2416-Pos Calculating Potentials of Mean Force for Large Biomolecules from Nonequilibrium Processes: Determination of Light Harvesting Complexes 2 Ring Sizes

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Board B531

Recently, several non-equilibrium methods, based on or related to the Jarzynski equality (JE), have been proposed for calculating potentials of mean force (PMFs) along a given reaction coordinate. However, most of these methods were applied to biomolecules of relatively small sizes, where sampling of many trajectories is attainable. In general, JE based methods fail when only a small number of trajectories can be sampled due to the lack of sampling of the extremely rare paths with negative dissipation work. To overcome this problem, the FR method [J. Chem. Phys. *124*, 064106 (2006)] was proposed for calculating PMFs from a small number of fast SMD pulling in both forward (F) and time reverse (R) directions. The FR method was developed by employing the Crooks transient fluctuation theorem and the stiff-spring approximation. This method is efficient and simple as both the PMF and the underlying diffusion coefficient can be expressed in terms of the mean work during the F and R pullings. To demonstrate the applicability of the FR method to generate PMFs efficiently for larger biomolecular systems, we describe here a methodology based on the FR method for determining the ring sizes of Light Harvesting Complexes 2 (LH2). Membrane embedded LH2 complexes of purple bacteria are found in octameric or nonameric form despite remarkable similarities among tertiary structure of monomers of LH2 from different purple bacteria. For the purpose of validation and evaluation of predictive power of the FR method, we apply developed methodology to predict ring sizes of LH2 complexes of Rhodospirillum (Rs.) molischianum (known, 8), Rhodopseudomonas (Rps.) acidophila (known, 9) and X (unknown, structure provided by an experimental group), given only the monomeric structure of complexes.

Computational Methods - II

2417-Pos Fully Flexible Four Site Polarizable Water Model With A Dynamic Extended Charge

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Board B532

Polarizable water model and its extension to computational studies of biomolecular systems have been a goal of active research for quite sometime [1–3; *and references therein*]. The polarizability aspect is quite important to obtain the critical binding information of drug molecules to protein active sites and to find the change in the reactivity of proteins and DNA's with substrates. The recent focus on dedicated hardware and parallel algorithm for molecular dynamics [4], has eased the computational restriction for the use of a polarizable model. However, appropriate modeling still remains a challenge. The modeling of electronic charge redistribution, using a point-dipole or fluctuating charge model, though provide the number, not necessarily provide a satisfactory charge re-distribution which is essential for critical binding or reactivity studies.

We worked out a four site fully flexible water model where a Gaussian extended charge is harmonically attached to the electronegative oxygen atom and it is also made visible to the hydrogen atoms using harmonic bonds so that it can respond to both intramolecular and inter-molecular changes. This model is optimally designed for use with self-consistent flexible constraints where both the geometry and the position of the fourth center are simultaneously optimized. This allows for a fully flexible water model without the associated problems of non-physical high-frequency heat capacity [5]. Details of the model, optimization procedure, and results will be reported at the conference.

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2418-Pos Non van der Waals treatment of hydrophobic solubilities

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Board B533

A quasi-chemical theory implemented on the basis of molecular simulation is derived and tested for the hydrophobic hydration of CF_4(aq). The theory formulated here identifies chemical contributions to the hydration that naturally arise from chemical contributions defined by quasi-chemical theory and fluctuation contributions analogous to Debye-Huckel or random phase approximations. As judged by the size of the fluctuation contribution, the resulting Gaussian statistical thermodynamic model is physically reliable in these applications. The specific results here confirm that unfavorable tails of binding energy distributions of the solute with water reflect few-body close solute-water encounters. The water near-neighbors are pushed by the medium into unfavorable interactions

with the solute, in contrast to suggestions that a preformed interface is pulled by the solute-water attractive interactions. The polyatomic model of CF_4(aq) studied gives a satisfactory description of the experimental solubilities including the temperature dependence. The proximal distributions evaluated here for poly-atomic solutes accurately reconstructs the observed distribution of water near these (non-spherical) solutes. Extensions of the above approach to the hydrophobic interaction of two methane molecules in water will be considered.

