quence of the PrPs from cat and dog differ only by four residues (within Res 121–230). But there is no report of TSE-infected dogs whereas TSE-infected cats have not been reported. Recently the structures of PrP in many species have been determined by NMR. In this study, we performed molecular dynamics simulation of the PrPs from mouse, dog, cat, pig, sheep, cattle, and human. We discuss the differences in dynamics and sequence of the PrP between these species, especially dog and cat.

2436-Pos Opening Mechanism of the Protein Conducting Channel Studied by Molcular Dynamics Simulation

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Board B550

Protein translocation, the transport of a protein through a pore is of great importance for all living organisms. It is essential for cells to have membrane channels which are able to transport proteins to different locations/compartments inside the cell where they are needed. An example for such a channel is the protein conducting channel SEC61. Here proteins are both translocated across as well as inserted into the membrane.

Two of the main structural features of this protein channel are a pore region, consisting of a ring of 6 hydrophobic residues located in the center of the channel as well as a "plug" consisting of a short alpha-helix located just below the pore region. Both features guarantee the correct functionality, meaning specific transport of polypeptides through the channel area while blocking the channel in the closed state.

Molecular dynamics simulations are performed to understand the overall mechanism of protein transport across the membrane and address questions concerning selectivity, sealing of the channel or transport rates of different polypeptides through the channel. Translocation processes usually take place on timescales (~ms) not accessible to standard molecular dynamics simulation. By using steered molecular dynamics simulation to accelerate the opening process together with statistical analysis using fluctuation theorems the potential of mean force for removal of the plug is obtained. In addition the PMF for translocating small molecules and ions in the pore region is calculated.

Computational Methods, Molecular Dynamics - III

2437-Pos Molecular Dynamics Simulations of Polyethylene Oxide with the CHARMM Ether Force Field

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Board B551

Polyethylene oxide (PEO) and polyethylene glycol (PEG) are used in biophysical studies as solvents for low temperature crystallography, modulators of osmotic pressure, and probes of pore sizes of membrane channels. This poster describes a revision to the recently published CHARMM ether force field (*J. Chem. Theory Comput. C* **2007**, *3*, 1120–1133) based on matching experimentally measured conformational populations of pure dimethoxyethane (DME, the subunit of PEO and PEG) and aqueous solutions at mole fractions 0.3, 0.6. Persistence lengths evaluated from molecular dynamics simulations of 9, 18, 27 and 36-mers of PEO in water ≈ 4 Å, and are within the experimental range of 3.8–4.3 Å. The exponent v relating the radius of gyration and molecular weight ($R_g = M_w v$) of PEO equals 0.5, in agreement with experimental observations on polymers of these lengths. Persistence lengths for PEG and PEO consisting of the same number of monomers are comparable.

2438-Pos Simulation Of Membrane Systems: Combination Of The Charmm Protein Force Field With Different Lipid Parameters

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Board B552

Cell membrane are complex, organized structure composed predominantly of lipids, proteins and sugars. The determination of the structure of their components remains an experimental challenge, mainly because of the lipid fluidity. That is why important efforts have been invested in the development of computer simulations of pure lipid membranes or lipid-protein mixtures. The accuracy of such simulations strongly depends on the quality of the force field used.

Some force fields offer a comprehensive set of parameters for all major biological compounds (protein, lipid, nucleic acid, sugar), but the majority of available force fields are independently developed for a particular class of compounds. In order to simulate a complete membrane system, one often has to combine different parameter sets. This strategy raises two problems:

1. a comprehensive parameter set does not guarantee that the parameterization method used is suited to all compounds
2. sets of parameters developed independently for different classes of compounds might not yield sufficient accuracy when combined together.

We have implemented and tested the CHARMM force field in the GROMACS molecular dynamics package. On one side, CHARMM provides parameters for various compounds, including lipids and amino acids. On the other side, the Berger's lipid parameters implemented in GROMACS have been shown to reproduce an area per lipid close to experimental values in tensionless bilayers, in contrast with CHARMM parameters. We comprehensively tested CHARMM amino acids in combination with CHARMM lipids and also with Berger's lipids and other parameter sets derived from CHARMM. Our main criteria for the comparison was the free energy of transfer from water to cyclohexane. Finally, the combinations were also tested on a fully hydrated DOPC bilayer with and without WALP23 peptides.

