1679-Pos Board B589
Mixing Martinis: Hybrid Atomistic/Coarse-Grained Models for Protein Molecular Dynamics
Tsjerk A. Wassenaar, Martti J. Louhivuori, Andrzej J. Rzepiela, Siewert-Jan Marrink.
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

based on the comparison of active and inactive structures and thermodynamic concepts. However, stiff regions of the protein might mask signal propagation, even though they are able to carry signals in form of high internal stresses.
We here present a new method, force distribution analysis(FDA Stacklies *et al*,2009a/b), that detects the distribution of stress upon external perturbations in macromolecules like proteins, other (bio-)polymers or even solids with high sensitivity. For tracing signal transfer through a protein structure, FDA calculates the changes, here caused by ligand binding, in the inter-atomic forces of the protein as sampled in Molecular Dynamics simulations.
The analyzed proteins are two homologues of the chaperone Hsp90 and the catabolite activator protein CAP.
We propose a new model for the signal transduction in the *E.Coli*(HtpG) and Yeast(Hsp82) homologues of Hsp90. The force differences between the apo, ADP and ATP bound states obtained by FDA based on all-atom trajectories totalling 540 ns revealed a cross-talk between the binding site and the middle domain via distinct paths.
The catabolite activator protein(CAP) is a major player in the *lac*-operon. CAP features a negative cooperativity for the binding of cAMP, which is interestingly based not on a change in structure but in flexibility (Popovych *et al.,2006)*. FDA of the apo, single- and double-bound state revealed a signaling network in CAP, which transfers a signal (first cAMP is bound) to the second binding niche without obvious structural changes, thereby explaining the observed cooperativity.
This work describes the effectiveness of FDA for resolving allosteric communication pathways, which are directly testable by experiments. As such, it has broad implications for our view on protein internal strain and function.

1685-Pos Board B595
Computational Study of Gas Diffusion Pathways in [FeFe]-Hydrogenase
Hai Long, Paul King, Maria Ghirardi, Kwiseon Kim.
The photobiological generation of hydrogen gas (H_2) by green alga is a promising method for affordable H_2 production. One of the key enzymes involves in this process is the [FeFe]-hydrogenase, which catalyzes the H_2 generation reaction at its catalytic center - H-cluster. There are two major gas diffusion pathways in [Fefe]-hydrogenase to allow the produced H_2 to leave the enzyme. However, small gas molecule such as O_2 or CO can also transport along those pathways and inactivate the enzyme rapidly by reaction with the H-cluster. In this research, we used molecular dynamics method to study the gas diffusion pathways in [FeFe]-hydrogenase. The hydrogenases investigated are DdH from *Desulfovibrio desulfuricans* and CpI from *Clostridium pasteurianum*. Two methodologies, implicit ligand sampling and adaptive biasing force, were applied to investigate the free energy profiles along the pathways for O_2 and CO. Out results indicate that the gas diffusion pathways in DdH are more favorable for gas transport than the ones in CpI. We also found several free energy barriers along the pathways, preventing the gas molecule to further transport to the H-cluster. However, the rate limiting step for the inactivation process may not be the gas diffusion, but the reaction that the gas molecule binds to the H-cluster. Nevertheless, raising the free energy barriers along the pathways is still helpful to slow down the inactivation rate and allow the enzyme less sensitive to O_2.

1686-Pos Board B596
Simulation Study on the Properties of Cationic Lipid Bilayers and Vesicles
Elham Afshinmanesh, Svetlana Baoukina, D. Peter Tieleman.
We are using molecular dynamics simulations to investigate the properties of ionizable cationic lipids forming bilayers and vesicles. This is important for rational design of lipid nanoparticle for delivery of nucleic acids (DNA, RNA). The process of transfection includes encapsulation of anionic biomolecules, binding of the nanoparticle to the membrane surface, endocytosis and release of the nucleic acids from the endosome. For ionizable cationic lipids the steps of this process are pH-dependent. In the acidic environment of the endosome, the charge density of the nanoparticle increases. Membrane disruption is believed to occur due to formation of the ion pairs between cationic lipids in the nanoparticle and anionic lipids in the endosome [Semple et al., Nature Biotech, 2010]. Due to favorable interactions between the headgroups, lipids in the ion pairs become cone-shaped and prone to form non-lamellar phases, such as the inverted hexagonal phase. We simulate cationic and anionic lipid mixtures in bilayers and vesicles and study the mechanism of membrane breakdown upon change of pH/charge density and variation in headgroup size.

