higher dimensional space. The grouping of cells (data points) having similar features, which is referred to as gating, is usually done manually by an expert. We developed software that performs efficient unsupervised gating determining the number of clusters, and the points belonging to each cluster. The program analyses the cross-sections of the histogram created from the data points. The method is particularly efficient in the case of large number of data points such as 10^4-10^6. The overall run time for the composite steps of the algorithm increases linearly by the number of data points. In our example 1 million data points, shown in the left part of the figure, were analyzed within 6 seconds on a standard laptop PC. The analysis resulted in 20 clusters, shown in the right side of the figure. The code number of the largest cluster is 1, the second largest is 2, etc.

3837-Pos

An Investigation of Glutamic Acid 242 as a Proton Pump Valve in Bovine Cytochrome C Oxidase using QM/MM Monte Carlo Simulations

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Cytochrome c Oxidase (CcO) is a mitochondrial inner membrane protein which catalyzes the reduction of oxygen to water and utilizes the free energy of this reaction to pump protons across the membrane from a lower concentration of protons (N-side) to a higher concentration of protons (P-side). This generates an electrochemical proton gradient which is ultimately used by ATP synthase to convert ADP to ATP. A key question is how CcO is able to maintain unidirectional translocation of protons across the membrane in the presence of this gradient. Glutamic acid 242 (bovine numbering) is a conserved residue in CcO which is found in the X-ray crystal structure to be a physical connection for protons from the N-side to the P-side of the membrane. It is hypothesized that Glu242 acts as a proton pump valve by delivering protons in one direction and preventing the backflow of these protons through protonation state dependent changes in its conformation. A model of CcO has been developed and the conformation space of Glu242 has been sampled using Monte Carlo simulations with energies calculated using the ONIOM QM/MM method. These calculations suggest a mechanism by which Glu242 facilitates unidirectional pumping and the prevention of proton leakage.

3838-Pos

Ionic Effect on MD-SAXS Profile

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The combination of small-angle X-ray solution scattering (SAXS) experiment and molecular dynamics (MD) simulation is now becoming a powerful tool for studying protein structures in solution at an atomic resolution. Several studies have developed the calculation methods of SAXS profile from protein atomic structures, in which scattering from hydration structure around the protein was calculated using uniform density layer or explicit water molecules in the MD simulations. Although general SAXS experiments of protein solutions are carried out at certain ionic concentrations, in these calculations the effects of ionic strength on SAXS profile has not been considered explicitly. In this study, we investigate the effect of ionic strength on the SAXS profile by using the MD simulations of hen egg white lysozyme at various NaCl concentrations.

At 0 mM NaCl, the calculation of the SAXS profile converged completely within ~ 200 ps MD simulation, but at concentrations larger than 100 mM NaCl, the convergence was not obtained even with 10-ns simulation due to large density fluctuations in the bulk region. We also observed certain dependencies of SAXS profile on NaCl concentrations. These results indicate that MD simulation at large NaCl concentrations is a disadvantage in obtaining accurate SAXS profile. To accommodate this problem, we investigated the dependency of solvation structure around the protein on NaCl concentration, and based on the obtained information, have develop the new calculation method that incorporates the effect of ionic strength in SAXS profile calculation derived from the MD simulation at 0 mM NaCl.

3839-Pos

Parameterization of CB1 Negative Allosteric Modulators for CHARMM Molecular Dynamics

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Recently, several allosteric modulators of the Class A G-protein coupled receptor CB1 were discovered. Among these modulators are PSNCBAM-1 and ORG27569 which act as CB1 negative allosteric modulators (M. R. Price, et al. Molec. Pharm. 68, 1484 (2005) and J. G. Horswill, et al. British J. of Pharm. 152, 805 (2007)). Molecular dynamics simulations would be useful in elucidating the interactions between these ligands and the CB1 receptor. In order to utilize molecular dynamics, CHARMM force field parameters for these ligands are necessary. The parameters that have been developed for molecular dynamics simulations using the CHARMM force field have mainly focused on proteins, lipids, and nucleic acids and therefore do not encompass many small molecules. Only recently have researchers begun to expand these parameters to small molecules that have compositions that differ from the more biological groups (K. Vanommeslaeghe, et al. J. Comp. Chem. Early View 2009). In order to prepare these CB1 allosteric modulators for use in molecular dynamics simulations, novel parameters were developed for PSNCBAM-1 and ORG27569 by calculating new atom charge, angle, and dihedral parameters that could not be found in the recently developed CGenFF database, which encompasses more small molecules than the previous CHARMM databases. The methods used to develop these parameters, developed by the MacKerrell group (http://dogmans.umaryland.edu/~kenno/tutorial/#charges_qm), will be reviewed, and the results of the parameterization will be presented.

Regulatory Networks & Systems Biology

3840-Pos

A Systems Biology Approach to Understanding Alzheimer's Disease

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A mathematical model for Alzheimer's disease (AD) has been developed using a systems biology approach. A cellular network of neurons, microglia and astrocytes has been created to model the levels of beta amyloid in the brain. The production and spatial distribution of beta amyloid, the key protein implicated in AD, has been modeled using the reaction-diffusion equation, where reaction rates have been modeled using stochastic functions. Neurons have been modeled using a previously developed McCulloch-Pitts neural network (Butz 2006) modified to account for neuronal cell death and loss of synaptic elements during high beta amyloid levels. Microglia are either in the ramified state (at rest) and modeled using a continuous random walk model, or in the activated state (actively moving towards a source of beta amyloid) and modeled using the Langevin equation of motion. Astrocytes are defined to set locations and contribute to removal of beta amyloid from the brain interstitial fluid. The roles that local cerebral blood flow, transport across the BBB, and local reactions play have also been modeled. Future work will look at the development of amyloid beta plaques in the cerebrovasculature and brain parenchyma, and their relationship to observed decreases in cerebral blood flow as the disease progresses.

3841-Pos

A Ratchet Mechanism for Low-Frequency Hearing in Mammals

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The sensitivity and frequency selectivity of hearing result from tuned amplification by an active process in the mechanoreceptive hair cells. The nature of the active process in the mammalian cochlea is intensely debated, for outer hair cells exhibit two forms of mechanical activity, active hair-bundle motility and membrane-based electromotility. Here we show theoretically that active hair-bundle motility and electromotility can together implement an efficient mechanism for amplification that functions like a ratchet: sound-evoked forces acting on the basilar membrane are transmitted to the hair bundles while electromotility decouples the active hair-bundle forces from the basilar membrane. Through a combination of analytical and computational techniques we demonstrate that the ratchet mechanism can naturally account for a variety of unexplained experimental observations from low-frequency hearing.

3842-Pos

Model of the Drosophila Circadian Clock: Loop Regulation and Transcriptional Integration

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Circadian clocks influence key features of daily life including timing of sleep, awakening, and feeding. Eukaryoticcircadian clocks include interconnected positive and negative feedback loops. The CLOCK-CYCLE dimer (CLK-CYC) and its homolog, CLK-BMAL1, are key transcriptional activators of central components of the Drosophila and mammalian circadian networks, respectively. In Drosophila, negative loops include period-timeless and vrille; positive loops include par domain protein 1. Clockwork Orange (CWO) is