consist of a 2D grid of energy corrections in (Phi,Psi) space. The resulting parameter set is validated against experimental data on relevant peptides.

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781-Pos Board B561

The Role of Backbone Dipole Interactions in the Formation of Secondary and Supersecondary Structures

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We present a generic solvated coarse-grained protein model that can be used to characterize the driving forces behind protein folding. Each amino acid is coarse-grained with two beads, a backbone and side-chain. While the backbone beads are modeled as polar entities, side-chains are either hydrophobic, polar or charged, thus allowing the exploration of how sequence patterning determines a protein fold. The change in orientation of the atoms of the coarse-grained unit is captured by the addition of two oppositely charged dummy particles inside backbone coarse-grained bead. These two dummy charges represent a dipole which can fluctuate thus introducing structural polarization into the coarse-grained model. Realistic alpha/beta content is achieved de novo without any biases in the force-field toward a particular secondary structure The dipoles created by the dummy particles interact with each other and drive the protein models to fold into unique structures depending on the amino acid patterning and presence of capping residues. We will present the role of dipole-dipole and dipole-charge interactions in shaping secondary and supersecondary structure of proteins. Since dipole interactions are influenced by the dielectric environment, the model is sensitive to the nature of the environment (low or high dielectric). Results on how changes in dielectric can tune the emergence of different folds will be presented.

782-Pos Board B562

Enhanced Conformational Sampling of Carbohydrates using Biasing Potential and Solute Tempering Replica Exchange: Application to the N-glycan on the HIV gp120 Envelope Protein

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Conformational sampling of complex molecular systems is always a challenge in computer simulations. To tackle this problem, a range of enhanced sampling methods have been developed. However, each method typically only shows distinct advantages in specific systems. Therefore, new approaches aim to combine the complementarity of different enhanced sampling algorithms to achieve a better performance. In this study, we propose a new algorithm to combine the advantages of two Hamiltonian replica exchange methods designed to improve sampling of specific degrees of freedom using biasing potentials and of global conformational properties, including solute-solvent interactions via solute tempering.[1-2] The new method produces improved sampling for polysaccharides with coupled linkages, including branch points. The method is applied to N-glycans found on the HIV gp120 envelope protein that show potential application in the design of HIV vaccines.

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783-Pos Board B563

DMD4B-HYDRA: Toward a Novel Discrete Molecular Dynamics Protein Model

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The task of protein structure prediction is computationally demanding, particularly for intrinsically disordered proteins (IDPs), which by definition lack a well-defined folded structure. IDPs include amyloidogenic proteins associated with human disease, such as Alzheimer's and Parkinson's diseases, which are known to be critically involved in the corresponding pathologies. For most protein and peptide sequences with significantly more than 100 amino acids, it is not yet possible to examine the details of the folding landscape by fully atomistic molecular dynamics (MD) in explicit solvent. This problem can be solved through a two-stage MD, first exploring the protein dynamics using coarse-grain (CG) protein models to sample the phase space at a diminished computational effort and second by using a wide range of CG structures converted into fully atomistic representation as initial conformations for all-atom MD in explicit solvent. We here use the four-bead protein model in combination with discrete molecular dynamics (DMD), known as DMD4B-HYDRA force field, which has been previously successfully applied to studies of amyloid b-protein folding and assembly, to examine protein folding dynamics of five proteins with known native structures. We elucidate both the ability of DMD4B-HYDRA force field to capture the folded structure of these proteins and aspects that are less well reproduced by the current force field. We then demonstrate that the follow-up all-atom MD dynamics compensates for structure prediction difficulties of the DMD4B-HYDRA force field itself and provides feedback to be used in the future DMD4B-HYDRA force field development. Our preliminary results thus confirm that DMD4B-HYDRA combined with fully atomistic MD in explicit solvent presents a powerful computational approach to studying IDPs and elucidate structural dynamics of a broad range of amyloidogenic proteins.