2439-Pos CHARMM Force Field Parameterization of Lipid A

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Board B553

Bacterial lipopolysaccharides (LPS) are major components of the outer membrane of Gram-negative bacteria and are known to trigger a variety of inflammatory reactions in macrophages and other cells having a CD14 receptor. LPS consist of a hydrophobic domain known as lipid A (or endotoxin), a nonrepeating "core" oligosaccharide, and a distal polysaccharide (or O-antigen). In this study it was obtained the parameterization of the Lipid A region of the LPS molecule for the CHARMM molecular mechanics force field.

It was used the structure of an integral membrane protein (FhuA) from E. coli, with the PDB [1] ID: 1FI1.

The parameters were derived using quantum chemical calculations at restricted Hartree-Fock level of theory using the 6–31G* basis set. All the quantum chemical calculations were completed using the NWChem v.5 [2] software. The RHF/6–31G* geometry optimized structure was used for QM frequency calculations yielding the bonded parameters terms by transforming the Hessian into internal coordinates. Van Der Waals parameters were assigned by finding equivalent parameters from "CHARMM22 proteins and CHARMM27 lipids" file.

The partial atomic charges were calculated using the supramolecular approach used in Paratool for the CHARMM style charges.

This parameters were tested by creating a hydrated bilayer consisted of Lipid A, dipalmitoylphosphoethanolamine and TIP3 water model molecules.

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2440-Pos Structure and Dynamics of Self-assembled Sodium Dodecyl Sulfate Micelles: A Simulation Study

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Board B554

Surfactants (e.g., lipids and detergents) are important interfacial agents in many biological and industrial systems. They consist of a polar head group and one or more hydrophobic tails, and self-aggregate above a critical concentration in an aqueous solution to form micelles and bilayers. This self-assembly mechanism lies at the heart of all biological membrane, vesicle and micelle formation, and many industrial solubilization processes.

While biologically and industrially extremely important, surprisingly little is known about molecular details of the self-assembly of surfactants and the dynamics of the formed structures. Here we extend our previous work of modeling and model construction of charged soft-matter systems [1,2] by a description of an anionic surfactant, sodium dodecyl sulfate (SDS) [3]. We present the results of large-scale Molecular Dynamics simulations of the formation dynamics and time-dependent structure of SDS micelles. We demonstrate that temperature significantly affects micelle morphologies and discuss the effect of SDS concentration on the micelle formation kinetics and structure. To our knowledge, this is the first systematic study of micellization starting from a random initial configuration with sufficient number of detergent molecules to form multiple micelles at the atomistic level with explicit solvent.

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2441-Pos Molecular Dynamics Study of the Effect of Cholesterol on the Properties of Lipid Monolayers at Low Surface Tensions

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Board B555

Lung surfactant forms a lipid monolayer at the aqueous lining of the lung alveoli. It reduces the surface tension at the gas exchange interface to near-zero, which is necessary for breathing. In adult respiratory distress syndrome (ARDS) this function is impaired due to an excess of cholesterol. The exact mechanism of lung surfactant inhibition is, however, not fully understood. We used molecular dynamics simulations to investigate the effects of cholesterol concentration on the properties of lipid monolayers at low surface tensions. In particular, we studied simple lipid mixtures of dipalmitoyl-phosphatidylcholine (DPPC), palmitoyl-oleoyl-phosphatidylglycerol (POPG) and cholesterol at ratios of 8:2:1 and 4:1:4, thus modelling the lipid component of the lung surfactant monolayer at normal and increased cholesterol concentrations. We investigated structural and dynamic properties of the two systems at various surface tensions, 0, 10, 15, and 20 mN/m, which span the physiological range of tensions observed at the gas exchange interface in the lungs. The calculations show that for a given surface tension the packing density of the hydrocarbon chains in the monolayer increases with the cholesterol concentration, resulting in both higher orientational order and slower dynamics. As a consequence, the monolayer with elevated cholesterol concentration remains in the liquid-condensed phase at surface tensions below 20 mN/m. In addition, we present an analysis of the free energy profile of pulling DPPC and cholesterol out of the monolayer into water and air.

