Exercise 08

Thermodynamic cycle

Deadline: Please, send your solutions to **luca.donati@fu-berlin.de** by **Friday, 3 July, 2.15 p.m.**

8.1 Markov chain Monte Carlo sampling (10 P)

Consider the four states - A, B, C, and D - from the exercise 07, which have the following harmonic potential energy functions:

$$\begin{aligned} V_A(x) &= 2 \cdot (x+2)^2 - 2 \\ V_B(x) &= 1.2 \cdot x^2 \\ V_C(x) &= 5 \cdot (x-1.5)^2 - 2 \\ V_D(x) &= 0.5 \cdot (x-3)^2 + 1 \end{aligned} \tag{1}$$

We are going to generate the trajectories which sample the Boltzmann distributions of the four states, using the Markov chain Monte Carlo algorithm. The procedure can be summarized by two steps:

1. A trial configuration x_{trial} is generated by drawing from a normal distribution which is centered at the current configuration x_t

$$x_{\text{trial}} \sim \mathcal{N}(x_t, \sigma^2) \tag{2}$$

2. The trial configuration is accepted or rejected by drawing a number k from a uniform distribution in $[0, 1[$ and comparing k with

$$p_{\text{acc}} = \exp(-\beta \Delta V) \tag{3}$$

where

$$\Delta V = V(x_{\text{trial}}) - V(x_t)\,. \tag{4}$$

If the trial configuration is accepted, it is added to the trajectory ($x_{i+1} = x_{\text{trial}}$), otherwise the current configuration is added to the trajectory ($x_{i+1} = x_i$). The table below shows the algorithm in pseudocode.

Markov chain Monte Carlo algorithm

Data : Potential energy function: V[x],
Variance of the Gaussian distribution: sigma,
Beta: 2/sigma^2
Number of timesteps: N,

x[1] = initialPosition;

for $t = 2$ **to** $t = N$ **do**
  xTrial = RandomGaussianNumber[x[t-1], sigma];
  deltaV = V[xTrial] - V[x[t-1]] ;
  k = RandomUniformNumber[0,1];
  if *k<exp[-beta * deltaV]* **then**
    x[t] = xTrial;
  else
    x[t] = x[t-1]
  end
end
Result : Full trajectory: x[1:t]

Algorithmus 1: Markov chain Monte Carlo algorithm to sample the Boltzmann distribution associated to a potential energy function $V(x)$.

(a) Analyze the algorithm and explain, with which probability a trial move is accepted if its energy is

- higher than
- equal to
- lower than

the energy of the current state. (2 P)

(b) Implement the algorithm and simulate trajectories in all four potentials. (6 P)

(c) Plot the distribution of x-values in your trajectories and compare them to the exact Boltzmann distribution that you found in exercise 07. (2P)

8.2 Free energy perturbation II (5 P)

Recalculate all possible free energy differences between the four states using the free energy perturbation method. But this time, estimate the ensemble average from the trajectories you have obtained in the previous exercise. Assume $\beta = 1$.
Compare your new results with those you found in exercise 07.

8.3 Thermodynamic cycle (5 P)

Let's now assume that the four previous potentials represent the states of two ligands "1" and "2", when they are bound or unbound to a receptor. In particular, we assume that:

- $V_A(x)$: ligand 1 is bound to the receptor
- $V_B(x)$: ligand 1 is unbound
- $V_C(x)$: ligand 2 is bound to the receptor
- $V_D(x)$: ligand 2 is unbound

The free energy differences ΔG_{AB} and ΔG_{CD} are respectively the quantities $\Delta G_{1,\text{binding}}$ and $\Delta G_{2,\text{binding}}$.
The free energy differences ΔG_{AC} and ΔG_{BD} are respectively the quantities $\Delta G_{12,\text{bound}}$ and $\Delta G_{12,\text{unbound}}$.

Verify the relationship:

$$\Delta\Delta G = \Delta G_{1,\text{binding}} - \Delta G_{2,\text{binding}} = \Delta G_{12,\text{unbound}} - \Delta G_{12,\text{bound}}$$

Which ligand binds better to the receptor?