784-Pos Board B564

Tetramolecular Parallel G-Quadruplex Validation Set for Molecular Dynamics Simulation with CHARMM 27 Force Field

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G-quadruplex DNA nanostructures have possible applications as biosensors [1]. These molecules are present in biological systems and their physical and chemical properties makes them a useful tool for the assembly of nanostructures that could perform complex and specialized functions. For example, there are structures based on these materials named aptamers capable of specific attachment to a substrate. These molecules are generated using artificial selection in which from a set of initial random structures, those with the greatest affinity and selectivity are selected and later enriched by PCR. This process could however be improved if an engineering of the structures for the initial set results from a computer aided design. A possible way to accomplish this could be based on results derived from molecular dynamics simulation [2, 3]. To this end, this paper studies the reliability of simulating these structures with one of the most widely used force fields for nucleic acids, CHARMM 27 as implemented in NAMD. As a validation set we used a group of experimentally derived structures (crystallography or NMR methods) specifically tetramolecular parallel G-quadruplexes. For this work the preparation of the models and data analysis was performed with VMD visualization package. Here, we report first the validation of the topology for the simulations as well as certain key indicators of convergence for the minimization phases and the correct equilibration for the molecular dynamics part as well as other structural descriptors. Comparison with suitable experimental values derived mainly from NMR and Crystallography were used as reference.

785-Pos Board B565

SAMBE: The New Webserver for Predicting the Effect of nssNP on the Protein-Protein Binding Free Energy

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Motivation: One of the most essential properties of all living organisms is the ability to conduct comprehensive "communication" between its individual components. At the molecular level, the communications are achieved via macromolecular binding. The corresponding protein complexes are involved in diverse processes including information transfer, immune system operation, inhibition or activation of particular functions, assembly of macromolecular structures into molecular machines, and much more. Any disruption of the biologically essential network (for example, due to protein missense mutations) may lead to pathological conditions resulting in diseases. Thus, the ability to model protein-protein interactions is essential for a wide range of biomedical applications.

Results: Here we report a new webserver, SAMBE (Single Amino acid Mutation related change of Binding Energy) webserver, which addresses the demand for computational tools of predicting the effect of single amino acid substitution on the binding free energy of protein complexes. It is based on the fast modified MM-PBSA protocol that is successfully tested and optimized for more than thousand experimental data points. The SAMBE is intuitive and easy to use

webserver which requires only coordinate file to be inputted and the user is provided with various, but easy to navigate, options. The output information including the change in hydrogen bonds network and binding energy due to amino acid substitution is displayed on the output and is available for download.

786-Pos Board B566

Bio.B-Gen: An Initial System Generator for Biological Molecular Simulations

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Atomistic and coarse-grained simulations can be a great help in uncovering the mechanisms of physical processes at microscopic and mesoscopic levels at time scales ranging from femtoseconds to milliseconds.

Any simulation study involves (1) setting up an appropriate simulation system representing the physical problem, (2) running the simulation and collecting information about the system, and (3) analyzing the collected data. The last step eventually leads to final conclusions about the system. Software for molecular simulation has been in development for many years and a number of high quality freely distributed general purpose simulation packages is available for researchers. Data analysis tools are usually less general as they often depend on a specific research project and the system under investigation. While many simulation packages come with a set of some general data analysis utilities, it is not unusual for such analysis tools to be developed on a per project basis inside research groups. Interestingly, there is a very limited set of available tools for setting up simulation systems, even though this is the very first and vital step of every simulation study. This lack of convenient general simulation system generators sometimes may even dictate the kind of simulations done based on the available initial systems rather than on the system being the best for a particular problem.

In this work we describe a general software tool, bio.b-gen, for the creation of initial systems for biological molecular simulations. A number of case systems are demonstrated using an atomistic force field as well as the coarse grained MARTINI force field. The tool is designed to generate initial systems for the GROMACS general simulation package.

787-Pos Board B567

Validation and Development of the Force Field Parameters for Drug and Drug-Like Molecules

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Highly optimized and well-validated parameters have been developed for structure refinement and computer simulation of biomolecules. However, the force fields for most drug and drug-like ligand molecules are not properly validated. Out of ~100,000 X-ray crystal structures in the Protein Data Bank (2014), >25,000 structures contain at least one of >17,000 chemically diverse ligand molecules. In addition, there is over a million ligand molecules of interest in databases such as NCI and Pubchem. Understanding interatomic interactions of a given ligand with its target acceptor is crucial in molecular modelling and the lack of precise force field parameters for small heteromolecules may result in failure of drug design efforts.

