u_{sol} describes the energy of H-bonds to solvent. These three model parameters are obtained by fitting to experimental C_p curves. Best fits on 19 different lysozyme mutants under the same thermodynamic conditions (pH, ionic strength, etc.) reveals that u_{sol} can be treated as constant. Moreover, u_{sol} can be robustly parameterized with as few as five experimental mutants (the standard error of 100 random quintets is $<12\%$). It was observed that a second degree of freedom could be removed due to a linear relationship (R=0.86) between the remaining two parameters (δ_{nat} and v_{dha}) indicating that a global balance in enthalpy-entropy compensation must be maintained. Consequently, over a fairly wide range of δ_{nat} values {0.4, 1.6}, the correlation between the experimental and theoretical T_m's is nearly constant (ranging from 0.68 to 0.72). Using the best parameter set, T_m can be predicted for new lysozyme mutants. Results on a validation set of an additional 81 lysozyme point mutations will be presented. This work is supported by NIH R01 GM073082.

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1536-Pos Board B380

Computational Studies of Nucleosome and Chromatin Folding

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Understanding the packaging of nucleosomes on DNA, including how various proteins interact with DNA, is important for understanding the dynamics of the cell. With this goal in mind, we have developed a shape-based model to map histone-DNA recognition quantitatively in terms of atomic contacts and DNA deformability. This method reduces the complexity of nucleosome structure from 3D visualization to a 2D mapping. Comparison of 32 available nucleosome crystal structures with this approach shows promise in deciphering the sequence-dependent binding mechanism of nucleosomes on DNA. We have also developed a novel Monte-Carlo method, involving multi-scale dinucleotide and dinucleosome modeling, to simulate the communication of proteins over long stretches of chromatin-compacted DNA. We compare our predictions of chromatin looping with recent experimental measurements of enhancer-promoter interactions, focusing on (i) the role of the histone tails in enhancing chromatin looping and (ii) the internal folding structures of chromatin under different ionic conditions.

1537-Pos Board B381

In Silico Examination Of The Influence Of Nucleotide Modifications And Magnesium Ions On tRNA Structure And Dynamics

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In our work the influence of chemical modificatons and ions on RNA structure and dynamics has been tested. The effect of nucleotide modifications on E. coli and yeast tRNA in solution has been examined with a molecular dynamics approach. Simulations show a decrease of helical content in RNA secondary structure due to those modifications. In another step magnesium ion binding effects on the same tRNA were looked at by performing simulations with and without ions bound to tRNA. Ions coordinating nucleotides in those simulations show them highly affecting local secondary structure motifs. Thus the simulations performed give new hints on the function of nulceotide modifications and ion binding to RNA.

1538-Pos Board B382

Estimating Orientational Entropies At Protein Interfaces

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Entropy effects of the surrounding water layer at the protein interface have been studied for a long time, and their relevance e.g. for protein folding is well recognized. In molecular dynamics simulations entropy estimates for surrounding explicit water molecules are difficult to calculate with established methods such as thermodynamic integration. Here we present a new method to calculate the orientational contribution to the solvent entropy near the protein interface. We exploit the permutation symmetry of the Hamiltonian such that we get trajectories of ''localized'' water molecules. Orientational correlations are unaffected by this transformation, which therefore enables us to obtain spatially resolved entropy estimates for the protein water shell.

1539-Pos Board B383

Hydration Dynamics As Revealed By The Fluorescence Stokes Shift: The Origin Of Slow Hydration Dynamics And Breakdown Of Linear Response

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Hydration dynamics in the immediate vicinity of a protein, probed by time-dependent fluorescence Stokes shift experiments, is critical to understand its biological function. Protein Stokes shifts typically exhibit biphasic relaxation following photo-excitation: fast relaxation occurs on a time scale of several picoseconds while slower components indicate additional hydration dynamics on a time scale of tens of picoseconds, or longer. Theoretical studies using both linear response and non-equilibrium molecular dynamics (MD) calculation qualitatively reproduce the observed biphasic behavior of time dependent Stokes shift for Trp-7 (W7) in myoglobin. Comparison with constrained MD simulations with protein frozen at the instant of photo-excitation reveals the molecular mechanism of slow hydration process and establishes the critical role of protein flexibility. Coupled protein-water motion is shown to be necessary for the observation of the slow component of hydration dynamics. Qualitatively similar results are found for a series of additional cases, such as monellin and staph. nuclease. We illustrate why tracking the separate contributions to the Stokes shift without constrained MD studies may not yield an accurate interpretation of protein hydration dynamics. Additionally, we examine the extent to which protein fluctuations obey Gaussian statistics and the linear response approximation to the Stokes shift is valid. Equilibrium fluctuations of the ground-excited energy difference, which control the absorption and fluorescence line shapes, in the ground and excited electronic states are not independent of each other. We illustrate how small differences from Gaussian statistics in one electronic state can be a signature of very significant deviations from linear response theory, such as isomerization, in the other electronic state.