1687-Pos Board B597
Conformation and Protonation Significantly Influence Methyl Dynamics Yielding Improved Rhodopsin Retinal Force Field
Blake Mertz, Michael Lu, Scott E. Feller, Michael F. Brown.
Recent ^{2}H nuclear magnetic resonance (NMR) studies on retinal in rhodopsin indicate a discrepancy in parameters for methyl rotation activation compared to previous molecular dynamics (MD) simulations [1,2]. Here we report *ab initio* quantum mechanical (QM) calculations of retinal potential energy surfaces that enable comparison to the results of ^{2}H NMR relaxation measurements [3,4]. Rotational dynamics of the retinal ligand were assessed via C5-, C9-, and C13-methyl dihedral scans in retinal model compounds that correspond to ^{2}H NMR data and allow us to validate the methyl dihedral contribution to the retinal force field [1,2]. We are able to accurately reproduce the retinal methyl rotational dynamics [3,4] by using larger retinal fragments and a higher level of theory (MP2/cc-pVDZ). Distinct behaviors for each retinal methyl group emerge in agreement with experiment [3,4]. Few differences exist between the QM and original MD calculations for the C5-methyl group. However, the C9-methyl shows a markedly lower dihedral energy barrier compared to previous models, due to intra-retinal steric affects. Moreover, the C13-methyl rotational barrier is lowered by two effects: (1) *cis* to *trans* isomerization increases hyperconjugation influences along the polyene chain, and (2) the protonated Schiff base charge is delocalized proximal to the polyene chain and methyl group. Accounting for these effects leads to development of new methyl dihedral parameters for the retinal force field. Our results are directly applicable to rhodopsin MD simulations and potentially enable the simulation of coupling of local dynamics to large-scale motions in rhodopsin activation. [1] P.-W. Lau *et al*. (2007) *JMB* **372**, 906-917. [2] K. Martínez-Mayorga *et al*. (2006) *JACS* **128**, 16502-16503. [3] M.F. Brown *et al.* (2010) *BBA* **1798**, 177-193. [4] A.V. Struts *et al*. *Nat. Struct. Mol. Biol.* (in press).

1688-Pos Board B598
Evaluation and Improvement of the AMBER ff99SB Force Field with an Advanced Water Model
Paul S. Nerenberg, Clare So, Ajay Tripathy, Teresa Head-Gordon.
A recurring concern when studying biomolecules with molecular dynamics (MD) simulations is the accuracy of the underlying force field and solvent model. These considerations are especially relevant for simulations of intrinsically disordered peptides and proteins, for which energy differences between conformations are small and interactions with water are enhanced. In this work, we investigate the accuracy of the AMBER ff99SB force field, combined with either the TIP3P or the TIP4P-Ew water model, using both conventional MD and replica exchange MD (REMD) simulations to generate conformational ensembles for (disordered) trialanine, triglycine, and trivaline peptides.
We find that the TIP4P-Ew water model yields significantly better agreement with experimentally measured scalar couplings - and therefore more accurate conformational ensembles - for both trialanine and triglycine. For trivaline, however, we find that the TIP3P and TIP4P-Ew ensembles are equivalent in accuracy. To address this discrepancy and further improve the force field, we derive new van der Waals parameters for alkanes in TIP4P-Ew water and a straightforward perturbation to the f backbone dihedral potential that shifts the β-PPII equilibrium. Of the two, we find that the revised f backbone dihedral potential is more effective and yields significantly improved conformational ensembles for both the trialanine and trivaline peptides in TIP4P-Ew water.

X-Ray Diffraction

1689-Pos Board B599
***In Situ* Study of Nanotemplate-Induced Growth of Lysozyme Microcrystals by Submicron GISAXS**
Claudio A. Nicolini, Eugenia Pechkova.
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Abstract
A new in situ μGISAXS technique was used to study at ESRF the nucleation and growth mechanisms of lysozyme microcrystals with and without the thin Langmuir-Blodgett lysozyme film surface. Following recent studies on thaumatin crystal growth only in presence of LB monolayers (1.2) , in this work ultrasmall Lysozyme microcrystals are grown by classical hanging vapor diffusion and by its modification using homologous protein thin-film template displaying a long-range order. Intensity fluctuations in the μGISAXS pattern versus time for the LB-induced crystallization process appears associated to rapid seed formation and crystal growth, while the classical method continuous shift of intensity in the Yoneda region is compatible with slow crystal growth. The nucleation and growth mechanisms of lysozyme microcrystals are thereby studied at the thin lysozyme film surface by the new *in situ* μGISAXS technique developed at the microfocus beamline of the European Synchrotron Radiation in Grenoble. New insight on the nucleation and crystallization processes appear to emerge.