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.


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-
position 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**


**Background Reading for Scheraga’s Lecture**