nearly 1000 molecular dynamics simulations of liquids containing drug-like atom types. We compare our simulations to an extensive database of physical properties from NIST's Thermodynamics Research Center. We also evaluate GAFF's performance using density measurements of neat liquids and binary mixtures performed on an in-house automation system.

920-Plat
Implementing Solution X-Ray Scattering Data as Active Constraints in MD Simulations
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X-ray and neutron solution scattering are powerful techniques that provide a measure of biomolecular structure and its diversity. The techniques are highly sensitive to conformational change - however, the measured intensities represent a single global average over all conformations and obscures the extent of structural variations as well as their relative frequency. Thus, the utility of scattering data in molecular simulations depend on the ability to generate the underlying conformational ensemble, guided by only the average values. To resolve this, we recently implemented an explicit-solvent approach to predict the ensemble SWAXS pattern of a biomolecule using molecular dynamics [Chen and Hub, Biophys. J. 107:435-447 (2014)]. By relying upon MD to explicitly sample fast degrees of freedoms in both solvent and solute, accurate predictions were computed for relatively stable proteins. The approach adopted also enables the use of SWAXS data as constraints that provide forces to guide the simulation trajectory, which permits the interpretation of experimental data by directing simulated proteins into compatible conformations. The application of SWAXS-driven MD to biological examples is given in an accompanying talk.
Here, we will address the derivation of such constraints, taking into account the sampling of different degrees of freedom and sources of uncertainty. We find that conformation-dependant SWAXS patterns can be derived over ~1 ns timescales, permitting fast equilibration in constrained-simulations. Uncertainty due to buffer subtraction dominates at low angles q, while experimental and statistical errors dominate at large q. Inclusion of these errors in the constraints do not affect the qualitative behaviour of resulting trajectories. The application of SWAXS-based constraints in the context of both single-state and heterogenous ensembles will also be discussed.

921-Plat
Constant pH Molecular Dynamics in Explicit Solvent with Enveloping Distribution Sampling and Hamiltonian Exchange
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We present a new computational approach for constant pH simulations in explicit solvent based on the combination of the enveloping distribution sampling (EDS) and Hamiltonian replica exchange (HREX) methods. Unlike constant pH methods based on variable and continuous charge models, our method is based on discrete protonation states. EDS generates a hybrid Hamiltonian of different protonation states. A smoothness parameter s is used to control the heights of energy barriers of the hybrid-state energy landscape. A small s value facilitates state transitions by lowering energy barriers. Replica exchange between EDS potentials with different s values allows us to readily obtain a thermodynamically accurate ensemble of multiple protonation states with frequent state transitions. The analysis is performed with an ensemble obtained from an EDS Hamiltonian without smoothing, which strictly follows the minimum energy surface of the end states. The accuracy and efficiency of this method is tested on aspartic acid, lysine, and glutamic acid, which have two protonation states, a histidine with three states, a four-residue peptide with four states, and snake cardiotoxin with eight states. The pKa values estimated with the EDS-HREX method agree well with the experimental pKa values. The mean absolute errors of small benchmark systems range from 0.03 to 0.17 pKa units, and those of three titratable groups of snake cardiotoxin range from 0.2 to 1.6 pKa units. This study demonstrates that EDS-HREX is a potent theoretical framework, which gives the correct description of multiple protonation states and good calculated pKa values.

922-Plat
Mesoscale Modelling of Biomolecules using Continuum Mechanics
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Biophysical techniques that provide structural information at the mesoscale, such as cryo-electron microscopy and 3D tomography, are now sufficiently mature that they merit their own online repository called the EMDataBank (EMDB). We have developed a continuum mechanics description of proteins which uses this new experimental data as input to the simulations. The model is a Finite Element algorithm which we have generalised to include thermal fluctuations, and which is therefore known as Fluctuating Finite Element Analysis (FFEA). While conventional molecular dynamics simulations provide a trajectory in which each individual atomic position fluctuates, an FFEA trajectory shows how the overall shape of the protein changes due to thermal agitation. We have used FFEA to show that the crowded environment of the axoneme impedes the thermal fluctuations of the largest cytoskeletal motor dynein, and have used our model to calculate the reach of the motor in situ. Our modelling highlights the importance of understanding the 3D architecture of biological structures at the mesoscale.

923-Plat
Multilevel Summation Method for Electrostatic Force Evaluation
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The multilevel summation method (MSM) offers an efficient algorithm for evaluating long-range forces in molecular dynamics simulations. MSM is competitive to the ubiquitous particle-mesh Ewald (PME) method, but handles periodic as well as semi-periodic and non-periodic systems. MSM, unlike PME, can calculate dispersion forces without cutoff. The version of MSM available in the simulation program NAMD is described, and its performance and accuracy compared with the PME method. The comparison involves water property calculations such as density, diffusion constant, dielectric constant, surface tension, radial distribution function, and the distance-dependent Kirkwood factor. Excellent agreement between MSM and PME is found also for interface potentials of air-water and membrane-water interfaces, where long-range Coulombic interactions are crucial. Through the use of nested interpolation of softened pair potentials in real space, MSM can be applied to simulations having semi-periodic or non-periodic boundaries. Simulations were performed with periodic boundaries along directions parallel to a membrane surface but not along the direction of the surface normal, to describe membrane pore formation induced by an imbalance of charge across a membrane. With a similar semi-periodic boundary condition, ion conduction through a graphene nanopore was simulated in the presence of an ion gradient. Proteins were also simulated inside a spherical water droplet without any periodic boundary. Finally, MSM is demonstrated to provide better parallel scaling than PME, making MSM more suitable for the simulation of large systems.

924-Plat
Using Long-Timescale Molecular Dynamics Simulations to Benchmark Enhanced Sampling Methods
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All-atom molecular dynamics (MD) simulation is a valuable technique for providing detailed information about the dynamics of biomolecules, but its computational expense can often be prohibitive. This limitation has motivated the development of ''enhanced sampling'' simulation methods - purely algorithmic changes to conventional MD that aim to accelerate the sampling of configurational states. Although many such methods are available, relatively few systematic studies of their performance have been done. Quantitative claims about the performance of enhanced sampling simulations are typically limited to (i) comparisons with conventional MD simulations of small, model systems, which may present qualitatively different sampling challenges than complex biological systems, or (ii) comparisons with experimental data, which may be complicated by discrepancies between the actual experimental conditions and the modeling of those experimental conditions in the enhanced sampling simulation, including errors in the physical model, or force field, used in simulation. An effective alternative approach to quantifying performance of enhanced sampling methods would be to compare the results they obtain on complex biological systems directly to those obtained by conventional MD simulations using the same force field. Here, we use long-timescale conventional MD simulations to assess the performance of certain commonly used enhanced sampling methods in accelerating the sampling of protein conformational changes, protein folding, and ligand binding.