2442-Pos The Distribution and Conformation of Very Long-Chain Plant Wax Components in a Lipid Bilayer

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Board B556

Plant wax contains long-chain alkanes and related components which are transported to the surface of the plant by specialized ABC transporters. Here, we determine the distribution and conformation of three wax components, nonacosane, nonacosan-15-one, and nonacosan-15-ol, using unbiased and umbrella sampling molecular dynamics simulations. The molecules all partitioned to the center of the bilayer, with a free-energy difference of −70 kJ/mol between bulk water and the center of the bilayer for the alkane and −55 kJ/mol for the two more polar molecules. All of the wax molecules were highly mobile in the bilayer, freely moving between opposite leaflets on a time scale of a few nanoseconds. Nonacosan-15-one and nonacosan-15-ol folded double to expose their hydrophilic group to the solvent, whereas nonacosane alternated between orientations spanning the full bilayer and orientations in the center of the bilayer.

2443-Pos The Role Of Lipid Monolayer Properties In The Regulation Of Surface Tension In The Lungs

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Board B557

In the lungs, gas exchange takes place at the air-water interface of the alveoli. This interface is covered by lung surfactant, a monolayer of lipids and proteins. It maintains the surface tension at the interface at values near zero, which is necessary for breathing. In acute respiratory failure, however, such low surface tension cannot be achieved. This condition was recently associated with changes in lung surfactant composition, which in turn changes surfactant properties. Surfactant replacement therapies aim at restoring the function of the original surfactant. A better understanding of lipid monolayer properties at low surface tensions is thus important for the design of improved therapies.

We report the effect of physical properties of the lipid monolayer on its ability to sustain low surface tensions. A variety of molecular compositions, temperatures, and rates of lateral compression were investigated using molecular dynamics simulations. We studied mixtures of dipalmitoyl-phosphatidylcholine, palmitoyloleoyl-phosphatidylglycerol and cholesterol. Upon lateral compression, the monolayer first formed small undulations, and then collapsed by buckling and folding into water. While surface tension remained low in monolayers with small undulations, it increased to the equilibrium spreading value for the collapsed monolayers with bilayer folds connected. Monolayer collapse and re-spreading allow a transfer of surfactant components between the interface and reservoirs during breathing. We thus hypothesize that lipid transfer from the lung surfactant monolayer to its reservoirs is slow at low surface tensions. At higher temperatures, the monolayers collapsed in the liquid-expanded phase and at higher tensions. Higher cholesterol concentration at lower temperatures induced monolayer transformation into the liquid-condensed phase, while at higher temperatures destabilized the monolayers. The surface tension of monolayer collapse decreased with increasing compression rates.

2444-Pos Simulation of Solvent-free Coarse-grain Membranes on Patterned Surfaces

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Board B558

Supported lipid bilayers have been studied for many years and now suitable solvent-free coarse-grain membrane models [Cooke, I. R. and M. Deserno (2005)] allow new studies of bilayer interactions with corrugated and patterned surfaces. The adhesion and conformation of biomembranes on solid surfaces provides insight into the mechanics of the membrane. Analytical solutions for bending energies of simple one and two dimensional shapes are known but these models allow straightforward measures of the membrane even on complex surfaces. As attractive forces between lipids and the solid substrates balance with thermal motion and entropic repulsion, observable anisotropies develop in the membrane. We present results for changes in bilayer density, compressibility, tension, and geometry as well as vesicle-surface fusion events.

2445-Pos Lamellar Phase Coexistence Induced By Pure Electrostatic Interactions

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Board B559

Highly charged bio-molecules can have an equilibrium at a small separation owing to the strongly correlated electrostatic interactions mediated by counterions. This phenomenon will lead to a condensation of a lamellar phase of charged membranes. This condensation will leave a very dilute (nearly pure water) membrane region in equilibrium with it much like emulsification failure for microemulsions. Although most of this phase is water, entropy will dictate that there should be at least a small number of membranes. As a result, there will be a coexistence of the two lamellar phases which is engendered by electrostatic interactions alone.

