Statistical Mechanics of Proteins

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- Equilibrium and non-equilibrium properties of proteins
  - Free diffusion of proteins
- Coherent motion in proteins: temperature echoes
- Simulated cooling of proteins
Simulated Cooling of Ubiquitin

- Proteins function in a narrow (physiological) temperature range. What happens to them when the temperature of their surrounding changes significantly (temperature gradient)?

- Can the heating/cooling process of a protein be simulated by molecular dynamics? If yes, then how?

- What can we learn from the simulated cooling/heating of a protein?
macromolecular properties of proteins, which are related to their biological functions, often can be probed by studying the response of the system to an external perturbation, such as thermal gradient.

“Small” perturbations are described by linear response theory (LRT), which relates transport (nonequilibrium) to thermodynamic (equilibrium) properties.

On a “mesoscopic” scale a globular protein can be regarded as a continuous medium. Within LRT, the local temperature distribution $T(r,t)$ in the protein is governed by the heat diffusion (conduction) equation

$$\frac{\partial T(r,t)}{\partial t} = D \nabla^2 T(r,t)$$
Atomic vs Mesoscopic

- Each atom is treated individually
- Length scale $\sim 0.1 \text{ Å}$
- Time scale $\sim 1 \text{ fs}$

- One partitions the protein in small volume elements and average over the contained atoms
- Length scale $\geq 10 \text{ Å} = 1 \text{ nm}$
- Time scale $\geq 1 \text{ ps}$
Heat Conduction Equation

\[ \frac{\partial T(r,t)}{\partial t} = D \nabla^2 T(r,t) \]

- Thermal diffusion coefficient
- Mass density
- Thermal conductivity
- Specific heat

- Approximate the protein with a homogeneous sphere of radius \( R \sim 20 \, \text{Å} \)
- Calculate \( T(r,t) \) assuming initial and boundary conditions:

\[ T(r,0) = T_0 \quad \text{for} \quad r < R \]
\[ T(R,t) = T_{\text{bath}} \]
Thermal diffusion coefficient $D=\

$D$ is a phenomenological transport coefficient which needs to be calculated either from a microscopic (atomistic) theory, or derived from \textit{(computer) experiment}.

“Back of the envelope” estimate:

\[
\frac{\partial T(r, t)}{\partial t} = D \nabla^2 T(r, t) \Rightarrow \frac{\Delta T}{\tau_0} \sim D \frac{\Delta T}{R^2} \Rightarrow D \sim \frac{R^2}{\tau_0}
\]

$R \sim 10 \, A = 10^{-9} \, m$, $\tau_0 \sim 10 \, ps = 10^{-11} \, s$

$\Rightarrow D \sim \frac{R^2}{\tau_0} \sim 10^{-7} \, m^2/s = 10^{-3} \, cm^2/s$

From MD simulation!
Solution of the Heat Equation

\[ \langle \Delta T(t) \rangle = \langle \Delta T(0) \rangle \times \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp \left( -n^2 \pi^2 t / \tau_0 \right) \]

where \( \langle \Delta T(t) \rangle \equiv \langle T(t) \rangle - T_{bath} \), \( \tau_0 = R^2 / D \)

averaged over the entire protein!
How to simulate cooling?

- In laboratory, the protein is immersed in a coolant and the temperature decreases from the surface to the center.

- Cooling methods in MD simulations:

  1. **Stochastic boundary method**

  2. Velocity rescaling (rapid cooling, biased velocity autocorrelation)

\[
\langle T(t) \rangle_{\text{sim}} = \frac{\sum_{i=1}^{N_d} m_i v_i^2}{N_d k_B} \quad \Rightarrow \quad v_i' = v_i \sqrt{\frac{T_{\text{new}}}{T_{\text{old}}}}
\]

  3. Random reassignment of atomic velocities according to Maxwell’s distribution for desired temperature (velocity autocorrelation completely lost)
6.3 Temperature Control and Equilibration . . . .50
  6.3.1 Langevin dynamics parameters . . . . .
  6.3.2 Temperature coupling parameters . .
  6.3.3 Temperature rescaling parameters . .
  6.3.4 Temperature reassignment parameters .
Stochastic Boundary Method

Heat transfer through mechanical coupling between atoms in the two regions

**coolant layer of atoms**

Motion of atoms is subject to stochastic Langevin dynamics

\[ m \ddot{r} = F_{FF} + F_H + F_f + F_L \]

- \( F_{FF} \rightarrow \) force field
- \( F_H \rightarrow \) harmonic restrain
- \( F_f \rightarrow \) friction
- \( F_L \rightarrow \) Langevin force

Atoms in the inner region follow Newtonian dynamics

\[ m \ddot{r} = F_{FF} \]
2-6-heat_diff: Simulated Cooling of UBQ

Start from a pre-equilibrated system of UBQ in a water sphere of radius 26 Å mol load psf ubq_ws.psf namdbin ubq_ws_eq.restart.coor

Create the coolant layer of atoms of width 4 Å

Select all atoms in the system:
set selALL [atomselect top all]

Find the center of the system:
set center [measure center $selALL weight mass]

Find X, Y and Z coordinates of the system's center:
foreach {xmass ymass zmass} $center { break }
Select atoms in the outer layer:

```
set shellSel [atomselect top "not ( sqr(x-$xmass$) + sqr(y-$ymass$) +
  sqr(z-$zmass$) <= sqr(22) ) "]
```

Set beta parameters of the atoms in this selection to 1.00:

```
$shellSel set beta 1.00
```

Select the entire system again:

```
set selALL [atomselect top all]
```

Create the pdb file that marks the atoms in the outer layer by 1.00 in the beta column:

```
$selALL writepdb ubq_shell.pdb
```
# Spherical boundary conditions
# Note: Do not set other boundary conditions and PME if spherical boundaries are used
if {1} {
  sphericalBC on
  sphericalBCcenter 30.30817, 28.80499, 15.35399
  sphericalBCr1 26.0
  sphericalBCK1 10
  sphericalBCexp1 2
}

# this is to constrain atoms
if {1} {
  constraints On
  consref ubq_shell.pdb
  consexp 2
  conskfile ubq_shell.pdb
  conskcol B
}
NAMD configuration file: ubq_cooling.conf

# this is to cool a water layer
if {1} {
  tCouple on
tCoupleTemp 200
tCoupleFile ubq_shell.pdb
tCoupleCol B
}

RUN THE SIMULATION FOR 10 ps

(5000 steps; timestep = 2 ps)

The (kinetic) temperature $T(t)$ is extracted from the simulation log (output) file; it can be plotted directly with namdplot TEMP ubq_cooling.log

Is this procedure of getting $T(t)$ correct?
Determine D by Fitting the Data

\[
\frac{\langle \Delta T(t) \rangle}{\langle \Delta T(0) \rangle} = \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(-n^2 \frac{x t}{t_0}\right)
\]

\[t_0 = 10 \text{ ps}, \quad x = \text{fitting parameter}, \quad D = \left(\frac{R}{\pi}\right)^2 \frac{x}{t_0}\]

\[
x \approx 1.41 \Rightarrow D \approx 0.97 \times 10^{-3} \text{ cm}^2/\text{s}
\]
Thermal Conductivity of UBQ

\[ K = D \rho c \]

\[ C_V = \frac{\langle \delta E^2 \rangle}{k_B T^2} = \frac{\left( \langle E^2 \rangle - \langle E \rangle^2 \right)}{k_B T^2} \]

\[ D \approx 0.97 \times 10^{-3} \text{ cm}^2/\text{s} \]

\[ \rho \approx 1 \times 10^3 \text{ kg/m}^3 \]