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

Dmitri Rozmanov, Peter Tieleman.
Biological Sciences and Centre for Molecular Simulation, University of Calgary, Calgary, AB, Canada.

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

Katarzyna B. Koziara[1], Martin Stroet[1], Alpeshkumar K. Malde[1], Alan E. Mark[1,2].
[1]The University of Queensland, Brisbane, Australia, [2]Institute for Molecular Bioscience, Brisbane, Australia.

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

Bartłomiej Zaborowski[1], Dawid Jagieła[1], Adam K. Sieradzan[1], Cezary R. Czaplewski[1], Anna Hałabis[2], Agnieszka Lewandowska[2], Wioletta Żmudzińska[2], Stanisław Ołdziej[2], **Jozef A. Liwo**[1].
[1]Faculty of Chemistry, University of Gdansk, Gdansk, Poland, [2]Intercollegiate Faculty of Biotechnology, University of Gdansk and Medical University of Gdansk, Gdansk, Poland.

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

Yihan Shao, Andrew Simmonett, Frank Pickard, Gerhard Koenig, Bernard Brooks.
NHLBI, Rockville, MD, USA.

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

Abhishek Singharoy[1], Danielle Chandler[1], Jacob Durrant[2], Melih Sener[1], Rommie Amaro[2], Klaus Schulten[1].
[1]Beckman Institute, University of Illinois, Urbana Champaign, IL, USA, [2]Chemistry, University of California, San diago, CA, USA.

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

Fabrizio Marinelli, José D. Faraldo-Gómez.
Theoretical Molecular Biophysics Section, National Institutes of Health (NHLBI), Bethesda, MD, USA.

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

reference to the experimental data, under the so-called maximum entropy principle. Recent practical formulations of this approach involve simulations carried out over multiple replicas or iterative ensemble-correction procedures based on the determination of several (Lagrange) parameters. Here, we present an alternative, self-learning approach to sample molecular ensembles compatible with experimental data with the minimal possible bias on the simulation trajectories. The method does not require multiple replicas and is based on adding an adaptive bias potential during the simulation that discourages the sampling of conformations that are not consistent with the experimental measurements. To illustrate this approach, we applied this novel simulation technique to spin-labeled T4-lysozyme, targeting a set of spin-spin distance distributions measured by DEER/EPR spectroscopy. We show how the proposed method is able to efficiently sample the experimental distance distributions without altering uncorrelated degrees of freedom. We anticipate that this new simulation approach will be widely useful to obtain conformational ensembles compatible with diverse types of experimental measurements of biomolecular dynamics.

792-Pos Board B572
Efficient High Accuracy Non-Bonded Interactions in the CHARMM Simulation Package
Frank C. Pickard, Andrew Craig Simmonett, Bernard Rigoberto Brooks.
Laboratory of Computational Biology, National Institutes of Health, Rockville, MD, USA.
Most molecular dynamics simulations are carried out using isotropic atom-atom potentials to model non-bonded interactions. Such potentials can be insufficient to accurately model a variety of physical properties present in biologically relevant molecules. A proper description of the anisotropy of the electrostatic interactions is of particular importance, as it directly affects a variety of structural and transport properties such as hydrogen bonding and diffusion. We have recently developed a novel, algorithm to efficiently calculate coulombic forces in the CHARMM simulation package using an arbitrary order multipole expansion. Further work has extended this algorithm to efficiently account for dipolar polarization and dispersion. We present details of the algorithm, its implementation and initial calculations on condensed phase water enabled by this work.

793-Pos Board B573
Towards a Polarizable Force Field for RNA based on the Classical Drude Oscillator
Justin A. Lemkul, Alexey Savelyev, Alexander D. MacKerell, Jr.
Pharmaceutical Sciences, University of Maryland, Baltimore, Baltimore, MD, USA.
RNA plays many important roles in the cell, including information transfer, gene regulation, protein synthesis, and catalysis. This diversity in function arises in part from the adoption of complex tertiary structures and interconversion between multiple conformational states in response to bound metabolites or changes in other cellular conditions. Modeling RNA with atomistic resolution using molecular dynamics (MD) simulations requires a high-quality empirical force field that can adequately describe the properties of both canonical and non-canonical structures and is sensitive to environmental conditions. To this end, we are developing a force field for RNA that includes the explicit treatment of electronic polarization using the classical Drude Oscillator model. Optimization is focused on the RNA 2′-hydroxyl group and the phosphodiester backbone targeting 2-D quantum mechanical (QM) potential energy and dipole moment surfaces in combination with condensed phase MD simulations of both canonical and non-canonical RNA structures. Parameter validation involves conducting MD simulations of various RNAs not included in the training set.

