Exam Practice Questions and Solutions

CS/BIOE/CME/BIOPHYS/BIOMEDIN 279

Fall 2021

Test Details

The exam will be held on Friday, December 10, 2021 from 3:30 PM PM - 6:30 PM (in 320-105). The exam will be closed-book, but you may consult one double-sided 8.5x11 page (or two single-sided pages).

Instructions

These are practice questions in the style of questions you might expect on the exam. Each question should be answerable in a few sentences (that is, you're not required to provide a great deal of detail).

Question 1: Compare and contrast the energy functions used for molecular dynamics simulations and those used for ab initio protein structure prediction.

Solution: Molecular dynamics simulations use a molecular mechanics force field. This is a potential energy function — it specifies the energy of each precise arrangement of atoms, and therefore allows one to compute the force acting on each atom. The terms in most molecular mechanics force fields are physics-based. Ab initio protein structure prediction generally uses an (approximate) free energy function, which specifies the energy associated with a set of atomic arrangements, and thus allows one to pose protein structure prediction as a minimization problem.

Question 2: How would you go about estimating how long it would take to run an MD simulation? What information would you need to consider?

Solution: You would need to consider

- Number of time steps (depends on total time being simulated.)
- Total number of atoms in the system (both protein and environment) being simulated.
- The average number of non-bonded interactions to be computed for each atom at each time step (non-bonded interactions will dominate the overall computation). This will depend on the algorithm being used to compute the non-bonded interactions.
- Time to compute each non-bonded interaction.

Question 3: We would like to estimate how tightly a particular drug candidate binds to a particular target protein.

(a) Provide a quantitative definition of binding affinity (i.e., "binding strength"). That is, what does it mean for one ligand to bind more tightly than another?

Solution: Ligand A binds more tightly (binds with higher affinity) than ligand B if A is bound to a target receptor/protein a larger fraction of the time, when A and B are at identical concentrations. Affinity can be defined either as a difference in free energy between the bound and unbound state of the ligand-protein system, or as the concentration of free ligand such that half the target molecules have a ligand bound and the other half do not.

(b) Suppose we have a single molecular dynamics simulation in which the drug candidate binds to the target and stays bound for the remainder of the simulation. Can we accurately estimate the binding affinity from that simulation? Why or why not?

Solution: No, you would need to see the ligand binding and unbinding many times in order to accurately estimate the fraction of time it will remain bound.

Question 4: Describe one common approximation made by ligand docking methods, and explain why it helps simplify the problem to be solved.

Solution: A common approximation is that the protein is rigid. This simplifies the problem because one doesn't need to consider all possible arrangements of the protein atoms (and weight the binding energy/score across possible arrangements).

Question 5: X-ray crystallography and single-particle electron microscopy are both techniques for determining the structure of a molecule or molecular complex. Why is single-particle electron microscopy typically used for larger molecules or complexes than x-ray crystallography?

Solution: 1) It is generally harder to form crystals of larger molecules/complexes than of smaller ones 2) In single-particle electron microscopy, its usually harder to solve the computational reconstruction problem for smaller molecules, because smaller molecules tend to have more similar projections from different orientations).

Question 6: Discuss the trade-offs of a stochastic particle-based reaction-diffusion simulation versus a continuum approach (in which concentrations of each type of molecule are represented in each voxel).

Solution: The continuum approach is often faster, particularly for large numbers of molecules, but it's less accurate for small numbers of molecules.

Question 7: There is a very efficient algorithm for computing the Fourier Transform known as the Fast Fourier Transform (FFT). Describe how this algorithm is useful for one of the methods covered in this course.

Solution:

- The FFT allows one to compute convolutions more efficiently. This is useful for filtering images, signals, etc.
- In x-ray crystallography, the FFT allows one to calculate efficiently the diffraction pattern associated with a hypothesized electron density.