fluidity and bending elasticity of natural lipid membranes. We illustrate the usefulness of our model by computing the response of a bilayer to mechanical perturbations, such as deformations caused by an extending filopod.

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Application of Large-Scale First Principles Quantum Mechanical Calculations With the ONETEP Program To Biophysical Problems

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Properties and processes at the molecular level are determined by the interactions between electrons and atomic nuclei whose motions are governed by the theory of quantum mechanics. Therefore, an unbiased and highly accurate approach for molecular simulations can be provided by quantum mechanical calculations from ''first principles'', which do not rely on empirical parameters. Density Functional Theory (DFT) is such an approach and is widely used because of its computational efficiency but the computational effort of conventional DFT increases with the third power of the number of atoms. As a result it is practically not feasible even on supercomputers to perform DFT calculations with more than a few hundred atoms. Novel reformulations of DFT based on the one-particle density matrix can lead to computational effort which increases linearly with the number of atoms and hence overcome this length-scale problem. I will briefly describe how this is achieved in our ONETEP linear-scaling DFT program which is designed to achieve the same high level of accuracy as conventional cubic-scaling approaches. Then I will give an overview of current applications we are performing with ONETEP, including quantum mechanical simulations of entire proteins with thousands of atoms participating in protein-protein and protein-ligand complexes.

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58-Plat

Recent Developments of the Molecular Dynamics Flexible Fitting Method

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Molecular Dynamics Flexible Fitting (MDFF) is a computational method that combines structural information from X-ray crystallography and cryo-electron microscopy (cryo-EM). Cryo-EM provides structural data on biomolecules in their functional states but not at atomic resolution, while X-ray crystallography yields atomic-resolution data but for molecules in crystalline form that renders them often non-functional. MDFF employs molecular dynamics (MD) simulations to bridge the two sets of data, by adding an attractive potential derived from cryo-EM maps to the MD force field, driving atoms toward high-density regions while maintaining a stereochemically correct conformation of the molecules. MDFF has already been successfully applied to study several macromolecular complexes such as the ribosome.

To further advance MDFF, we have created a test set consisting of different types of biomolecules in different conformational states. Using this test set, MDFF has been optimized for different types of molecules and conformational changes, providing a useful guideline for users applying MDFF to different biological systems. Moreover, helical symmetry restraints have been incorporated into MDFF as many biological systems studied by MDFF have helical symmetry, such as the family of microbial nitrilases. Information about helical symmetry can now be included in MDFF, improving the quality of the fit on these kinds of systems.

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On Bootstrap Techniques For Classifying Projections in Single Particle Electron Microscopy

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In single-particle reconstruction methods [1], projections of macromolecules at randomly unknown orientations are collected by an electron microscope. Often, several classes of conformations or binding states coexist in a sample. To obtain structures with high accuracy, it is required to separate the classes before reconstruction of the structures takes place. In this work, we take a close look at bootstrap techniques for classifying the projection data.

In the bootstrap techniques for variance estimation [2], the projection images or particles are randomly sampled with replacement from the dataset and a bootstrap volume is reconstructed from each sample, assuming known orientations. In a recent extension of the bootstrap technique to classification [3], each particle is assigned to a volume in the space spanned by the bootstrap volumes, such that the projection of the assigned volume (in the same orientation as the particle) best matches the particle. Finally, a clustering algorithm applied to the assigned volumes determines the class to which the particle belongs.

In this work we explain the rational of these techniques by discussing the nature of the bootstrap volumes: i.e., how they relate to the underlying structural classes. Furthermore, several statistical analyses become easy to study in our framework. Finally, the way the particles are assigned to volumes in the space spanned by the bootstrap volumes is closely examined.

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Mypal, a Multi-Resolution Approach For Interactively Locating Functionally Linked Ion Binding Sites

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Metal ions drive important parts of biology, yet it remains experimentally challenging to locate their binding sites. Here we present an innovative computational approach. We use interactive steering of charged ions or small molecules in an electrostatic potential map in order to identify potential binding sites. The user interacts with a haptic device and experiences tactile feedback related to the strength of binding at a given site. The potential field is the first level of resolution used in this model. Any type of potential field can be used, implicitly taking into account conditions such as ionic strength, dielectric constants or the presence of a membrane. Furthermore, we represent the accessibility of all binding sites by modelling the shape of the target macromolecule via non-bonded van der Waals interactions between its static atomic or coarse-grained structure and the probe molecule(s). The third level concerns the representation of the molecular probe itself. Ion selectivity can be assessed by using multiple interacting ions as probes. This method was successfully applied to the DNase I enzyme, where we recently identified two new cation binding sites by computationally expensive extended molecular dynamics simulations.

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GNEIMO: Constrained Molecular Dynamics Methods For Long Time Scale Simulation of Macromolecules

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The two leading causes for the limitation of the all-atom molecular dynamics (MD) simulation timescales are: 1. calculation of forces that scale as the square of the number of atoms and, 2. the integration time step is limited to 1fs due to the high frequency modes in the protein. High performance technologies and better force calculation algorithms have addressed the former, and we address the latter issue in this work.

Here we report a constrained MD method, GNEIMO (Generalized Newton-Euler inverse mass operator method), that is capable of achieving stable dynamics with integration time steps as large as 10 to 20fs. The GNEIMO method provides a platform to perform long time scale hierarchical simulations ranging from all-atom simulations, coarse-grained dynamics of clusters of few atoms, to dynamics with larger motifs constrained, at lesser computational expense compared to all-atom MD. GNEIMO method uses spatial operator algebra to solve for the internal coordinate dynamics with computational cost scaling linearly as the number of degrees of freedom.

The current implementation of GNEIMO is capable of performing constant temperature Nose-Hoover dynamics, with continuum Generalized Born solvation. We use adaptive step size integration to provide stable dynamics with larger time steps. We have carried out tens of nano-seconds of stable dynamics for proteins with time steps as large as 10 to 20fs for different integrators. We report results from conformational changes of domains in proteins from long time scale dynamics. This implementation integrates the force-field module from the MD program LAMMPS, with constrained dynamics module from NASA-Jet Propulsion laboratory.