We use numerical simulations to study the possibility of this coexistence when the charge density of macroions is large, for example like DNA which has 0.9e/nm^2, and the valence of the counterions is greater than 2. We also investigate the effects of counterion size and salt. Salt can destroy the phase coexistence.

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2446-Pos Formation of Nano-Domain in a Three-Component Bilayer: a Computer Simulation Study

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Board B560

Lipid rafts in eukaryotic cells are implicated in the assembly of transient signaling platforms and more permanent structures such as the immunological synapse, as well as in the sorting of proteins for entry into specifc exocytic and endocytic trafficking pathways. Although, the determination of size and composition of cholesterol/sphingomyelin-rich domains (rafts) has received considerable attention, a clear understanding of the physical basis of their formation is yet to be achieved.

The aim of this study is to identify and quantify the molecular interactions in ternary mixtures that maybe responsible for the formation and stability of phase-separated domains. To this end Molecular Dynamics simulations have been carried out for a three-component bilayer made of phosphatidylcholine, sphingomyelin and cholesterol. Since lipid exchange occurs on the time scale of hundreds of nanoseconds and the time scale probed by classical MD is inadequate to assess this rate, coarse-grained (CG) simulations are employed to describe the long-time dynamics of lipid bilayer, sampling the intermolecular aggregation that leads to the formation of lipid domains.

During the course of the mesoscopic simulations, the CG sites representing saturated and unsaturated lipids may phase separate to form liquid ordered and liquid disordered domains. These domains will be characterized in terms of their size distribution and lifetime, as well as the timescale for the exchange of coarse-grained sites between domains. The partitioning of cholesterol between liquid ordered and liquid disordered domains will also be analyzed.

2447-Pos Molecular Dynamics Simulated Annealing of Phospholipid-rich HDL

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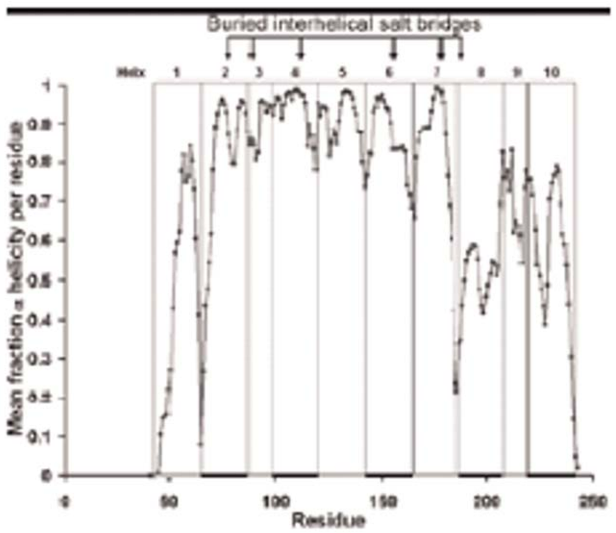
Board B561

All-atom MD simulations by us of an atomistic double belt model for discoidal HDL produced particles where the apoA-I belt underwent conformational changes coordinated with a distortion of the bilayer disc into a minimal surface patch. Due to short simulations, these particles might represent kinetically trapped intermediates. Here we report all-atom MD simulated annealing as a more robust approach to particle structure. Temperature jumps, in explicit water without constraints, were performed on the published 100:2 particle (molar ratio = POPC:Δ40apoA-I). While 525K produced rapid vaporization, three 500K simulations for 20ns produced no vaporization. Analyses of average changes in structural parameters during simulation showed: i) SASA of acyl chains rapidly increased 5-fold, then plateaued, a result of expansion of an intact bilayer. ii) Total apoA-I helicity decreased from 95% to 72%. iii) SASA of the lipid-associating hydrophobic residues of apoA-I increased 60%. Using stability at 500K as one measure of helix stability, the figure above shows changes in helicity of individual residues within tandem helical repeats averaged over the three simulations. We conclude that much of apoA-I in PL-rich HDL has no “fixed” conformation, end domains being more labile than central ones.



