Computational biology methods and approaches

Summary/goals:

Theory and practice of computer simulation methods for biomolecules and interpretation of the results.

Brief description:

The course will give a broad overview on problems and approaches in computational biology, ranging from to QM to coarse-grained techniques. It teaches how to generate abstract models for biological problems, such as understanding structure or activity of a protein. It discusses conceptual issues related to method selection, and provides a theoretical background for each method. It will detail technical questions, which are relevant for the results and give instructions how to analyze the data in a meaningful way. We will also discuss how the results can be interpreted and mis-interpreted. Many lectures will involve scientific debates and demonstrating how computational biology and state-of-the-art methods can go wrong. The students will learn to think about biological problems or tackle complex systems computationally. The lectures will also include some practical applications from science to industry.

Topics:

1. Problems and models in structural biology.

How to ask questions, which are meaningful for the computer? How to generate good and bad models? Major biological questions and their significance.

2. Forcefield development. Molecular mechanics.

What potentials mean and the tricks to develop them. How forcefields affect/determine the results? Simple ways to walk on/explore PES. What we can derive from this?

3. Molecular dynamics and analysis on proteins. Structural biology applications.

The world of ensembles and the relevance to structure determination of proteins. Good and bad protocols. How to evaluate the results? What do they mean?

4. Monte Carlo methods for biomolecules. Biased sampling.

Some history, MC in the past and now. Benefits and bottlenecks of MC. Unique applications.

5. Protein structure prediction, homology modelling.

Simulations and bioinformatics — a joint game. Where messy physics may be useful. Limitations.

6. Microscopic and macroscopic approaches to electrostatics in proteins.

Calculation of solvation free energies and pKa values. Practical considerations on what to follow. Many different facets of electrostatic effects in proteins (binding , catalysis).

7. Free energy calculations in proteins.

A hiking experience — how to explore complex landscapes properly? Free energy perturbation, thermodynamic integration, enhanced sampling and convergence issues.

8. Quantum mechanical approaches to enzymatic reactions.

What can be achieved by fancy functionals? How to publish meaningless results?

9. Solvent effects on chemical reactions.

Where catalysis starts — getting back to electrostatics. May not be simple to evaluate, proteins are highly inhomogeneous.

10. Activation free energies for enzymatic reactions. Reaction coordinates.

State-of-the-art. Conceptual considerations and tests. Critical factors, complexity and surprising observations.

11. Origin of enzymatic catalysis. From tunneling to reorganisation.

Computational biology without a computer. Thinking can help. Problem phrasing and understanding enzymes.

12. Rational drug design.

Structure-activity relationships. Combining and simplifying methods. Practices, achievements and future.

13. Problem-solving.

Projects and interactive lesson related to the interest of the students.

Students:

Physicist, structural biologists, chemists, molecular biologists, biotechnologists, who are interested in molecular models and mechanisms, or computational approaches. Background in physical chemistry, statistical mechanics or quantum mechanics is helpful, but not absolutely necessary.

References:

Andrew Leach: Molecular modelling, principles and applications
Arieh Warshel: Computer modeling of Chemical Reactions in Enzymes and Solutions
Daan Frenkel: Understanding Molecular Simulations From Algorithms to Applications
M.P. Allen: Computer simulation of liquids

various journal articles, which will be distributed.