

the stability change by the mutation. These predictions give us clues to improve the target without synthesizing/expressing the target. However, calculating the free-energy change is a tedious and complex procedure. In this poster, I present an open-source free-energy calculation pipeline called FEP suite, which includes (1) free-energy perturbation with absolute binding free-energy (FEP-ABFE), primarily designed for ligand-receptor binding, and (2) free-energy perturbation enhanced by replica exchange solute tempering (FEP/REST), primarily designed for relative free-energy change calculation by introducing mutations. The pipeline eases the tasks of estimating the free energies for hundreds of candidate molecules or mutations. The pipeline is built upon GROMACS molecular dynamics software and is tightly integrated with various batch job systems to run the programs routinely. The design decisions behind the pipeline will be discussed and the benchmark including a therapeutic application will be presented.

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Atom probe tomography: Computational challenges and perspectives

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A novel procedure for the application of atom probe tomography (APT) to the structural analysis of biological systems has been recently proposed, whereby the specimen is embedded by a silica matrix and ablated by a pulsed laser source. Based on this technique, our group at the University of Trento is actively collaborating to the efforts of a recently funded EIC-pathfinder consortium, named MIMOSA, whose ultimate goal is to provide an alternative to 4D microscopy with a disruptive technology enabling a high spatial resolution and a chemical sensitivity analysis of biosamples. However, this technique poses several challenges that can be tackled only by a close interplay between the experimental and the modelling/computational efforts. For instance, APT requires that the silica primer be properly inert and bio-compatible, keeping the native structural features of the system at hand while condensing into an amorphous, glassy like coating. We have proposed a molecular dynamics protocol aimed at depicting and characterizing the earliest stages of the embedding process of small biomolecules in a solution of water and orthosilicic acid, here taken as a precursor of the silica matrix. In this first preliminary step, we observe a negligible influence of orthosilicic acid on the behavior of stable folded systems (such as ubiquitin and GFP), while it affects the fluctuations of intrinsically disordered and unstable peptides. However, the entire project presents several challenges that can be tackled (or at least addressed) with the available computational techniques, whether classical or ab initio. I will present our most recent applications in this direction and offer some perspectives for discussion.

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Update of the CHARMM36 force field for anionic lipids

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The CHARMM36 lipid force field (C36) has been optimized for use with both a force-based switching function on Lennard-Jones (LJ) interaction with long-range electrostatic particle-mesh Ewald (PME) and for long-range LJ particle-mesh Ewald (C36/LJ-PME). For zwitterionic lipids, both treatments of the LJ potential agree well with experiment. However, for negatively charged lipids phosphatidylserine (PS) and phosphatidylglycerol (PG), the current force field yields less than satisfactory results. For POPG bilayers in 100 mM NaCl, C36 overestimates the surface area per lipid by 3.7 Å². For POPS bilayers in 100 mM NaCl, surface area per lipid are underestimated by 5.7 Å² and deuterium order parameters are overestimated. This study makes use of a recently developed global optimization scheme based on thermodynamic reweighting. Due to the strong influence of solvent interactions with charged lipids and the paucity of published experimental data, compression isotherms of POPS and POPG monolayers with various ions were measured and included in the optimization. To account for changes that influence

ion-headgroup interactions, nonbonded pairwise exceptions are fit to osmotic pressure and QM data after each iteration. The optimization method shows improvement with experimental values when using PME and will be extended to both LJ-PME and the Drude polarizable models.

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Neighbor list artifacts in molecular dynamics simulations

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Molecular dynamics (MD) simulations are widely used in biophysical research. To aid non-expert users, most simulation packages provide default values for key input parameters. In MD simulations using the GROMACS package with default parameters, we found large membranes to deform under the action of a semi-isotropically coupled barostat. As the primary cause, we identified overly short outer cutoffs and infrequent neighbor list updates that result in missed long-range non-bonded interactions. Small but systematic imbalances in the apparent pressure tensor then induce unphysical asymmetric box deformations that crumple the membrane. We also observed rapid oscillations in averages of the instantaneous pressure tensor components and traced these to the use of a dual pair list with dynamic pruning. We confirmed that similar effects are present in MD simulations of neat water in atomistic and coarse-grained representations. Whereas the slight pressure imbalances likely have minimal impact in most current atomistic MD simulations, we expect their impact to grow in studies of ever-larger systems with coarse-grained representation, in particular in combination with anisotropic pressure coupling. We present measures to diagnose problems with missed interactions and guidelines for practitioners to avoid them, including estimates for appropriate values for the outer cutoff r_l and the number of time steps n_{list} between neighbor list updates.

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Binding free-energy calculation tools: Towards maturity?

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Predicting binding free energies from explicit simulations, remains a challenging process in many respects. We introduce powerful tools for this task, from the core of alchemical free energy estimation to the experimentally testable prediction of binding titration curves. Our approaches are conceptually and procedurally straightforward and robust, simplifying decision-making and demanding only a few simulations while improving the sampling of orthogonal degrees of freedom. They are made available in popular open-source academic software by leveraging the portable Colvars library, thereby enabling applications to non-polarizable as well as polarizable models. A new tutorial provides a gentle introduction to the procedure. While the field may seem mature, human expertise remains essential for making the crucial modeling choices that lend scientific significance to computed free energies, and for interpreting the information generated by the simulations. By streamlining the technical aspects, our aim is to free scientists to focus on those more meaningful questions.

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LOOS: A library and suite of tools for analyzing molecular dynamics simulations

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The enormous improvements in computational power in recent years means that we can routinely runs simulations of biologically interesting systems out to the microsecond scale or longer. However, in many cases their scientific impact is limited by an inability to extract useful information from this wealth of data. We created LOOS to unlock this previously unrealized potential. Molecular dynamics is unique among biophysical techniques in that the raw data can be interrogated in a multitude of ways; getting the most out of the data usually requires exploration and iterative refinement. LOOS is designed to make this process easy and efficient, to minimize the friction between a user and her data. LOOS can be viewed in two ways: 1) It is a suite of well-validated,