2448-Pos Temperature Effects on Structural Properties of Active Sites: Molecular Dynamics Simulations of Cruzipain Isoforms

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Board B562

The Chagas’ disease, caused by the protozoa *Trypanosoma cruzi*, constitutes a significant health and socio-economic problem in the most part of Central and South Americas and Mexico, with some cases described in Canada, United States and Europe. Nearly 100 years after the discovery of Chagas' disease, there are no appropriate therapies that lead to cure this illness in the acute or in the chronic phases.

Cruzipain, a cysteine protease from the papain family, is considered a molecular target for the development of drugs against Chagas' disease. Its catalytic activity is modulated by temperature variations and it has been proposed that this effect occurs due the presence of a possible temperature dependent allosteric site. We investigated by molecular dynamics simulations, at 298K (invertebrate vector temperature) and 310K (vertebrate host temperature), the structural variations of papain (used as control) and isoforms 1 and 2 of cruzipain.

The solvent accessible surface (SAS) analysis showed that papain and cruzipain1 close their active site at 310K while cruzipain2 opens this region increasing the SAS. Our results do not corroborate the hypothesis of an allosteric site existence. Moreover, we observed that the presence of an acidic residue in position 158, near the catalytic triad CYS25-HIS159-ASN175, favors a catalytic site structural reorganization triggered by temperature variation. This reorganization generates a catalytic triad conformation similar to the one found in serine proteases (ASP-HIS-SER), particularly with the mutation SER->CYS.

Our results suggest that the catalytic efficiency in cruzipain isoforms can be linked to temperature effects on structural variations of the active sites, indicating a possible adaptation of each isoform to distinct development stages of the parasite in vectors/hosts.

2449-Pos Molecular Dyanamics Studies of the cannabinoid type 1 (CB1) GPCR. Implications for activation

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Board B563

Central to this study is the behavior of the cannabinoid type 1 (CB1) GPCR. CB1 is an unusual GPCR in that 1) it's endogenous ligands, anandamide and 2-arachydonyl-glycerol (2-AG), are very lipophilic implying an unusual lipid based entrance/exit pathways; and 2) a high degree of constitutive activity has been reported. Recent theoretical and experimental studies (1–4) have provided evidence that direct lipid-protein interactions affect protein function. Given that these studies suggest an intimate interaction of lipids not only with the protein surface but their interiors as well, we have speculated that lipid-protein interactions play a central role in the constitutive activity behavior of the CB1 receptor. In order to address these issues we have performed and present here, multiple nanosecond molecular dynamics simulations of the CB1 receptor in an explicit POPC (palmitoyloleoyl-phosphatidylcholine) lipid bilayer. These results support the idea that lipids can and do probe the interior of GPCRs. Of particular note our results indicate that specific lipid-protein interactions can mediate side chain motions and alterations which are known to occur in the activation of rhodopsin. This notion is particularly true for CB1 receptors as their endogenous ligands are highly lipid-like and these results suggest a likely mechanism for the unusually high level of constitutive activity in CB1.

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2450-Pos Computational Studies Of Herbicide Interactions In The Qb Site Of Photosystem Ii

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Board B564

The study of herbicide-inhibitors in the Q_b binding pocket of photosystem II (PSII) has been the subject of research interest for many years. It is well established that some inhibitors compete for binding with plastoquinone at the Q_b site, although the specific inhibitor-protein interactions remain poorly understood. In fact, many of the commercially available herbicides (*e.g.*, atrazine and DMCU) were discovered experimentally. Improving their quality and efficiency has been hindered by the lack of understanding of the specific interactions responsible for binding. While extensively applied, some of these herbicides have already raised environmental concerns since they may be teratogens, or carcinogens. Furthermore, some plants have become resistant to herbicides whose binding can be significantly affected by single point mutations. Therefore, the development of green and effective herbicides is currently a problem of significant interest that would greatly benefit from reliable computational methods capable of providing molecular insights into the binding mechanisms. In this work, we model herbicides binding in the photosynthetic reaction center from Rhodopseudomonas *Virdis* and in PSII from the cyanobacterium *Thermosynechococcus elongatus*. We use an efficient scoring algorithm for pre-screening a wide range of possible binding configurations and state-of-the-art density functional theory (DFT) quantum mechanical/molecular mechanics (QM/MM) methods for structural refinement of the best pre-selected structures. Linear correlation between experimental binding energies and those calculated computationally are reported. The analysis of the computational results provides fundamental insights into the binding interactions and guidelines for the development of robust and efficient inhibitors of PSII.