2419-Pos Classical/Ab Initio Molecular Dynamics and Quasichemical Approaches to Study Hydrophobic/ Hydrophilic Hydration Phenomena

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Board B534

We present a computational approach to the study of hydrophobic and hydrophilic hydration based on the combination of classical/ab initio molecular dynamics and quasichemical theory. Specifically, we implement these methods to study the structural and thermal properties of small hydrophobes and hydrophiles in water, with a special interest in krypton atom and rubidium ion as they are isoelectronic species. Thermodynamic properties are evaluated by utilizing two different quasichemical approaches: 'direct' and 'cluster.' In the 'direct' approach, the thermodynamic property can be determined from structural information obtained by molecular simulation of the liquid state solution; while in the 'cluster' approach, the solute molecule of interest is successively solvated by an increasing number of surrounding solvent molecules. Both approaches have proven useful in studies of the hydration of hydrophobic/hydrophilic species that include applications to selective ion partitioning between water and biological ion channels.

2420-Pos Recent Advances in the FMO-MD method

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Board B535

FMO-MD [1] is an *ab initio* molecular dynamics method based on the Fragment Molecular Orbital method (FMO, [2]). FMO-MD is suitable for quantum MD simulations of large molecular systems thanks to the high parallel efficiency of FMO. FMO-MD was once implemented by combining PEACH, an MD program, and ABINIT-MP, an FMO program [3], but was recently reimplemented by using the latest versions of both programs. The new FMO-MD system was in particular designed for chemical reactions in an explicit solvent. Hence, in addition to the usual canonical ensemble, the blue moon ensemble method [5] was newly introduced to calculate the free energy profile in the course of a chemical reaction.

In this poster, we describe the software structure of the FMO-MD system, along with benchmark data are presented for the pure water solvent. Then, a few examples of FMO-MD studies are shown: conformation sampling of H_2CO in solvent, comparison of free energy profiles of the Menschutkin reaction in the presence and absence of the solvent, and so on. Finally, we will discuss the possibility of the application of FMO-MD to biological molecules.

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2421-Pos QM/MD Simulations Of The Vinca Alkoids

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Board B536

The binary Vinca alkaloids are a class of anti-mitotic cancer drugs based on naturally occuring alkaloids from the Periwinkle plant. Following the discovery and isolation of several active compounds in the Periwinkle plant in the 1950s, several Vinca drugs have found common use in cancer chemotherapy. The first two drugs used are natural products: Vinblastine and Vincristine have been in clinical use for over four decades. Semi-synthetic compounds Vindesine and Vinorelbine are more recent discoveries and are also in clinical use. Vinflunine is a new semi-synthetic drug and is currently in advanced clinical trials. Despite a high degree of homology between the five drugs mentioned above, their effects are very different in many ways, supporting the observation that small variations in the chemical structure of Vinca drugs can cause profound effects in their activity. Thus, rational drug design has the potential to lead to more potent Vinca drugs with less toxic side effects. Despite this prospect, very little is known about the binding of the Vinca drugs to their target protein tubulin and their structure-activity relationship. In an attempt to gain more insight into the above, QM/MD simulations have been performed on these five Vinca drugs both alone in aqueous solution at the AM1/TIP3P level and bound to tubulin at the AM1/FF03/TIP3P level. The major focus has been on the geometry of the drugs and functional group interactions with tubulin amino acids.

2422-Pos Molecular Dynamics Study of Proteins in hydrated Glycerol solutions

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Board B537

Anhydrobiosis in Nematodes and Tardigrades has been attributed in some cases to increased glycerol concentration. Details about the structure and dynamics of proteins during the increase in glycerol concentration remain poorly understood.

We have carried out a 20ns Molecular Dynamics simulations of proteins in glycerol solutions of 0, 10, 20, 30 and 100% by weight glycerol. Microscopic details about the organization of water and glycerol around the protein surface were revealed. The molecular mechanism behind this arrangement stems mainly from the hydrophobic and hydrogen-bonded interactions. The strengths of these interactions have been studied as a function of solvent concentration. Glycerol has been found to form a hydrogen bonded network around the protein mechanically entrapping the water within.

2423-Pos All Atom Free Energy Decomposition For Amino Acids

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Board B538

Traditional approaches such as all-atom molecular dynamics or Monte-Carlo simulations are impractical to calculate protein thermodynamics. A key bottleneck in simulation-based methods has to do with obtaining accurate estimates of the conformational entropy. Previously we have developed an all-atom Distance Constraint Model (DCM) based on a free-energy decomposition scheme combined with constraint theory [1–3]. In this work, we attempt to build a sophisticated free energy decomposition scheme for the 20 amino acids naturally incorporated into proteins. This entails assigning an energy and entropy contribution to each coarse-grained macrostate of each amino acid. An empirically derived tabulation of these contributions is determined by first constructing a molecular partition function to define macrostates of an amino acid. Second, we assign energy to these states based on a commonly employed molecular mechanics energy function, and then we solve the inverse problem to calculate conformational entropies. Solving the inverse problem requires data mining high quality protein structures from X-ray crystal structures obtained from the top 500 protein dataset [4], and incorporating model compound transfer experimental data [5–6]. The high dimensional dihedral angle space is decomposed into pairwise correlation functions to account for coupling between sidechain rotamer states with backbone phi/psi states. Our scheme accounts for accessible conformational changes in local structure and the effect of polar/non-polar solvent environments.

