Molecular Dynamics III

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Increasing the Performance and Extensibility of Collective Variable Simulations

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The collective variables module (Colvars) is a software library that is tightly integrated with molecular simulation and analysis programs (Fiorin et al, Mol Phys, 2013). It is freely available in community programs for molecular dynamics such as NAMD and LAMMPS, and the visualization and analysis program VMD. Colvars implements reusable functions to reduce the dimensionality of complex chemical and biophysical systems, and a set of algorithms for enhanced sampling and statistical analysis. Recent updates have brought performance improvements for large systems and costly methods, a more flexible scripting interface, and the addition of more stable free energy estimators. We illustrate each advance through examples from biophysics, chemistry and materials science.

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Making Classical and Hybrid (QM/MM) Molecular Dynamics Easy and Fast with QwikMD

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''Everything that living things do can be understood in terms of jigglings and wigglings of atoms.'' Richard Feynman's remarks in the early 1960's summarize what is today widely accepted, namely, that molecular processes can be described by the dynamics of biological molecules, therefore connecting protein function with protein dynamics. Molecular dynamics (MD) simulation, in this regard, is the major methodology employed in structural biology to explore the dynamical behavior of macromolecules. Although the use of MD simulations has consistently increased over the last decades, the barrier imposed by the initial learning curve of the MD packages is still high. To assist new users in overcoming this barrier, and to help the more advanced users to speed up tedious preparation steps, we developed QwikMD(1). This user-friendly program connects the widely used molecular graphics program VMD to the widely adopted MD program NAMD. Employing QwikMD, a user is able to setup an MD simulation in just a few minutes, allowing quick studies of point mutations, partial deletions or even atomic force microscopy experiments. Within the different modules of QwikMD, one can adopt a myriad of simulation protocols, from single protein in vacuum to hybrid QM/MM simulations. QwikMD makes it easy for a new user to perform MD simulations, while it also serves as a learning tool. Many ''info buttons'' provide the theoretical background underlying the MD procedures carried out in modern MD simulations.

1. J. V Ribeiro *et al.*, QwikMD — Integrative Molecular Dynamics Toolkit for Novices and Experts. *Sci. Rep.* **6**, 26536 (2016).

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A Flexible, GPU - Powered Fast Multipole Method for Realistic Biomolecular Simulations in Gromacs

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The calculation of electrostatic interactions is typically the computational bottleneck of molecular dynamics (MD) simulations and thus decisive for the overall simulation performance. Further, biomolecules typically contain many sites whose electrostatic charge distribution changes over time, e.g. due to uptake and release of protons or tautomerism at protonatable sites, or electron transfer between redox-active cofactors. Besides computational efficiency, a physically accurate electrostatics treatment therefore has to account for this variability, too, thus aggravating the bottleneck. Taking advantage of the computational power of GPUs through innovative algorithms, high-throughput simulations of large systems become feasible. To that aim, we have developed a fast multipole method (FMM) for the rapid computation of the electrostatic interactions that are required for a lambda-dynamics treatment of the interconversion between the different site forms during the simulation. The tree data structure used by the FMM allows one to include alternative charge distributions of the different protonation forms without requiring redundant computations. Therefore, our FMM enables efficient computation of electrostatic forces and interaction energies between large numbers of titratable sites with a small, nearly constant computational overhead. For taking full advantage of GPUs, the FMM implementation ensures that the computational work is evenly distributed among the large number of GPU processing units. To this aim, our parallel GPU-implementation optimally matches hardware and algorithmic requirements, resulting in very good scaling properties.

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Towards Dynamic Pharmacophore Models by Coarse Grain Molecular Dynamics

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Pharmacophore models play a key role in computer aided drug discovery e.g. in virtual screening of chemical databases, *de novo* drug design, and lead optimization. Structure-based methods for developing pharmacophore models are of particular importance, and there have been a number of studies combining such methods with the use of molecular dynamics (MD) simulations to model protein flexibility. At the same time, ongoing developments in multi-scale simulations, in which atomistic and CG MD simulations are combined in a sequential fashion, have been successfully used to explore the interactions of proteins with membranes and their lipids [1,2]. Here we describe the use of CG-MD simulations to explore the interactions of CG-particle probes with proteins, combined with cavity detection methods, in order to identify potential protein binding sites. Using cyclin dependent kinase 2 (CDK2) as a test case, we demonstrate the potential of this approach for identification of ligand binding sites, and as part of an overall process of structure-based development of pharmacophore models.

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Couplings between Local and Global Conformational Changes in Proton-Coupled Oligopeptide Transporters

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Here we report on an extensive set of equilibrium and nonequilibrium all-atom molecular dynamics (MD) simulations of a bacterial proton-coupled oligopeptide transporter (POT), namely GkPOT, in an explicit membrane/water environment. Using several microseconds of unbiased MD trajectories, we have characterized both the local and global conformational dynamics of the transporter upon the proton and/or substrate binding, within the simulation timescales. Our results reveal a distinct behavior for local conformational dynamics in the absence and presence of the proton at the putative proton binding site. Particularly, we find that the substrate binding conformation is drastically different in the two conditions; the substrate binds to the protein in an either lateral or vertical manner, in the presence or absence of the proton, respectively. This behavior is consistently observed in multiple sets of independent simulations for different substrates. On the other hand, we do not observe any statistically significant distinctive behavior in terms of the global conformational changes under different simulation conditions. On the other hand, the linear regression analysis of quantities associated with the global conformational fluctuations provides evidence for a mechanism involving the concerted motion of the transmembrane helices, consistent with the rocker-switch mechanism proposed for major facilitator superfamily transporters. Employing a novel biasing scheme based on extrapolating the global rotational fluctuations of the transmembrane helices, we have reconstructed the inward- to outward-facing conformational transition of the GkPOT transporter in the presence and absence of the substrate/proton. Unlike the unbiased equilibrium simulations, a strong correlation is observed between the local and global conformational changes observed in our nonequilibrium simulations. These observations provide evidence for a strong coupling between the protein global conformational changes and local binding site conformational changes. However, these couplings are not observed, in a statistically sound manner, when only the unbiased equilibrium simulations are considered, even on the microsecond timescale. Our results, therefore, call into question the implicit assumption behind MD studies that use short simulations to speculate on long-timescale behavior of the membrane transporters, which often function on timescales much longer than those currently accessible to unbiased MD.