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Algorithms and software for efficient biomolecular simulation

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Summary

Over the last fifty years, continuous development of simulation algorithms and software has made classical molecular dynamics simulation into a powerful tool to investigate biomolecular processes in atomistic detail. After a short introduction of classical simulation with special attention to biased sampling of configurational space and some techniques to calculate free energies, the latest version of the Groningen Molecular Simulation package is introduced:
GROMOS05. In this version, the heart of the package is delivered in two variants. An enhanced version of PROMD, the FORTRAN simulation engine, and MD05, written in C++. MD05 strives for higher modularity and readability by making use of object oriented features and generic programming techniques. All algorithms presented in the other chapters are integrated into MD05.

A brief overview and classification of searching methods is given in *Chapter 3* before a closer look is taken at entropies calculated by replica-exchange stochastic dynamics simulations. For the simple test system complete sampling of configurational space can be achieved. Therefore the entropies calculated from standard stochastic dynamics simulations should match the ones obtained from the replica-exchange simulations. This was found to be true. At low temperature and incomplete sampling of the configurational space, replica-exchange simulation can be more efficient if the simulation parameters are carefully selected. The procedure of rotationally fitting structures to decompose entropy into configurational, translational and rotational entropies has a significant impact on this decomposition, often disfavouring configurational entropy at low temperatures.

An algorithm to combine fine-grained (atomistic) simulations with coarse-grained ones is introduced in *Chapter 5*. The algorithm allows to either continuously vary the grain-level of the simulation from fully fine-grained to coarse-grained and back, or, using replica exchange, simultaneously simulate a system at fine-grained, at coarse-grained and at some intermediate grain levels. The higher the grain level the bigger the simulation time-step may be, therefore increasing sampling efficiency. Through replica exchange, the replicas at lower grain-level can profit from the faster sampling available at the higher levels.

A different way to improve sampling is shown in the next chapter, where the simulation is restrained to follow a reaction coordinate from a given state *A* to a state *B* for obtaining the free energy difference between these two states. Opposed to standard methods, the restraining

functions are chosen to have zero potential energy and forces in the end states (*A* and *B*). This permits the calculation of a path independent free energy difference. The method, implemented in terms of distance and dihedral restraints is applied to ion-complexation in a cyclic peptide and the calculation of the relative stability of two different chair conformations of a glucopyranoside. For the second case a comparison with a potential of mean force calculated using dihedral-angle constraints is given.

Further on, restraints can be used to force a simulation to reproduce experimental data. If the force field is not well suited to represent a biomolecule or if the simulation time is not long enough to sample the relevant part of the configurational space, experimental properties might not be reproduced by simulations. Both problems may be overcome by adding restraints. In *Chapter 7* adaptive restraints based on local-elevation simulation are introduced. Adaptive restraints have two main advantages: First, as the restraint force slowly builds up over the simulation time, and only if the restraint is not fulfilled, a minimum of force is added, which leads to the least possible disturbance of the simulation. Second, as the adaptive restraint is based on local-elevation simulation, locally enhanced sampling is achieved, until the restraint is fulfilled.

In the next two chapters the focus is no longer on restraints but on constraints. But these are flexibilized using an approximate, but fast algorithm, which enables simulations to use a comparatively large time-step but still have the constraints slowly adapt to changes in the environment. Using this technique, fast bond vibrational frequencies can be avoided. The method is applied to neopentane simulations under high pressure and to a comparative study of different models of flexibility. In this study, the free energy difference of water and methanol is calculated by thermodynamic integration.

Finally, in *Chapter 10* an outlook of future development with regard to simulation software and configurational sampling is provided.