamma}{\int e^{-U_A/kT} d\Gamma}$$

$$= -kT \ln \frac{\int e^{-U_B/kT} e^{+U_A/kT} e^{-U_A/kT} d\Gamma}{\int e^{-U_A/kT} d\Gamma} = -kT \ln \frac{\int e^{-(U_B-U_A)} e^{-U_A/kT} d\Gamma}{\int e^{-U_A/kT} d\Gamma}$$

$$= -kT \ln \left\langle e^{-(U_B-U_A)/kT} \right\rangle_A$$

FEP (Zwanzig's formula)

Free Energy Perturbation (FEP) and Thermodynamic Integration (TI) Methods

We consider two systems, A and B, described by potentials U_A and U_B

$$\text{Let } U(\lambda=0) = U_A \text{ and } U(\lambda=1) = U_B \rightarrow \Delta F = \int_0^1 \frac{\partial F}{\partial \lambda} d\lambda$$

$$\frac{\partial F(\lambda)}{\partial \lambda} = -kT \frac{\partial \ln Z(\lambda)}{\partial \lambda} = -kT \frac{1}{Z} \frac{\partial Z(\lambda)}{\partial \lambda}$$

$$= -kT \frac{1}{Z} \frac{\partial}{\partial \lambda} \int e^{-U(\lambda)/kT} d\Gamma = \frac{\int \frac{\partial U(\lambda)}{\partial \lambda} e^{-U(\lambda)/kT} d\Gamma}{\int e^{-U(\lambda)/kT} d\Gamma}$$

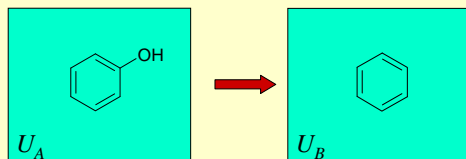
$$= \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_\lambda \rightarrow \Delta F = \int_0^1 \frac{\partial F}{\partial \lambda} d\lambda = \int_0^1 \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_\lambda d\lambda$$

TI (integration formula)

Free Energy Perturbation (FEP) and Thermodynamic Integration (TI) Methods

We consider two systems, A and B

$$\Delta U = U_B - U_A$$



FEP (Zwanzig's formula)

$$\Delta G = G_B - G_A = -\beta^{-1} \ln \langle \exp(-\beta \Delta U) \rangle_A$$

$$U_m = (1-\lambda_m)U_A + \lambda_m U_B = U_A + \lambda_m \Delta U$$

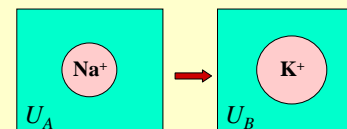
$$\Delta G = G_B - G_A = -\beta^{-1} \sum_{m=1}^{n-1} \ln \langle \exp[-\beta(U_{m+1} - U_m)] \rangle_{m}$$

TI (integration formula)

$$\Delta G = \int_0^1 \frac{\partial G(\lambda)}{\partial \lambda} d\lambda$$

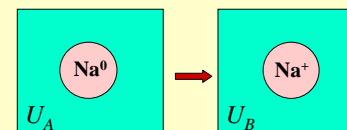
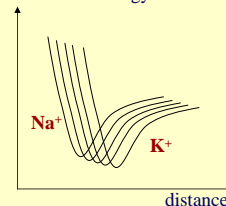
$$\Delta G = \int_0^1 \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_\lambda d\lambda$$

Examples of vdW and charge transformations



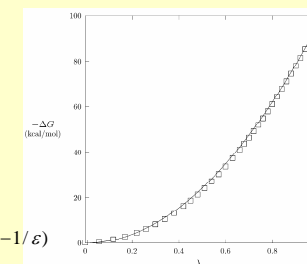
$$\Delta U = U_{K^+}^{LJ} - U_{Na^+}^{LJ}$$

ion-water LJ energy



$$\Delta U = U_{Na^+}^{el}$$

Look, it obeys Born's formula! $\Delta G = -\frac{Q^2}{2R} (1-1/\epsilon)$
linear response



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With close spacing between λ -points FEP becomes equivalent to TI

$$\Delta G = G_B - G_A = -\beta^{-1} \sum_{m=1}^{n-1} \ln \langle \exp[-\beta(U_{m+1} - U_m)] \rangle_m$$

$$\Downarrow$$

$$\Delta G = -\beta^{-1} \sum_{m=1}^{n-1} \ln \langle \exp[-\beta \Delta U \Delta \lambda_m] \rangle_m$$

$$\Downarrow$$

$$\Delta G = -\beta^{-1} \sum_{m=1}^{n-1} \ln \left\langle \exp \left[-\beta \frac{\partial U_m}{\partial \lambda_m} \Delta \lambda_m \right] \right\rangle_m$$

$$\Downarrow$$

$$\Delta G = \sum_{m=1}^{n-1} \left\langle \frac{\partial U_m}{\partial \lambda_m} \right\rangle_m \Delta \lambda_m \quad \Rightarrow \quad \Delta G = \int_0^1 \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_\lambda d\lambda$$

$$\Delta U = U_B - U_A$$

$$U_m = (1 - \lambda_m) U_A + \lambda_m U_B$$

$$\Delta \lambda_m = \lambda_{m+1} - \lambda_m$$

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Free Energy Perturbations (FEP) simulations

thermodynamic cycle approach

$$\Delta \Delta G_{bind} = \Delta G_{bind}(L') - \Delta G_{bind}(L) = \Delta G_{mut}^p - \Delta G_{mut}^w$$

$$U_m = (1 - \lambda_m) U_A + \lambda_m U_B$$

$$\Delta G = G_B - G_A = -\beta^{-1} \sum_{m=1}^{n-1} \ln \langle \exp[-\beta(U_{m+1} - U_m)] \rangle_m$$

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FEP/TI in practice: problems with vanishing (or appearing) atoms

- numerical problem with infinite energies (and forces in MD)
- sampling problem – "pin-ball" effect
- timescale problem with large conformational changes

What to do?

- transform LJ into softer potential
- shrink bonds to vanishing atoms
- use denser λ -spacing near end-points

Still, this limits FEP/TI to small perturbations...

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FEP/TI in practice: problems with vanishing (or appearing) atoms

- transform LJ into softer potential
- shrink bonds to vanishing atoms (beware of pmf contribution)
- use denser λ -spacing near end-points

ClC(Cl)(Cl)Cl >> ClC(Cl)Cl