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2424-Pos Binding Free Energy Calculations using a Polarizable Force Field

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Board B539

Molecular mechanics potentials have been parameterized for many purposes, including molecular dynamics simulations and docking predictions. The more widely used forcefields for systems involving proteins, which include Amber, CHARMM and OPLS, employ partial charges for the electrostatics energy contribution. However, when calculating the binding free energy for a protein-ligand complex, partial charge forcefields may not accurately capture the complexity of the system's electrostatics, particularly when there are highly polar groups at the binding site or on the ligand. Polarizable forcefields, such as the AMOEBA forcefield from Ponder, hold the potential to significantly improve such energy estimates. Here we calculate the relative binding energies of several complexes using both the Amber and AMOEBA forcefields. Calculations are performed on complexes of trypsin and several benzamidine-derived ligands, all with high resolution crystal structures, and they show how well each forcefield performs in distinguishing between similar ligands and how polarization can affect the prediction of binding affinities.

2425-Pos Different Sites of Local Anaesthetic Action in Different Kv Channels

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Board B540

Previous electrophysiological results suggest that the local anaesthetic bupivacaine blocks Kv channels by a common open-state dependent mechanism, but that different channels behave differently at closure when bupivacaine is bound. Kv1 and Kv3 channels seem unable to close when bupivacaine is bound, while Kv2.1 allows a partial closure.

In a subsequent molecular dynamics study we could show that in a Kv1.5 homology model, using KcsA as template, the preferential bupivacaine binding sites were located in the PVP-region, assumed to form the gating structure. This finding supports the hypothesis that Kv1.5 cannot close in bound state, since binding to the PVP region is likely to interfere with the closing mechanism.

In the present study, we have reanalyzed the bupivacaine action on Kv1.2 and 2.1 by voltage clamp experiments on *Xenopus* oocytes in combination with molecular dynamics calculations, using the recently obtained crystal structure of Kv1.2 as template for homol-

ogy modeling of Kv2.1. The conformational properties and partial atomic charges of bupivacaine were determined from quantum mechanical calculations with inclusion of solvent effects. Automated docking and MD calculations, as well as linear interaction energy estimates of the binding free energies, show that the preferential binding site in Kv1.2, in agreement with previous studies of Kv1.5, is in the PVP region, while the preferential binding site in Kv2.1 is close to the selectivity filter in the upper part of the pore, suggesting, also in agreement with the previous experimental studies, less interaction with the closing mechanism.

2426-Pos Computational Studies of Ligand Binding to Hexokinase

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Board B541

The overexpression of the enzyme hexokinase II (HKII) has been implicated in some types of cancers, such as pancreatic cancer and brain tumors. As a result, HKII is a promising target for the development of therapeutic treatments. Despite interest in this enzyme, there are few known ligands that bind to and inhibit this enzyme, and there is very little structural data available for it. However, there is an analogous enzyme, human hexokinase I, whose structure has been well characterized. This enzyme also has a nearly identical sequence with HKII, with the exception of the C-terminal tail. The human hexokinase I has much structural information available and is used in these studies of ligand binding. Using the software package MOLARIS [1], the free energy of binding of a known inhibitor, glucose-6-phosphate (G6P), is calculated. This software will also be used to calculate the binding free energy of analogues of G6P.

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2427-Pos Comparison of Computational Binding Affinity Estimates Using Equilibrium and Non-Equilibrium Methods

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Board B541.01

We compare computational estimates of binding affinities using equilibrium and non-equilibrium methods. Specifically, we employed equilibrium techniques such as adaptive integration, and the non-equilibrium Jarzynski method, to estimate protein-ligand binding affinities of the FKBP protein. FKBP proteins are immunophilin and have been widely studied in the drug industry for their potential immunosuppressive and neuroregenerative effects. The proteins are ideal for a comparative study of binding affinity approaches because (a) experimental data are readily available; (b) FKBP proteins have been widely used in previous computational studies; and (c) the system size is relatively small. Our results are very promising; the studies have collectively revealed a close agreement between the computational estimates and experimental data. Based on the results, we discuss the advantages and disadvantages of each method in terms of parallelization, computational efficiency, accuracy, and precision.