A web accessible Automated force field Topology Builder (ATB; http://compbio.biosci.uq.edu.au/atb/) and Repository was developed to facilitate the generation of force field parameters for chemically diverse ligand molecules. The ATB performs quantum mechanical calculations combined with a knowledge-based approach to ensure compatibility with a biomolecular force field. The topologies and parameters created can be used in simulations, computational drug design and X-ray refinement.

Most importantly, a fully automated validation of the force field parameters has been incorporated into the ATB methodology. Recent work on the validation of parameters against structural and thermodynamic data as well as the outcome of participating in the SAMPL4 community challenge for the prediction of hydration free energy of drug-like molecules will be presented. Further refinement strategies to improve the parameters by scaling of the van der Waals and electrostatic interactions will be discussed as well.

788-Pos Board B568

A Novel Method for Force-Field Calibration Based on Maximum-Likelihood Approach and Thermal Unfolding Data

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Calibration is the final and critical stage of the design of the force fields for proteins and other biological macromolecules. For proteins, the usual goal of this procedure is to optimize the force-field parameters to reproduce the native structures of selected training proteins. However, the resulting force fields are usually not sufficiently predictive, because only the structures of folded proteins are used. Thus, a force field is not sufficiently trained to distinguish folded structures from misfolded ones. In this work, we propose a novel approach, in which a force field is calibrated with the ensembles of structures determined by NMR at various temperatures that encompass the region of thermal unfolding. The method is based on applying the maximum-likelihood principle. Each conformation of the NMR-determined ensemble at a given temperature is an experimental point and the theoretical probability-density function is represented by a sum of Gaussians centred at the decoys from the corresponding ensembles generated by simulations; in this work the replica exchange molecular dynamics procedure was used. The maximum-likelihood function (-logL) is minimized using the current decoy set, then new decoys are generated with the optimized force-field parameters. The procedure is iterated until convergence. The method was applied to the physics-based coarse-grained UNRES force field developed in our laboratory. On the first attempt, NMR structures of a small alpha-helical protein, the tryptophan cage, were used. The resulting force field predicted correctly the structures of 13 out of 14 alpha-helical proteins with different helix-packing topology and size from 36 to 104 amino-acid residues. Results of the calibration of the UNRES force field with more proteins, including villin headpiece (alpha), the C-terminal fragment of the IGG protein (beta), and full-sequence design 1 (alpha+beta), will be presented.

789-Pos Board B569

Quantum Mechanical Molecular Mechanical Calculations using AMOEBA Force Fields

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We report an implementation of quantum mechanical molecular mechanical (QM/MM) calculations with AMOEBA force field applied to water molecules in the molecular mechanics region. Three AMOEBA parameter sets (AMOEBA03, iAMOEBA, and AMOEBA14) are employed, and compared to TIP3P and other water models in terms of their performance in QM/MM calculations. The effect of the MM polarization (MM induced dipoles due to QM electron density) will also be discussed.

790-Pos Board B570

The Do's and Do Not's of a 100 Million Atom Molecular Dynamics Simulation

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The ever so growing prowess of petascale computing resources has pushed the envelope of biomolecular modeling, simulation, and analysis into the regime of hundred million atom systems. To bring a very challenging organelle-scale system under simulation control often involves substantial modifications of existing computational tools. Using two ongoing simulations of a bacterial chromatophore and the influenza virion coat, we demonstrate VMD-, NAMD-, MDFF-, and python-based innovations that enable large-scale biomolecular simulations. The protocol involves new semi-automated, yet high throughput, ways of large-scale atomic model construction, including in disordered membrane environments, their solvation, ionization, and equilibration, particularly for system sizes in excess of tens of million atoms. Discussions will extend to tools for characterizing the physical properties of a hundred million atom system, such as long-range electrostatics. Finally, the scientific purpose of performing such simulations will be justified in the light of results obtained from whole-chromatophore and whole-virion-coat simulations.

791-Pos Board B571

Minimally-Biased Metadynamics Method to Sample Conformational Ensembles Compatible with Experimental Measurements

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A primary goal in computational biophysics is to harness experimental measurements to obtain information on the structure and dynamics of biomolecules. However, most biophysical techniques such as NMR and EPR spectroscopy provide signals that arise from an ensemble of multiple molecular conformations. Thus, it is typically not straightforward to extract detailed structural information from the experimental data. A possible strategy is to bias the conformational sampling obtained in a molecular dynamics simulations in