Übung: revision – Free energy calculations, unusual Monte Carlo and Molecular Dynamics

SS 2010 Übung zu Struktur und Simulation

14-Jun-10

We start on these questions on Tuesday 15 June.

1. Overview

This is a revision Übung which requires no computer. The questions are typical of what will be in the final exam.

2. Questions

1. I run an MD simulation of a protein without a temperature bath and find the temperature to be 310 K. I want to simulate at 300 K. I want to adjust the velocities to have the correct temperature. What factor should I multiply the velocities by ? Do not use a calculator. Give an answer as an exact expression.
2. I have the coordinates for a protein. At a certain site, it has an alanine. I would like to predict the stability if this alanine is mutated to a glycine. I suggest that we run an MD simulation of the native protein in water and the mutant in water. I then look at the average potential energy that my MD program prints. Why is this meaningless ?
3. I claim that the stability of the protein is given by ΔG_{fold}, which is the free energy change as the protein goes from the unfolded state(s) to the native state(s). When I try with either the alanine or glycine protein, the protein never folds, so I cannot estimate either ΔG_{fold}^{ala} or ΔG_{fold}^{gly}.

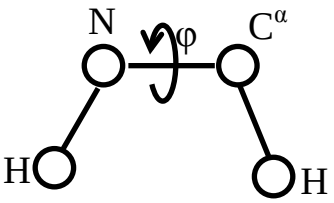
   Describe exactly what you could simulate in order to find the difference in stability of the native (ala) and mutant (gly) proteins.
4. I have the crystal structure of a protein bound to a small molecule. In the binding site, there is an alanine. I want to predict the change in binding energy if I mutate the alanine to a glycine. It

is proposed to do a perturbation/free energy calculation by gradually changing the alanine to a glycine, integrating over the total energy (Hamiltonian) as I change the system.
Why will this not give me the correct free energy difference ?
Write a set of free energy differences which should, in principle, give me the correct answer.

5. I do not know whether to use simple Monte Carlo or simulated annealing when simulating a protein. Which would I use to find the density at 300 K ?

6. I have invented a physical measurement which detects H-bonds between atoms in a protein. In my protein simulation, I do not see the H-bonds being formed. I would like to push the simulation so it forms the measured H-bonds. Describe a simple quasi-energy term which would serve this purpose.

7. From NMR spectroscopy, I can use *J*-coupling constants to estimate the angle φ.



The angle is related to the measured *J* value by $J = A\cos^2\varphi + B\cos\varphi + C$ for some constants *A*, *B* and *C*. How could one implement an artificial (pseudo-) energy term which would persuade a protein to change its conformation and reflect the measured *J* coupling ?

8. I would like to use Monte Carlo / simulated annealing to optimize a protein sequence without disturbing the structure. I have a function *U*(**R**, *S*) which acts on the set of coordinates, **R**, and *S* the ordered set of residues and returns an quantity like energy. Describe a Monte Carlo scheme which will find sequences that are compatible with a structure.

9. I have a drug "D" which binds to a protein "P". By every experimental method known to man, the binding appears instantaneous. It is suggested that I can mix the drug and protein, measure the concentrations and estimate the free energy of binding by saying $\Delta G = RT \ln \frac{[D][P]}{[DP]}$ If the binding / unbinding is really instantaneous, why may this be meaningless ?