2428-Pos Detecting The Canonical Protein Surface Pockets Used For Ligand Binding, Substrate Binding, And Biological Function

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Board B542

An enzyme can achieve specificity for a given substrate by presenting a binding surface that is complementary to that substrate in terms of shape and chemical features. This "lock and key" model has been a cornerstone for research into methods for enzyme function prediction, docking, drug design, and enzyme classification by searching for similarities between local surface features of enzymes with similar function. However, a problem arises when the same substrate is able to bind to several different surface pocket shapes. Here, we use structural and compositional information to combine all pockets that share a given trait such as a common ligand, substrate, or set of GO terms into a smaller set of general pocket shapes, or canonical pockets. To generate these canonical pockets we use a sequence order independent structure alignment algorithm to align pairwise all surfaces at the atomic level. We then use hierarchical clustering to iteratively combine similar pockets until a certain threshold of similarity is met. We tested our method on a set of 117 non-redundant hemoglobin pockets. We found that 98 of those pockets could be described by one of four canonical pocket shapes, which differ in such features as heme orientation and iron coordination. Information about all pocket shapes, together with their chemical properties, that are suitable for binding of a particular substrate or for carrying out a specific biological function would improve accuracy of protein function prediction and further our understanding of the relationship between enzyme structure and its biological function. We are expanding our method to the detection of the canonical pockets within enzymes that share a common set of GO terms. The results of this work will be discussed.

2429-Pos Investigation Of The Role Of Electrostatics On Protein-protein Binding Affinity

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Board B543

Proteins perform various biological functions in the cell by interacting and binding to other proteins, DNA, and other small molecules. There are many factors that contribute to the binding energy of protein-protein complexes. Among these factors, the electrostatic force, being a long range force, plays an important role. However the role of electrostatics on protein-protein binding remains a controversial issue. Here we investigate the role of electrostatics on the free energy of binding on a set of 260 hetero- and 2617 homo- protein-protein complexes. Such a large and diverse set of protein complexes has never been studied before. The calculations were done using minimized and non minimized 3D structures, applying different force fields, varying the value of internal dielectric constant and representation of molecular surface. The results demonstrate that absolute magnitude of the electrostatic component of the binding energy is very sensitive to the parameters of computational protocol; however, the general trend is that the electrostatics opposes binding. A comparison of the electrostatic component of the binding energy calculated with different force fields shows that Charmm, Amber and OPLS are strongly correlated and different from the results obtained with PARSE parameters. However, the correlation declines as molecular surface description approaches van der Walls definition.

2430-Pos A Monte Carlo computational method for modeling of receptor-ligand binding-mediated processes

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Board B544

We have developed a Monte Carlo simulation procedure for modeling receptor-ligand binding and cellular signaling processes. Individual molecules are explicitly simulated as discrete particles on a lattice and can diffuse or react with other molecules according to specific probabilistic transition rules. Instead of an energy-based Metropolis approach, our method uses probabilistic reaction and diffusion rates that are directly obtained from their experimentally measurable counterparts, such as the diffusion coefficient and association constant. In addition, diffusion in our simulation is treated in a rigorous manner, rendering possible the comparison of our model's length and time scale with those of physical experiments. The stochastic nature of our method gives rise to fluctuations in output that are analogous to the variations that occur in single cell data, while the discrete nature of our procedure makes possible the modeling of spatial effects such as molecular crowding. We demonstrate our method using the process of B cell activation as an example.

2431-Pos Application Of A Generalized Born Method For Accurate Prediction Of Electrostatic Contributions To Protein-protein Binding Energy

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Board B545

Most proteins function by specifically interacting with other biomolecules. A fundamental property of specific interactions is the binding energy. Computational methods that reliably predict binding energies are thus highly desirable. Developing such methods is a formidable task, since the free energy of binding is a small difference between two large numbers, namely the free energy from the interactions within the complex and with the solvent environment and the solvation energy of the components in their unbound state. The Poisson-Boltzmann (PB) equation has found great success in modeling electrostatic contributions to protein-protein binding energies [1, 2]. We developed a generalized Born (GB) method called GBr^6, which, at a fraction of the computational time, reproduces PB results with high accuracy for single protein solvation energy [3]. The reduced computational cost opens new avenues for more realistic modeling of electrostatic effects, such as inclusion of protein conformational sampling. However, the small magnitudes of binding energies pose a challenging demand on the accuracy of calculation. We developed a scaling scheme on GBr^6 to meet this demand. The scaled GBr^6, when applied to conformations sampled from molecular dynamics simulations of the complexes formed by two Rho GTPases and the Wiskott-Aldrich syndrome protein, agrees closely with PB in the electrostatic contributions to the binding energies. Moreover, the calculated salt and mutation effects on the binding energies of the two complexes are in quantitative agreement with experiment data. The scaled GBr^6 promises to be a prototype for a new generation of fast continuum solvation models.

