2951-Plat
Constant pH Simulations In Explicit Solvent Using The Lambda-Dynamics Approach
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pH is an important parameter in condensed phase systems as it determines the protonation state of ionizable groups and consequently influences the structure, dynamics and function of molecules in solution. In the past ten years, few approaches have been applied to model the pH of a solution in the framework of Molecular Dynamics (MD) and Monte Carlo (MC) simulation methods. These include stochastic and mean field approximation methods to model the (de)protonation events and methods based on the lambda-dynamics approach, where the dynamics of the titration coordinate lambda is driven by the free energy gradient between the protonated and deprotonated states. In particular, the latter approach was so far limited to implicit solvent. We present here a method for constant pH simulations in explicit solvent that is based on the lambda-dynamics approach. The method has been implemented in the MD package Gromacs. The titration curve of single amino acids and small peptides and the shift in the pKa of an active site glutamic acid in the enzyme triosephosphate isomerase were correctly predicted. This preliminary tests suggest that the approach can be applied to simulate (bio)molecules with multiple titrating sites at constant pH.

2952-Plat
Using the Isotropic Periodic Sum Method to Calculate Long-Range Interactions of Heterogeneous Systems
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Isotropic periodic sum (IPS) is a method for the calculation of long-range interactions in molecular simulation based on the homogeneity of simulation systems. Three IPS models, 3D IPS, 2D IPS, and 1D IPS have been developed for three common types of homogeneous systems. Based on the fact that 3D IPS can well describe the long-range interactions of a heterogeneous system if a local region larger than the homogeneity scale is used, this work presents a method based on 3D IPS to calculate long range interactions for all kinds of simulation systems, including homogeneous, heterogeneous, and finite systems. Unlike the original 3D IPS method that uses a local region defined by the cutoff distance, this method uses a local region larger than that defined by the cutoff distance to reach the homogeneity scale. To efficiently calculate interactions within such a large local region, this method split long range interactions into two parts, a cutoff part and a long-range part. The cutoff part is calculated by summing over atom pairs within a cutoff range (about 10 Å), and the long-range part is calculated using the discrete fast Fourier transform (DFFT) technique. This method is applied to electrostatic and vdw interactions for both periodic and non-periodic systems. Example simulations demonstrate that this method can accurately and efficiently calculate long range interactions for molecular simulation.

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Virtual Screening for Experimentalists _ a Xgrid-Powered Web Server
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Virtual-screening has emerged as an attractive strategy for discovering inhibitors of biological systems, especially for systems in which appropriate high-throughput assays are absent. Despite the potential benefits, challenges such as insufficient computational resources and lack of experiences often present a barrier that consequently limit a wider use of the technology among experimentalists. A virtual-screen web server aimed at lowering this barrier and providing a practical tool to the general scientific community has been developed (http://omg.phy.umassd.edu/xvHTS/). The server offers ''experience'' and resources by incorporating a validated screening protocol, and utilizing distributed computing resources, a concept that mirrors the Folding@Home project. The user-friendly interface of the server provides graphical supports that enables novice users to start a virtual screening project by simply providing a PDB code, and optionally customize by a few mouse-clicks. The back-end is driven by xgrid technology, a built-in capability in the Macintosh operating platform that efficiently utilizes idle computing resources over the grid-network. When in execution, parallel docking processes are dispatched onto the grid, the results are analyzed, and returned to the users in an easy-to-interpret fashion. This xgrid-powered virtual-screening web server lays out a foundation for large-scale screening with great growth potential. The ''embarrassingly parallel'' nature of virtual-screening allows virtually unlimited scalability as more idle CPUs become available over the grid-network. Joining the grid is trivial, and does not require any installation. This website is beneficial to the general scientific community, and thus deserves exposures to both potential users and donors. A successful application of the screening protocol is presented in the discovery of novel inhibitors of the Epidermal Growth Factor Receptors (EGFR). Without the availability of high-throughput assays, two anti-EGFR inhibitors are discovered by virtual-screening a compound library, and confirmed by subsequent low-throughput biochemical assays.