Assignment 7: Molecular Mechanics Force Fields: Approximations, Variations, and the Assessment of Results with respect to Experiment and other Simulations

1. **Reading**. This assignment deals with the series of four articles below, which raise both general and specific problems in biomolecular simulations. At issue is the validation of conformational predictions by various molecular mechanics force fields. You may also wish to refer to the Lipkowitz article from Assignment 5 (on the pitfalls of molecular mechanics) and the van Gunsteren and Mark article from Assignment 1 (on validating molecular dynamics simulations). Begin by reading these papers (included in the Coursepack, see (Appendix B)) and thinking about the modeling issues as you read them.
   - I. K. Roterman, M. H. Lambert, K. D. Gibson, and H. A. Scheraga, "Comparison of the CHARMM, AMBER and ECEPP Potentials for Peptides. I. Conformational Predictions for the Tandemly Repeated Peptide $(\text{Asn-Ala-Asn-Pro})_9$", *J. Biomol. Struct. Dyn.* **7**, 391–419 (1989a).
   - I. K. Roterman, M. H. Lambert, K. D. Gibson, and H. A. Scheraga, "Comparison of the CHARMM, AMBER and ECEPP Potentials for Peptides. II. ϕ–ψ Maps for N-Methyl Amide: Comparisons, Contrasts and Simple Experimental Tests", *J. Biomol. Struct. Dyn.* **7**, 421–453 (1989b).
   - P. A. Kollman and K. A. Dill, "Decisions in Force Field Development: An Alternative to Those Described by Roterman *et al.*", *J. Biomol. Struct. Dyn.* **8**, 1103–1107 (1991).
   - K. B. Gibson and H. A. Scheraga", "Decisions in Force Field Development: Reply to Kollman and Dill", *J. Biomol. Struct. Dyn.* **8**, 1109–1111 (1991).

2. **Preparation for Class Discussion.** You will be divided into three groups (assignments will be given in class): (1) the moderators, (2) the ECEPP group, and (3) the AMBER and CHARMM group. Each group will have to prepare material, as described below, for class presentation and discussion. *All materials should be prepared on overhead projector slides.* You should meet with your group members in advance to plan your presentation and debate strategies.

   The *moderators* will be in charge of presenting in detail the *facts*: what studies were performed, what questions were asked, and what analyses were made. You should be prepared to answer any background questions (e.g., definitions of polymer quantities analyzed).

   The *ECEPP* group will endorse the point of view taken by Roterman, Gibson, Scheraga, and co-workers. Besides understanding your po-

sition well, you will need to bring to the debate *concrete examples from the literature* to support your position. Be creative and try to find interesting examples.

The *AMBER* folks and *CHARMMers* will endorse the approach taken in these two molecular packages and, in particular, the point of view taken by Kollman and Dill in their reply to Roterman *et al.*. As above, besides understanding well your molecular mechanics packages and position taken in the reply, you will need to bring to the debate *concrete examples from the literature* to support your position. Be creative in your supporting materials and strategies.

3. **Useful Recommendations**. Summarize in brief the useful recommendations and comments that emerged from all the above articles, as well as additional ones, for practitioners of molecular modeling. That is, propose *concrete procedures* that biomolecular simulators can use to gain as much confidence as possible in their conclusions and predictions.

   Remember, uncertainties and approximations in numerical modeling and simulations will always exist! The field of modeling biomolecules on modern computers involves as much art as science. But despite their obvious limitations, modeling methodologies are improving continuously. The goal of every practitioner should be to realize the highest possible accuracy as is compatible with the model and methods utilized. Like any calculation, 'error bars' in the broad sense should be attributed to the results and conclusions claimed.

4. **Points to Keep in Mind**. Throughout this assignment, think about the following important issues in molecular modeling:

   - Accuracy versus approximation
   - Theory versus experiment
   - Dependence of simulation results on the protocols used
     - starting configuration
     - model assumptions
     - force field
     - algorithms (minimization, adiabatic mapping, etc.)
   - Assessment of Results:
     - How can you distinguish between bona fide physical *trends* and numerical *artifacts*?
     - How can you decide whether the model is wrong (energy, assumptions, etc.) or the method is inappropriate?
     - What are appropriate comparisons with experimental results?

Summary of Items to Hand in:

(a) Brief description of the issues raised in the four articles regarding molecular mechanics predictions.
(b) Your work in preparation of the class debate.
(c) Proposals of procedures to be used to attain the maximum possible confidence from biomolecular simulations.

Have Fun!

Background Reading from Coursepack

- J. Skolnick and A. Kolinski, "Simulations of the Folding of a Globular Protein", *Science* **250**, 1121–1125 (1990).
- F. M. Richards, "The Protein Folding Problem", *Sci. Amer.* **264**, 54–63 (1991).
- H. A. Scheraga, "Predicting Three-Dimensional Structures of Oligopeptides", in Reviews in Computational Chemistry, K. B. Lipkowitz and D. B. Boyd, Editors, Vol. 3, pp. 73–142, VCH Publishers, New York (1992).
- A. Neumaier, "Molecular Modeling of Proteins and Mathematical Prediction of Protein Structure", *SIAM Review* **39**, 407–460 (1997).

Background Reading for Scheraga's Lecture

- J. Lee, A. Liwo and H. A. Scheraga, "Energy-Based *de novo* Protein Folding by Conformational Space Annealing and an Off-lattice United-Residue Force Field: Application to the 10-55 Fragment of Staphylococcal Protein A and to apo calbindin D9K", *Proc. Natl. Acad. Sci., USA* **96**, 2025–2030 (1999).
- J. Lee, H. A. Scheraga and S. Rackovsky, "Conformational Analysis of The 20-Residue Membrane-Bound Portion of Melittin by Conformational Space Annealing", *Biopolymers* **46**, 103–115 (1998).
- R. J. Wawak, J. Pillardy, A. Liwo, K.D. Gibson and H. A. Scheraga, "Diffusion Equation and Distance Scaling Methods of Global Optimization: Applications to Crystal Structure Prediction", *J. Phys. Chem.* **102**, 2904–2918 (1998).
- A. Liwo, R. Kazmierkiewicz, C. Czaplewski, M. Groth, S. Oldziej, R. J. Wawak, S. Rackovsky, M. R. Pincus, and H. A. Scheraga, "United-Residue Force Field for Off-Lattice Protein-Structure Simulations; III. Origin of Backbone Hydrogen-Bonding Cooperativity in United-Residue Potentials", *J. Comput. Chem.* **19**, 259–276 (1998).

- J. Lee, H. A. Scheraga and S. Rackovsky, “New Optimization Method for Conformational Energy Calculations on Polypeptides: Conformational Space Annealing”, *J. Comput. Chem.* **18**, 1222–1232 (1997).