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2432-Pos Solving the Linearized Posion-Boltzmann Equation for a Dielectric Sphere Using Image Point Multipoles

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Board B546

Hybrid shell models are commonly used to calculate solvation free energies with computational efficiency. For this type of model, we consider a sphere of low dielectric inside a homogeneous medium of high dielectric. First worked out by C. Neumann in 1883, an image charge solution for a point charge placed within the sphere can be expressed as an integral over a line charge density to solve the Poison equation. Starting from this exact expression, we demonstrated in previous work [J. Comp. Phys. *223*(2):846–864 (2007)] that the reaction field is accurately approximated using multiple image charges along a radial line passing through the source charge. The magnitude of the image charges and their locations along the radial line were based on the Jacobi-Gauss quadrature of Neumann's integral. Typically two or three image charges provide good accuracy. Arbitrary accuracy can be achieved by increasing the number of image charges. Unfortunately, the linearized Posion-Boltzmann equation for finite ionic strength is not subject to the same analytical solution. Consequently, finding the appropriate quadrature is problematic. In this work, we present empirically derived values for the charges of a set of image point multipoles to accurately represent the reaction field inside the sphere as a function of ionic strength. The method we employ solves the inverse problem of determining the image multipole charges by minimizing the least squares error with respect to the exact solution expressed as an infinite series involving modified spherical Hankel functions. This approach produces substantially more uniformly distributed residual error in the reaction field within the sphere than the residual errors previously obtained, but higher order point multipoles are necessary to obtain low error.

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2433-Pos Introduction of intramolecular flexibility into Brownian dynamics simulations

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Board B547

In this work, we show progress in the development, implementation, and testing of a novel computational algorithm based on BD that allows the simulation of intramolecular, domain-scale motion. Conventionally, BD is used to study the diffusion of rigid bodies through a dielectric continuum on time scales of micro- to milliseconds. Often these are models of proteins or other macromolecules that contain varying degrees of detail, but the models are nearly always rigid. To take advantage of the long-time sampling of BD but allow intramolecular motion, we identify domains, treat them as separate rigid bodies in a BD framework, and connect them via an empirical energy function that mimics a flexible peptide linker. For the successful development of this method several considerations are tested: these include the proper treatment of electrostatic and desolvation forces, volume exclusion terms, and the form of the linker energy function. To properly test these different parameters, direct comparison to both computational benchmarks and currently available neutron spin-echo spectra of the T. aquaticus DNA polymerase I are employed. When completed, "Tethered Brownian Dynamics" (TBD) will be a powerful method to investigate intramolecular motions and a straightforward way to add molecular flexibility to BD simulations.

2434-Pos Constraint-Based Prediction of Essential Degrees of Freedom in Proteins

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Board B548

Principal component analysis of molecular dynamics trajectories has shown that most motion in proteins occurs within an essential subspace spanned by a small number of collective coordinates. The remaining degrees of freedom experience only small fluctuations about their mean values, effectively constrained. In this work, we aim to predict the essential motion of proteins, for both large and small movements, starting from a set of constraints. The chosen constraints partition space into an allowed subspace and a disallowed subspace. We explore the allowed subspace with a constraint-based sampling method that we introduce here, and compare the allowed subspace to the essential subspace found from molecular dynamics. We define a constraint-enforcing energy landscape that is flat in the allowed region and increases quadratically outside that region. We sample configurations by perturbing the degrees of freedom, then performing conjugate-gradient minimization of the constraint-enforcing energy to restore the system constraints. A momentum-like perturbation strategy facilitates exploration of large collective motions. The sampling method described here is related to another constraint-based method, FRODA [1], the new method being distinguished from FRODA primarily by its use of an explicit energy function to impose constraints.

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2435-Pos Interidiate Structure Analysis of Prion Protein through Molecular Dynamics Simulation

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Board B549

Dynamics Differences among Species of Prion Protein: Molecular Dynamics Simulation of Mouse, Dog, Cat, Pig, Sheep, Cattle, and Human

Prion protein (PrP) has very similar 3D structures among many species in C-terminal region: they have an intramolecular disulfide bridge, three α-helices, and a short double-stranded β-sheet. PrP is related to transmissible spongiform encephalopathies (TSEs). A central theme in PrP researches is revealing the process of conformational transition from the normal cellular form (PrPC) to pathologic isoform (PrPSc). Previous studies have shown that the se-

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