1540-Pos Board B384

Effect of Temperature on the Structural and Hydrational Properties of Human Islet Amyloid Polypeptide in Water

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Structural and hydrational properties of full-length human islet amyloid polypeptide 1-37 (hIAPP) were studied in relation to the hydration water properties in a temperature range from 250 to 450 K by MD computer simulations. At all temperatures studied, hIAPP does not adopt a well-defined conformation. The alpha-helical content and the number of intrapeptide H-bonds of hIAPP decrease with temperature. The distribution of residues showing dihedral angles characteristic of beta-sheets and poly(L-proline) II helices along the peptide chain is close to random, whereas a clear trend towards cooperative ''condensation'' is seen for residues showing alpha-helical dihedral angles. This cooperativity is suppressed by heating or by introducing the native intramolecular disulfide bond. Intrinsic volumetric properties of hIAPP were estimated by taking into account the difference in the volumetric properties of hydration and bulk water. The temperature dependence of the density of hydration water indicates that the effective hydrophobicity of the hIAPP surface is close to that of carbon-like surfaces. Similarly to the case of the Aβ(1-42) peptide, the thermal expansion coefficient of hIAPP is negative: upon heating, it continuously decreases from $\sim -3\cdot10^{-4}$ to $\sim -2\cdot10^{-3}$ K^{-1}. A spanning H-bonded network of hydration water, which covers hIAPP homogeneously at low temperatures, breaks via a quasi-2D percolation transition, whose midpoint is at about 320 K. Approximately at this temperature, the experimentally measured lag time of hIAPP aggregation drops in a drastic way. We discuss the possible role of the temperature-induced percolation transition of hydration water on the conformational changes and aggregation propensity of amyloidogenic peptides.

1541-Pos Board B385

A Modified Primary Hydration Shell (PHS) Method Allows Up To Two Orders Of Magnitude Time Saving In Molecular Dynamics Simulations: Application To Large Systems And Lipid Bilayers

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A realistic representation of water molecules is essential in molecular dynamics simulation of proteins. However, the standard method of solvating biomolecules, i.e. immersing them in a box of water with periodic boundary conditions, is computationally very expensive. The primary hydration shell (PHS) method, developed more than a decade ago [1], uses only a thin shell of water around the system of interest, and so greatly reduces the computational power needed for simulations [2]. The method, however, was not perfect especially when large proteins are concerned. We have modified the PHS method in several ways to improve its performance when large systems are simulated [3]. The model is applied to several systems with different sizes, and both water and protein behaviors are compared with those obtained from standard simulations with periodic boundary conditions and with experimental data. Specifically, Lipari-Szabo order parameters for the proteins of interest are shown to be in good agreement with those derived from standard simulations and NMR relaxation

measurements. Finally, the results of the application of the modified PHS method to simulating the cytoplasmic region of the transmembrane protein Plexin B1, and its interaction with the membrane are discussed.

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1542-Pos Board B386

Image Charge Methods for a Hybrid Solvation Model with Transition Layer

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We present a novel three dielectric layer hybrid solvation model for treating electrostatic interactions of biomolecules in solvents using the Poisson-Boltzmann equation. In this model, the interior spherical cavity contains the solute and explicit solvent molecules. An intermediate buffer layer is introduced, which also contains solvent molecules. Outside the spherical shell defines the exterior layer, where bulk solvent is modeled implicitly and characterized by a dielectric constant. Within the intermediate layer, a special dielectric permittivity profile is constructed to give a continuous transition from the interior cavity to the exterior layer. The selection of this special profile using a harmonic interpolation allows an analytical solution of the model by generalizing the classical Kirkwood series expansion. To speed up numerical calculations of the electrostatic potential solutions, discrete image charges are employed following previous work [1]. Two approaches for constructing discrete image approximations to the potentials are considered: Semi-analytical and least square methods. Both methods are employed for the reaction field of solvents without and with finite ionic strength. Numerical results are presented to validate the accuracy and effectiveness of the image charge methods. This work is supported by NIH 1R01 GM083600-02. Z. Xu is also partially supported by the Charlotte Research Institute through a Duke Postdoctoral Fellowship.

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1543-Pos Board B387

Molecular versus van der Waals-like Surfaces: Revisiting The Choice Of Solute-solvent Boundary Definition In Implicit Solvent

