Final Exam for Modeling Molecular Systems I

Answer the following five discussion questions. Several articles are suggested in the questions, and these are available on the course web site. Use of other articles you may discover in researching the questions is encouraged. Please submit your answers by Friday, December 12th to Jay Ponder as hard copy or via email (ponder@dasher.wustl.edu).

Question 1: Two of the basic paradigms in molecular simulation are the Monte Carlo and molecular dynamics methods. There have been several published comparisons of the efficiency of MC and MD algorithms. Consider the following three papers, and any others you can find related to this topic: (A) Monte Carlo *vs* Molecular Dynamics for Conformational Sampling, W. L. Jorgensen and J. Tirado-Rives, J. Phys. Chem., *100*, 14508-14513 (1996), (B) Sampling Efficiency of Molecular Dynamics and Monte Carlo Method in Protein Simulation, H. Yamashita, S. Endo, H. Wako and A. Kidera, Chemical Physics Letters, *342*, 382-386 (2001), and (C) Monte Carlo *vs* Molecular Dynamics for All-Atom Polypeptide Folding Simulations, J. P. Ulmschneider, M. B. Ulmschneider, A. De Nola, J. Phys. Chem. B, *110*, 16733-16742 (2006).

Provide a written summary of points to consider in MC and MD simulation of a large biopolymer. In your answer, comment on the details of the simulation algorithm and protocol that effect efficiency (*ie*, there are many possible variants of both MC and MD). What are some possible methods for effectively increasing the time step in MD simulation? What MC move sets and sampling methods might increase efficiency of MC simulation? Consider the effects of coordinate representation (Cartesian, torsional, rigid body, *etc*.), explicit *vs* implicit solvent, form of the potential (pairwise *vs* polarizable force fields; all-atom *vs* coarse grained models).

Question 2: Please read the following paper: Continuum Method for Determining Membrane Protein Insertion Energies and the Problem of Charged Residues, S. Choe, K. A. Hecht and M. A. Grabe, J. Gen. Physiol., *131*, 563-73 (2008).

Discuss how this approach could be used to calculate the pKa's and titration states of amino acids at different depths in a lipid bilayer using the types of continuum methods we discussed in class. Be sure to answer the following questions in your discussion:

– What dielectric constant would you use for the bilayer? Why?

– Will the explicit nature of water be important? Where and why?

– Imagine a transmembrane potential were present. How would this affect the pKa's of amino acids?

– How might the thickness of the bilayer affect amino acid titration states?

You might find the following paper and other related papers useful when preparing your answer: On the Thermodynamic Stability of a Charged Arginine Side Chain in a Transmembrane Helix. S. Dorairaj and T. W. Allen, Proc. Natl. Acad. Sci. USA, *104*, 4943-4948 (2007).

Question 3: Read the following paper: Assessing the Role of Polarization in Docking, Illingworth *et al.*, J. Phys. Chem. A, *112*, 12157-12163 (2008). Provide a 1-2 page written summary, analysis and critique of the paper, and try to put this in the context of other parts of the class (polarization, electrostatics, etc.). Also, please consider the following points in your answer.

– What, in your assessment, is the benefit-cost ratio for each of the 5 improved methods as compared to the standard AutoDock method used as method 1? In other words, for the amount of work that each subsequent method requires (and they are basically presented in order of increasing amount of work), what method would you choose?

– What other factors are still ignored and what potential improvements could be made?

– The trends you observe when moving from method 1 to method 6 generally show improvement, but not always (*eg.*, 1LGR, 4TSI, 1ETT). In your opinion, what are the potential reasons for this observation?

Question 4: Based on the review by Dunker et al. on intrinsically disordered proteins, rationalize the following:

Nature optimizes rates and specificity, not affinities. What role do intrinsic proteins play if this is a true hypothesis?

Question 5: Critique ***one*** of the following three papers (either A, B or C) and answer the specific relevant questions listed for your chosen article:

Paper A: Crystal Structure of a Ten-Amino Acid Protein, S. Honda, *et al.*, JACS, *130*, 15327-15331 (2008).

– Why do the authors consider a ten-residue peptide a "protein"?

– How significant are the differences between the crystal and the NMR structures?

– Is there a significant difference between the NMR solution structure and an ensemble of conformers whose average properties are consistent with the NMR structure? How could you tell the difference?

– How dependent are the results of the MD simulations on the force field used and the time of the simulations?

Paper B: Extra Precision Glide: Docking and Scoring Incorporating a Model of Hydrophobic Enclosure for Protein-Ligand Complexes, R. A. Friesner, R. B. Mutphy, *et al.*, J. Med. Chem., *49*, 6177-6196 (2006).

– What is the physical basis for adding an addition term to hydrophicity?

– Does the validation in the paper convince you this is an improvement to current implicit solvent approaches? Why?

– How would this additional term improve the estimates of binding entropies?

Paper C: ROSETTALIGAND: Protein-Small Molecule Docking with Full Side-Chain Flexibility, J. Meiler and D. Baker, PROTEINS, *65*, 538-548 (2006).

– Does the data presented justify validation of the scoring function used?

– How important is the inclusion of side-chain flexibility in docking?

– What differences distinguish the scoring function used from most of the other scoring functions used in docking?