794-Pos Board B574
Implementation of Replica-Exchange Umbrella Sampling to the DFTB+ Simulation Package
Shingo Ito, Yuko Okamoto, Stephan Irle.
Nagoya University, Nagoya, Japan.
We have investigated the computational methods which combined the self-consistent-charge Density Functional based Tight Binding (DFTB) method [1] for fast calculations of quantum effects and the Replica-Exchange Umbrella Sampling (REUS)[2] for enhanced conformational sampling. One of the excellent QM-MD simulation package named DFTB+ does not have REUS method incorporated. We thus modified DFTB+ to include the REUS method. We will compare the results of DFTB+ calculations with those by another simulation package. We will present the two comparative results for proton transfer reactions in small molecules.
[1] M. Elstner, D. Porezag, G. Jungnickel, J. Elsner, M. Haugk, Th. Frauenheim, S. Suhai, and G. Seifert, Phys. Rev. B 58, 7260 (1998).
[2] Y. Sugita, A. Kitao, and Y. Okamoto, J. Chem. Phys. 113, 6042 (2000).

795-Pos Board B575
CHARMM Gui Membrane Builder Updates
Xi Cheng, Yifei Qi, Jumin Lee, Sunhwan Jo, Wonpil Im.
Center for bioinformatics, The university of kansas, Lawrence, KS, USA.
CHARMM-GUI, http://www.charmm-gui.org, is a web-based user interface designed to generate various molecular simulation systems and input files to facilitate and standardize the usage of common and advanced simulation through an automated optimized process. We have made a significant amount of efforts to implement basic and common molecular dynamics simulation techniques into web interface and the web interface has generated a multitude of positive feedback from our users. In this work, we describe our latest efforts to bringing more advanced molecular modeling and simulation techniques to the web interface, including (1) HMMM builder establishing the high mobile membrane-mimetic model, (2) martini maker building coarse-grain models in Martini force fields, (3) NAMD, GROMACS, OpenMM equilibration and production inputs.

796-Pos Board B576
Experimental and Theoretical Approaches to the Study of Probe Diffusion in Macromolecular Solutions
Preston Donovan[1], Yasaman Chehreghanianzabi[2], Muruhan Rathinam[1], Silviya Zustiak[2].
[1]Mathematics and Statistics, University of Maryland Baltimore County, Baltimore, MD, USA, [2]Biomedical Engineering, Saint Louis University, Saint Louis, MO, USA.
Diffusion in macromolecular solutions and networks is a topic of vast importance in many fields related to medical devices, biotechnology, tissue engineering, or drug delivery. Thus, effort has been devoted to developing techniques for measuring and models for predicting diffusion in macromolecular solutions and networks. However, very few techniques are capable of probing diffusion *in situ*, real time, and non-invasively and while many models of diffusion exist, all of them have their drawbacks. Ideally a model starting from basic physics using rigorous mathematical principles should be developed that is also supported by experimental findings.
First, we present measurements of probe diffusion in polymeric solutions conducted by Fluorescence Correlation Spectroscopy (FCS). We have shown that FCS is an excellent tool for real time, non-invasive study of diffusion in complex media. Here, we present studies identifying several transport regimes – without interaction, and with interaction between the probe and the macromolecule. In the latter regime the nature of the interaction determines the specifics of the sub-diffusional process. We discuss two interaction examples – one where a ''permanent'' polymer/probe complex is formed, and one where ionic interaction is responsible for the decrease in probe diffusivity.
We have also developed a novel mathematical model based on homogenization theory, to describe the effective diffusion process. To the best of our knowledge, homogenization theory, has not been used previously to describe the diffusion of probes in macromolecular solutions. The homogenization theory was confirmed by Monte Carlo simulations. An excellent agreement between the homogenization theory and Monte Carlo simulations as well as comparison to experimental data provided evidence for the utility of the homogenization theory for predicting diffusion in macromolecular solutions.

797-Pos Board B577
A Coupled Two-Dimensional Main Chain Torsional Potential for Protein Dynamics
Ya Gao[1], Yongxiu Li[1], John Z.H. Zhang[1,2], **Ye Mei**[1,2].
[1]State Key Laboratory of Precision Spectroscopy, East China Normal University, Shanghai, China, [2]NYU-ECNU Center for Computational Chemistry at NYU Shanghai, Shanghai, China.
A new AMBER compatible force field is proposed for balanced representation of secondary structures. In this modified AMBER force field (AMBER^{2D}), the main chain torsion energy is represented by 2-dimensional Fourier expansions with parameters fitted to the potential energy surface generated by quantum mechanical calculations of small peptides in solution at M06 2X/aug-cc-pvtz//HF/6-31G** level. Solvation model based on solute electron density (SMD) developed in Truhlar's group was considered. The benchmark systems used in the validation of this force field include capped dipeptides (Ace-X-NME, XP), tripeptides (XXX, XA, G, V}; GYG, Y {A, V, F, L, S, E, K, M}), alanine tetrapeptide, Ac-(AAQAA)$_3$ -NH2, and ubiquitin. Besides, we also investigate the folding of two representative proteins (PDB ID 2I9M and 1LE1). The results demonstrated that this 2D main chain torsion is effective in delineating the energy variation associated with main chain torsions. Furthermore, the electrostatic polarization effect is very important for long peptides or proteins. This work also serves as an implication for the necessity of