2451-Pos Molecular Dynamics Simulations Unveil Dynamic Flexibility of Retinal within Binding Pocket of Rhodopsin

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Board B565

Rhodopsin is the only G protein-coupled receptor (GPCR) whose structure is known at atomic resolution. We focused our work on the structure and dynamics of its retinylidene inverse agonist with the aim of understanding the mechanism of receptor activation . We analyzed a total of 23 independent, 100-ns all-atom molecular dynamics simulations of rhodopsin embedded in a lipid bilayer in the microcanonical (N,V,E) ensemble [1]. The prediction of retinal hydrogen-out-of-plane (HOOP) wagging modes from our simulations is consistent with those found in Raman vibrational spectroscopy. In addition, our simulations show that the polyene chain is rigidly locked into a single, twisted conformation. Most surprising, however, the β-ionone ring is mobile within its binding pocket; its interactions are non-specific and the cavity is sufficiently large to enable multiple conformations. We find that sampling and ergodicity of the ensemble of simulations are crucial for determining the accurate distribution of this structural heterogeneity. The MD simulations define two of the most prevalent conformations for the β-ionone ring, viz. positively and negatively twisted 6-*s-cis* enantiomers. These two conformations are contrary to most previous assumptions. Our result, while unexpected, strongly agrees with experimental solid-state ^{2}H NMR spectra [2]. Correlation analysis identifies the residues most critical in retinal mobility; specifically, we find that Trp265 moves away from the ionone ring prior to conformational transition. We believe that this might play an important role in rhodopsin activation [1–3]. Overall, our findings reinforce how molecular dynamics simulations challenge conventional assumptions for interpreting membrane protein experimental data, especially where existing models neglect conformational fluctuations.

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2452-Pos Light-induced Processes in Biological Systems: From First Principles to Biotechnology

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Board B566

We are using multi-configurational (CASSCF) QM/MM molecular dynamics together with surface hopping to directly simulate photochemical processes in biological systems. Our simulations do not only allow us to correctly predict measurable quantities, such as fluorescence lifetimes and structures of intermediates, but also to provide structural and dynamical information at a resolution well beyond what is achievable experimentally.

The talk will focus on recent applications on ultra-fast excited-state decay in DNA[1,2] and on photoactivation of photoreceptor proteins.[3,4] Our most recent work concerns the effects of mutations on the photochemistry in these proteins and will also be discussed. Our ultimate aim is to re-design photoactive proteins for biotechnological applications, such as data storage and biomolecular imaging.

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2453-Pos Reversible Photoswitching Mechanism of the Fluoroprotein asFP595 from Molecular Dynamics Simulations

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Board B567

Fluorescent proteins have been widely used as genetically encodable fusion tags for biological imaging. Recently, a new class of fluorescent proteins was discovered that can be reversibly light-switched between a fluorescent and a non-fluorescent state. Such proteins can not only provide nanoscale resolution in far-field fluorescence optical microscopy much below the diffraction limit, but also hold promise for other nanotechnological applications, such as optical data storage. To systematically exploit the potential of such photoswitchable proteins and to enable rational improvements to their properties requires a detailed understanding of the molecular switching mechanism, which is currently unknown.

Here we have studied the photoswitching mechanism of the reversibly switchable fluoroprotein asFP595 at the atomic level by multiconfigurational ab initio (CASSCF) calculations and QM/MM excited state molecular dynamics simulations with explicit surface hopping. Our simulations explain measured quantum yields and excited state lifetimes, and also predict the structures of the hitherto unknown intermediates and of the irreversibly fluorescent state. Further, we find that the proton distribution in the active site of the asFP595 controls the photochemical conversion pathways of the chromophore in the protein matrix. Accordingly, changes in the protonation state of the chromophore and some proximal amino acids lead to different photochemical states, which all turn out to be essential for the photoswitching mechanism.

