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Implementations of nonequilibrium methods for free energy calculations: forthcoming developments of the ORAC molecular dynamics simulation code

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ORAC is a FORTRAN suite to simulate complex biosystems at the atomistic level[1, 2]. The program's engine is supplemented by multiple time steps integration, smooth particle mesh Ewald method, constant pressure and constant temperature algorithms. Quite recently, several advanced techniques for enhanced sampling in atomistic systems have been implemented, including replica exchange with solute tempering[2], metadynamics[2], steered molecular dynamics[2], serial generalized ensemble simulations[3, 4] and nonequilibrium alchemical transformations[5]. All these computational technologies have been devised for parallel architectures using the standard MPI communication protocol.

Further instances are being implemented in the ORAC code, concerning algorithms aimed at improving speedup of nonequilibrium molecular dynamics simulations. In particular, two quite recent computational schemes, called path-breaking[6, 7] and dynamical freezing[8], are currently under study. The former approach is specifically addressed to unidirectional nonequilibrium simulations for the calculation of free energy differences via Jarzynski's equality[9]. The method faces one of the most important drawbacks of unidirectional nonequilibrium simulations, which deals with the large amount of realizations necessary to reach suitable convergence of the work exponential average featuring the Jarzynski's relation. In this respect, a significant improvement of the performances has been obtained by finding a way of stopping nonequilibrium simulation trajectories, featured by negligible contribution to the work exponential average, before their normal end. This is just achieved with path-breaking schemes, which are essentially based on periodic checks of the work dissipated during the pulling trajectories. Such schemes can be based either on breaking trajectories whose dissipated work exceeds a given threshold or on breaking trajectories with a probability increasing with the dissipated work. In both cases, the computer time needed to carry out a series of nonequilibrium trajectories is reduced up to a factor ranging from 2 to more than 10, for processes of almost different nature, such as the helix-coil transition of deca-alanine and the pulling of the distance between two methane molecules in water solution (simulation tests can be found in Ref. [6]). The efficiency of the method depends on several aspects, such as the nature of the considered process, the number of check-points along the pathway and the pulling rate as well.

Path-breaking into ORAC is being devised to make affordable calculations on different typologies of computing architectures. The first target, which is currently under development, is to design a code for a distributed computing grid made of non-homogeneous cores, with negligible inter-core communications. The second possibility is to implement path-breaking under Message Passing Interface environment, eventually suitable for calculations on High Performance Computing platforms.

Combination of path-breaking with bidirectional nonequilibrium simulations for free energy calculations[7] is also possible and will be addressed in future developments of the ORAC project.

The other nonequilibrium technique (dynamical freezing) under study for implementation in the ORAC code is based on a different concept, even if it also deals with the difficulties of nonequilibrium pulling simulations in recovering free energy differences, especially due to the poor convergence of path-ensemble averages. As already stated, a large number of nonequilibrium trajectories is necessary to achieve free energy estimates with acceptable accuracy. Dynamical freezing improves free energy estimates by lowering the computational cost of steered molecular dynamics simulations employed to realize such trajectories. This is accomplished by generating trajectories where the particles not directly involved in the driven process are dynamically frozen. Such a freezing is dynamical rather than thermal because it is reached by a synchronous scaling of atomic masses and velocities keeping the kinetic energy of each particle unchanged. The forces between dynamically frozen particles can then be calculated rarely. Thus, it is possible to generate realizations of a process whose computational cost is not correlated with the size of the whole system, but only with that of the reaction site. The method is on the up grade by borrowing the concept of configurational freezing, implemented for Monte Carlo simulations[10]. A sphere of mobility of established radius is enforced around the site of the process, while all other particles are fixed. Both approaches, path-breaking and dynamical freezing, are planned to be integrated with nonequilibrium alchemical transformations already implemented in the ORAC code.

ORAC is an open-source program distributed free of charge under the GNU general public license (GPL) http://www.chim.unifi.it/orac.

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