Project 10

Free energy calculation: thermodynamic cycle

Keywords: Free energy calculation, free energy perturbation, thermodynamic integration
Deadline: Please, hand in your report by **Tuesday, 29 July 2014**

1 Introduction

Drug molecules are often small molecules which bind to a receptor in the human body. To judge whether a given molecule has the potential to act as a drug on a specific receptor, one needs to know its binding free energy. Ideally, one would like to scan a series of potential drug molecules and calculate their binding free energies using computational methods, and only afterwards synthesize the most promising candidates

The Gibbs free energy difference between two states A (ligand unbound) and B (ligand bound) is given as

$$\Delta G_{AB} = G_A - G_B = -\frac{1}{k_B T} \ln \frac{Q_A}{Q_B} \tag{1}$$

where G is the Gibbs free energy, k_B is the Boltzmann constant, T is the absolute temperature, and Q_A and Q_B are the partition functions of state A and B, respectively. This free energy difference can be estimated from molecular dynamics simulations using the free-energy perturbation method or the thermodynamics integration method. However, both of these methods only work if the two state A and B are rather similar, i.e. if they sample similar conformations. A direct estimation of the binding free energy is therefore typically not possible. Instead one resorts to calculating relative binding free energies using a thermodynamic cycle.

2 Outline of the project

1. Choose suitable one-dimensional potential energy functions to model a series of ligands in the bound and in the unbound state. Construct suitable thermodynamic cycles and analytically calculate the free energy differences, the relative and absolute binding free energies.
2. Sample the potential energy functions using the MCMC sampler which you implemented in exercise 7. Recalculate the relative binding free energies using the thermodynamic integration method and the free energy perturbation method. Interpret and discuss your results.
3. Demonstrate the effect of (limited) sampling on the accuracy of the free energy estimate for one of the free energy differences in your thermodynamic cycle.
4. Plot the free energy difference between the λ-points as a function of λ. What is a suitable strategy to choose the λ points in a free energy perturbation?

3 Literature

- Lecture notes and exercises.
- Chapters 7 and 10 in: D. Frenkel, B. Smit, "Understanding Molecular Simulation - From Algorithms to Applications", Academic Press, Elsevier (USA) 2002.
- D. L. Mobley, P. V. Klimovich, "Perspective: Alchemical free energy calculations for drug discovery", *J. Chem. Phys.* **137**, p. 230901 (2012).
- C. D. Christ, A. E. Mark, W. F. van Gunsteren, "Basic ingredients of free energy calculations: a review", *J. Comp. Chem.*, **31**, p. 1569-1582 (2009).

Project requirements

- Describe the results of the your project in a report of 5 to 12 pages (font size 11 pt).
- The report should also contain a short description of the theory and the methods. If you implement an algorithm, briefly describe the algorithm.
- Hand in your program along with the report.
- You will present the results of your project in a 20-minute presentation, after which we will have about 10 minutes time for discussion.
- Besides questions which are directly related to the results of the project, the discussion will also cover the theory of the project and the course content which is relevant to the project.
- If you run into problems during the project or have questions, please contact us
  - Bettina Keller, bettina.keller@fu-berlin.de
  - Francesca Vitalini, francesca.vitalini11@gmail.com
- During the lecture hours (Thu, 2.15 - 3.45 pm) one of us will be in the library to answer questions.