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Implicit treatment of the solvent environment offers an optimal balance between efficiency and accuracy that greatly extends our ability to simulate protein structures and conformational transitions. The most accurate description so far is achieved by continuum dielectric solvation models, including generalized Born (GB) and Poisson-Boltzmann (PB) theories. The precise definition of the solute-solvent boundary is one of the most important features in continuum dielectric models. While it is believed that so-called molecular surfaces (MS) should provide the most physical description, most existing GB models are based on van der Waals-like (VDW) surfaces for computational simplicity and efficiency. VDW surfaces do not capture so-called reentrant surface. While it has been pointed out that VDW surface definition leads to small, solvent-inaccessible (and thus unphysical) high dielectric pockets in large proteins, the precise consequences of using VDW surfaces in simulation of smaller peptides are not well understood. In particular, it is believed by many that one might be able to compensate for drawbacks of VDW surfaces through optimization of certain parameters such as intrinsic radii of atoms. Here, we first demonstrate that such optimization has limited capability to compensate for systematic errors of VDW surfaces, which is particularly problematic for describing charged side chains and has important implications in conformational equilibrium of even small peptides. We then describe an efficient approximation of MS within the frame work the generalized Born with a simple switching (GBSW) model. The new model is as efficient as the original VDW surface based GBSW model, but is able to reproduce the Born radii calculated from the MS PB theory with a correlation of 0.98. Preliminary results of optimization of the new model on peptide simulations will also be discussed.

1544-Pos Board B388

Introducing A Software Package For The Simulation Of Biomacromolecules Using The ABSINTH Implicit Solvation Model

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Computer simulations of biomolecules offer detailed insight into the molecular driving forces and mechanisms of fundamental biological processes such as protein folding or aggregation. This insight is accompanied by two major caveats, i) how authentic is the description of the system by the chosen model, and ii) how reliable are the data obtained in a statistical sense, *i.e.*, what is the quality of sampling.

The ABSINTH model, published recently (Vitalis & Pappu, *J. Comput. Chem.*, 2008, DOI 10.1.1002/jcc.21005) tries to satisfy the second concern by coarse-graining of the solvent degrees of freedom. This leads to considerable speed-up of the simulations and allows for the study of hitherto inaccessible length and timescales *in silico*. Furthermore, ABSINTH has been shown to satisfy the first concern well, as a careful calibration with respect to various pieces of experimental data on relevant systems has been carried out.

Here, we present the software package our laboratory has developed to study biological systems using the ABSINTH model primarily via a Monte Carlo sampling approach. We lay out the strategies employed to achieve maximal sampling quality given the challenging nature of the systems we study with finite computational resources. In addition, we provide a brief overview of the many options the program offers, which will make it a user-friendly and flexible tool that could become an important addition to the existing suite of packages and tools for the molecular simulation community. The software package will be freely available under a public license (open-source) and is not tied to any commercial interests whatsoever. To further make the case for ABSINTH, we will present new calibration results on a range of complex systems obtained using the ABSINTH paradigm.

1545-Pos Board B389

The Rankwise Distributed Multipole Analysis (RWDMA) of the Electrostatic Field of Large Biomolecules

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Electrostatic interactions play an essential role in many molecular processes in living organisms. However, given the large size of the macromolecules typically involved in such processes, the accurate representation of the electrostatic potential is difficult to achieve in simple and computationally efficient ways. Among the methods used to reduce the complexity of such models, the multipolar expansions provide a systematic method to separate essential features of the electrostatic field according to spatial scale. Yet, the dependence of the multipole moments on the center of expansion makes the method ambiguous and the accuracy unreliable. We present the Rankwise Distributed Multipole Analysis (RWDMA) method, which removes the ambiguity associated with the center of expansion and, at the same time, provides a recursive minimization of the truncation error of the multipole expansion. We illustrate the method with the example of the electrostatic potential generated by the histone core of a nucleosome complex.

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1546-Pos Board B390

Cooperative Sucrose Metabolism In Yeast Is A Snowdrift Game

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Understanding the conditions required for the initiation and maintenance of cooperation is a classic problem in evolutionary biology. In order for the budding yeast S. cerevisiae to grow on sucrose the disaccharide must first be hydrolyzed by the enzyme invertase. This hydrolysis reaction is performed outside of the cell, in the periplasmic space between the plasma membrane and the cell wall, suggesting that invertase production may represent a cooperative behavior. Here we demonstrate that the vast majority (~99%) of the monosaccharides created by sucrose hydrolysis diffuse away before they can be imported, thus making invertase production and secretion a cooperative behavior. In competition experiments we find coexistence between the wildtype cooperator strain and a mutant cheater strain that does not produce invertase, implying that the interaction is governed by the snowdrift game in which the optimal strategy is the opposite of one's opponents. A simple model of the cooperative interaction incorporating nonlinear benefits is able to explain this coexistence and also produces a phase diagram predicting that the outcome of the competition can be altered by varying either the cost of cooperation or the glucose concentration in the media. We are able to confirm the predictions of this phase diagram and also find that increasing the availability of glucose can have the surprising effect of decreasing the growth rate of the culture. Finally, we have characterized the wildtype invertase production strategy and find that the response is appropriate for the snowdrift game–wildtype cells cooperate when competing against cheater cells but cheat when competing against cells that always cooperate.

1547-Pos Board B391

Sensing and uptake of glucose in Saccharomyces cerevisiae

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Maintaining diverse cellular activities while consuming enough nutrients to sustain them is an essential task for all organisms. For the budding yeast