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Editorial

Editorial preface

Computer simulation methods for studying macromolecular structural dynamics, function and energetics have evolved very rapidly in recent years. This is due to significant progress both with regard to methodology and computational power. On the methodological side there is intense activity in the areas of force field development, improved sampling techniques, free energy calculations and multiscale modeling. Molecular dynamics (MD) and related computer simulations techniques are now applied to address problems involving molecular machines, membrane proteins, and other large protein and nucleic acid complexes. This type of methodology has now reached a stage where quantitative predictions can be made regarding, for example, molecular recognition events and biochemical reactions. This special issue highlights many of these recent developments and their applications to biochemical and biophysical problems of key importance. The four sections in this special issue contain a mixture of reviews and reports of original research dealing with methodological aspects and applications to proteins and nucleic acids.

In molecular dynamics simulations conformations are generated along a trajectory on an energy surface, which in classical simulations is an empirical approximation to the true Born–Oppenheimer surface. The quality of the results thus depends both on the force field and on the ability of the simulation to sample relevant conformations; a rule-of-thumb is that in a standard MD simulation it takes ~100 ns to overcome barriers of ~10 k_BT. The first section opens with an overview of the current status of additive and polarizable force fields by Vanommeslaeghe and MacKerell Jr [1]. Since the introduction of umbrella sampling along a reaction coordinate in the 1970's quite a large variety of algorithms have been devised, and here we can only present a small sample of enhanced sampling techniques. Schulten and coworkers [2] compare replica-exchange, metadynamics and simulated annealing, with regard to their ability to sample different system properties, and, for example, generalized simulated annealing is indicated to be well suited for very flexible systems at relatively low cost even for large complexes. Accelerated molecular dynamics, and a variant working in the space of rotatable dihedral angles (RaMD), are described by Doshi and Hamelberg [3]. RaMD has the potential to allow satisfactory sampling of thermodynamically relevant states separated by transitions occurring at multiple time-scales. For larger systems the characterization of kinetic rates remains a challenge. Trapping in metastable states is one reason behind inefficient sampling, and Caflisch et al. [4] show that exploration of phase space is enhanced with the help of a simulation protocol that terminates and restarts trajectories in a more productive direction if they are found to be re-sampling overlapping regions of phase space. Paci et al. [5] use external forces to increase sampling of otherwise undersampled peptide conformations (either very extended or more compressed). Length distributions can be measured experimentally, and the force enhanced sampling is shown to agree with experiment for a series of short peptides of varying amino acid composition. Another approach to tackle the sampling problem is demonstrated by Reuter and coworkers [6], who analyze dynamic properties of multiple proteins using elastic network models, in which the intricate (and long-ranged) interactions in atomistic models are replaced by a set of particles interconnected by springs.

The second section deals with different aspects of quantitative energetic calculations. Pettitt and coworkers [7] compare and analyze different methods for describing protein hydration structure, using myoglobin as a test case. Both 3D integral equation theory with long-range Coulomb contributions and proximal radial distribution functions are used together with all-atom MD simulation to determine solvent density inside the protein with encouraging results, showing that the more approximate methods can indeed be useful. König and Brooks [8] revisit the problem of accounting for the contributions of constraints in free energy simulations. Different benchmark systems are considered and a post-processing approach based on harmonic analysis is explored. It is shown that better convergence and higher precision can be obtained through the combined use of constraints and this technique. Woodcock and coworkers [9] focus on free energy calculations along given pathways with applications, e.g., to QM/MM potential of mean force profiles. An off-pathway simulation method utilizing a precomputed reference path is introduced and implemented within a distributed replica framework. The method is validated with suitable benchmarks and its efficiency demonstrated. Kamerlin et al. [10] review the concept of QM/MM free energy calculations using reference potentials. The idea behind this approach is that a lower-level potential energy description, that allows extensive sampling and free energy calculations to be carried out, is used to obtain higher-level QM or QM/MM free energies as a perturbation to the reference potential. The approach is illustrated by several prototypic examples. Jorgensen and coworkers [11] report a thorough analysis of FEP simulations for typical inhibitor design problems. The basic approaches with either Monte Carlo or MD sampling are compared using a FEP/replica exchange procedure for the case of inhibitor binding to HIV reverse transcriptase. It is shown that the two methods yield similar results and ligand conformational sampling even with rigid protein backbone in the MC calculations. Homeyer and Gohlke [12] deal with the combination of atomistic MD simulations of membrane protein systems and subsequent MM-PBSA calculations of binding energies. Besides some simpler validation systems, the authors also consider inhibitor binding to the M2 proton channel of influenza A virus, where they obtain a good ranking of compounds with their approach.

The next section covers applications of MD simulations to some central problems regarding protein structure and dynamics. van Gunsteren and coworkers [13] address the problem of protein stability and folding equilibria, by comparison of wildtype and mutant WW domains. Extensive simulations are reported which highlight the importance of proper sampling of the unfolded state. The authors point out the problems with interpreting thermal denaturation parameters as well as chaotropic (hydrogen bonding disruption) folding equilibria in terms of standard free energies of folding in water at a given temperature. Meuwly et al.

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[14] explore ligand binding dynamics in truncated hemoglobin by multiple MD simulations with O_2 and NO. Microstates are analyzed with a transition network scheme that allows the passage between different microstates to be quantitatively analyzed. The coupled dynamics between ligand and protein motion is demonstrated and emphasized. Simonson and coworkers [15] address the biologically very important issue of conformational switching in GTPases. This switching is triggered by the single phosphate group that differs between GTP and GDP (similarly, in ATPases) and the thermodynamic complexity of this process is analyzed in detail. The authors show how this problem can be attacked by computer simulations and free energy calculations, where electrostatics is very challenging. Sansom et al. [16] analyze the complex interactions of the EGFR juxtamembrane and transmembrane domains with anionic lipids in mixed lipid bilayers of different compositions. Both coarse-grained and all-atom MD simulations are used and authors are able to study in depth how the anionic lipids may influence EFGR activation and stability. Dejaegere and coworkers [17] study the important process of recognition of posttranslational histone modifications by so-called PHD domains, which bind to the methylated histone tails. MD simulations are used to sample different PDH-histone peptide complexes, which are then subjected to energetic analysis by MM-PBSA calculations. It is demonstrated that this approach can yield reliable predictions of which PHD domains are binders to a given modification.

In the last section we have four contributions on nucleic acids. Cheatham et al. [18] present very long (up to 44 μs) simulations of a double stranded 18-mer B-DNA helix in explicit solvent and find that the structure is essentially converged in ~1–5 μs. Judging the quality of simulations in the end requires comparison to experimental data, and using simulations of crystals of RNA and DNA duplexes Case and coworkers [19] find that structural details that are smeared out in solution simulations are better preserved in the crystal simulations; the crystal lattice did however degrade slowly during the simulation. Sponer et al. [20] have used extensive, multiple, simulations to characterize the potential catalytic arrangement, including dominant protonation states of key residues, of the Csy4/CRISPR endonuclease, an RNA-protein (RNP) complex. They conclude that MD simulations provide useful information for RNP enzymes, but that there are limitations in sampling and force field accuracy that make these simulations quite challenging. Finally van der Vaart [21] gives an overview of recent atomistic simulations of the conformational dynamics of protein-DNA complexes, with a focus on DNA deformations that may aid in defining specific binding sites.

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