1679-Pos Board B589
Mixing Martinis: Hybrid Atomistic/Coarse-Grained Models for Protein Molecular Dynamics
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In recent years, the development and deployment of coarse grained models for simulations of proteins has taken an enormous flight. The main reason for this is that such models provide significant alleviation of the time scale limits that otherwise restrict the use of molecular simulations for biological processes. Coarse graining allows assessment of processes that occur on the scale of microseconds and micrometers, rather than nanoseconds and nanometers, albeit with the obvious consequence that detail is lost. This loss of detail has proven acceptable in many cases, but poses problems for the assessment of mechanical features of proteins, especially where local dynamics is intimately linked with overall conformational changes.
To bring back the detail, yet only where it is needed, we have developed an integrative approach, coupling a Martini Coarse Grained model to an atomistic description of part of the system. This method involves a novel treatment of the interaction of the all-atom parts with the surrounding coarse grained particles, using virtual sites, rather than specific cross interactions. The potential applications of the method are manifold and include high-throughput protein-ligand binding studies, adsorption and protein folding.

1680-Pos Board B590
An NMR Resource for Structural and Dynamic Simulations of Membranes
Avigdor Leftin, Klaus Beyer, Michael F. Brown.
Computational methods are powerful in capturing the results of experimental studies in terms of force fields that both explain and predict biological structures [1]. Validation of molecular simulations requires comparison with experimental data to test and confirm computational predictions. Here we report a comprehensive database of NMR results for membrane phospholipids with interpretations intended to be accessible by non-NMR specialists. Experimental ^{13}C and ^{2}H NMR segmental order parameters and spin-lattice relaxation times are summarized in convenient tabular form for different lipid head group types, length and degree of acyl unsaturation, and the presence of additives such as detergents and cholesterol. Segmental order parameters give direct information about bilayer structural properties, including the area per lipid and volumetric hydrocarbon thickness [2]. In addition, relaxation rates provide complementary information about molecular dynamics [3]. Particular attention is paid to the magnetic field dependence of NMR relaxation rates in terms of various simplified power laws. Model-free reduction of relaxation studies in terms of a power-law formalism shows relaxation rates for saturated phosphatidylcholines follow a single dispersive trend within the MHz regime. We show how analytical models can guide the continued development of atomistic and coarse-grained force fields. Interpretations suggest that lipid diffusion and collective order fluctuations are implicitly governed by viscoelasticity of the liquid-crystalline ensemble. Collective bilayer excitations are emergent over mesoscopic length scales falling between the molecular and bilayer dimensions, and are important for lipid organization and lipid-protein interactions. Future conceptual advances and theoretical reductions will foster understanding of biomembrane structural dynamics through a synergy of NMR measurements and molecular simulations. [1] R.W. Pastor *et al.* (2002) *Acc. Chem. Res.***35**, 438-446. [2] H.I. Petrache *et al.* (2000) *Biophys. J.***79**, 3172-3192. [3] M.F. Brown in *Biological Membranes* (1996) Birkhäuser, Basel, pp. 175-252.

1681-Pos Board B591
Molecular Dynamics Simulations Reveal Distinct Conformational Changes of Three Cullins in Cullin-Ring E3 Ubiquitin Ligases
Jin Liu, Ruth Nussinov.
Cullin-RING E3 ubiquitin ligases (CRLs) facilitate ubiquitin transfer from E2 to the substrate, thus tagging the substrate for degradation. CRL contain four components: substrate binding protein, adaptor, cullin and Rbx protein. Our previous studies[1-3] showed that substrate binding proteins and Rbx proteins are flexible allowing the shortening of the distance between E2 and the substrate for initiation of ubiquitination, or the increase of the distance for accommodating the polyubiquitin chain. However, the role of cullin in the function of ubiquitination remains unclear. Is cullin a rigid scaffold or does it have the flexibility for conformational control of ubiquitination? Why are there seven cullins in the human genome? With highly conserved structure and sequence, how do these cullins specifically facilitate ubiquitination for different substrates? To answer these questions, we performed MD simulations on three cullins with available crystal structures, cul1, cul4A and cul5. In all three cases, we observed large conformational change during the 60 ns simulations. These conformational changes either shorten or increase the distance between E2 and the substrate to facilitate mono- or polyubiquitination, suggesting that cullins allosterically regulate the ubiquitination process. We further observed that rotation hinges and degree of flexibilities are significantly different for these three cullins, which may be attributed to the long loops in different positions for these three cullins. We propose that the long loops may specifically regulate the conformational control of ubiquitination for different cullins with different substrates. Funded by NCI NIH contract HHSN261200800001E.
1. Liu, J.; Nussinov, R.; Biophys J., 2010, 99(3), 736-44.
2. Liu, J.; Nussinov, R.; J Mol Biol., 2010, 396(5), 1508-23
3. Liu, J.; Nussinov, R.; PLoS. Comput. Biol. 2009, 5(10), e1000527.