We have identified the tight coupling of trans-cis isomerization and proton transfers in photoswitchable proteins to be essential for their function and propose a detailed underlying mechanism, which provides a comprehensive picture that explains the available experimental data. The structural similarity between asFP595 and other fluoroproteins of interest for imaging suggests that this coupling is a quite general mechanism for photoswitchable proteins. These insights will also guide the rational design and optimization of photoswitchable proteins.

Computational Methods, Cellular - IV

2454-Pos Modeling Diffusion In 3-dimensions In Brain Extracellular Space: Comparison With Microfiberoptic Photobleaching Measurements

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Board B568

Diffusion through the extracellular space (ECS) in brain is important in drug delivery, intercellular communication, and extracellular ionic buffering. The ECS comprises ~20% of brain parenchymal volume, and contains cell-cell gaps down to ~50 nm. We developed a random-walk model of macromolecule diffusion in brain ECS in 3-dimensions using realistic ECS dimensions. Model inputs included ECS volume fraction (α), cell size, cell-cell gap geometry, intercellular 'lake' dimensions, and the molecular size of the diffusing solute. The model output was relative solute diffusion in water vs. brain ECS (D_o/D). Experimental D_o/D was measured using a microfiberoptic fluorescence photobleaching method involving stereotaxic insertion of a micron-size fiber into mouse brain. Measured D_o/D for the small solute calcein was 3.3 ± 0.1 in brain cortex and 4.1 ± 0.4 in cerebellum. D_o/D was size-dependent, with 5.6 ± 1.1 fold slowing in deep brain nuclei for 20 kDa FITC dextran. Moderate water intoxication (3% body weight) increased D_o/D from 3.4 ± 0.3 to 4.0 ± 0.1 at 10 min and 4.8 ± 0.3 at 20 min. Simulation of measured D_o/D using realistic α, cell size and cell-cell gap required the presence of intercellular 'lakes' at multi-cell contact points and cell-cell contact length of at least 50-fold smaller than cell size. With ECS geometric parameters fixed, the model predicted D_o/D for different solute sizes and cell-cell gap heterogeneity. The effect of cell swelling on ECS geometry was accurately simulated by altering the input parameters, revealing the importance of cell-cell gaps for diffusion through brain ECS. Our model establishes the geometric constraints to account quantitatively for the relatively modest slowing of solute and macromolecule diffusion in brain ECS.

2455-Pos Towards Realistic Modeling Of Dynamic Processes In Cell Signaling: Quantification Of Macromolecular Crowding Effects In Several Model Systems

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Board B569

One of the major factors distinguishing molecular processes in vivo from biochemical experiments in vitro is the effect of the environment produced by macromolecular crowding in the cell. To achieve a realistic modeling of processes in the living cell based on biochemical data it becomes necessary, therefore, to consider such effects. We describe a protocol based on Brownian dynamics (BD) simulation to characterize and quantify the effect of various forms of crowding on diffusion and bimolecular association in a simple model of interacting hard spheres. We show that by combining the elastic collision method for hard spheres and the mean field approach for hydrodynamic interaction (HI), our simulations capture the correct dynamics of a monodisperse system. The contributions from excluded volume effect and HI to the crowding effect are thus quantified. The dependence of the results on size distribution of each component in the system is illustrated, and the approach is applied as well to the crowding effect on electrostatic-driven association in both neutral and charged environment; values for effective diffusion constants and association rates are obtained for the specific conditions. The effects of crowding on both diffusion-limited and chemistry-limited reactions can be quantified through this protocol based on BD simulations. To investigate the contributions of other features of proteins, beyond the hard sphere, to the macromolecular crowding, a coarse-grained model has been incorporated into the simulation protocol. The quantitative results from these simulation approaches can be incorporated directly in the modeling of cell signaling to improve them without significant computational burdens.

2456-Pos Super-Diffusion in a Model for Diffusion in a Molecularly Crowded Environment

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Board B570

We present a model for diffusion in a molecularly crowded environment. The model consists of random barriers in percolation network. Random walks in the presence of slowly moving barriers show normal diffusion for long times, but anomalous diffusion at intermediate times. The effective exponents for square distance versus time usually are below one at these intermediate times, but can be also larger than one for high barrier concentrations. Thus we observe sub- as well as super-diffusion in a crowded environment.

2457-Pos The Effect of Crowding on Rod Ordering

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