1682-Pos Board B592
Multiresolution Molecular Dynamics Simulations of Crystalline Nanofibrils
Giovanni Bellesia, Antonio Redondo, Paul Langan, Peter Goodwin, S. Gnanakaran.
We introduce a multiresolution computational approach for the study of crystalline nanofibrils.
Our multiresolution approach integrates fully-atomistic and coarse-grained levels of detail and it's particularly suited for the study of structural transitions between crystalline allomorphs. First, fully-atomistic simulations are used to gain a detailed understanding of the main structural differences between the crystalline phases under consideration. Second, we introduce a new coarse-grained, off-lattice model for the crystalline fibrils whose relevant degrees of freedom have been identified from the analysis of our fully-atomistic simulations. Both the structural transition and the relative thermal stability of the two allomorphs are studied at the coarse-grained level by means of Replica exchange molecular dynamics. The structural transition is analyzed within the framework of the Ginzburg-Landau formalism. As an example application of our method we consider two different allomorphs of crystalline cellulose nanofibrils, namely cellulose I-beta (the naturally–occurring form of cellulose) and cellulose III(I) (obtained from cellulose I-beta via ammonia pretreatment). Recent experiments show that the enzymatic degradation rate increases 2-5 times in cellulose III(I) respect to cellulose I-beta. Understanding the factors that regulate enzyme degradation of crystalline cellulose is a major challenge in the context of biofuels production from cellulosic biomass. Our multiresolution computational approach sheds new light on how the main structural and thermodynamic differences between these two cellulose crystalline forms affect their different enzyme activity rates.

1683-Pos Board B593
Rational Design of Unimolecular Star Copolymer Micelles for Drug Delivery: Molecular Dynamics Study of Solvation, Aggregation, and Drug Binding Properties
Loan Huynh, Chris Neale, Régis Pomès, Christine Allen.
Multimolecular micelles are excellent delivery vehicles with one major flaw: they spontaneously disassemble and release their cargo when the concentration of unimer falls below critical micelle concentration. One way to circumvent critical-micelle-concentration-based instabilities is to tether the unimers together at the center of the micelle and generate a unimolecular micelle. Star-shaped block copolymers (SCPs) represent a possible material for unimolecular micelles - as long as the molecules can be engineered to avoid self-aggregation. Amphiphilic SCPs, with central hydrophobic blocks surrounded by terminal hydrophilic blocks, can be used for the solubilization of hydrophobic solutes. With the intention of rationally designing a stable unimolecular SCP, we use atomistic molecular dynamics simulations in explicit solvent to systematically evaluate the solution properties of hydrated SCPs successively as unimers, at high concentration, and in the presence of a small molecule drug mimetic. In these studies, the average number of water molecules bound per PEG repeat unit was comparable to experimental results. As well, the water accessible surface area of the PCL core was highly correlated with the molecular weights of PCL and PEG moieties. We postulate that the propensity for aggregation of SCPs is due to hydration of hydrophobic moieties in the unimeric state. SCPs with a PCL core less than 2kDa per arm are predicted to be fully protected from water and may form thermodynamically stable unimolecular micelles at low concentrations when the PEG blocks approach 14.6kDa per arm. Accordingly, simulations of SCPs at high concentration confirm that aggregation reduces exposed hydrophobic surfaces. Finally, simulations of SCPs in the presence of small molecule drug mimetics are performed in an attempt to predict drug loading properties and the impact of drug loading on SCP aggregation.

1684-Pos Board B594
Force Distribution Analysis of Allosteric Mechanisms
Christian Seifert, Frauke Graeter.
Revealing the pathways of signal transfer in allosteric proteins has remained a challenge for today's biophysical methods. Previous approaches are primarily