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.

Regulatory Networks, Systems Biology, & Computational Cellular Biophysics

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

Saccharomyces cerevisiae, glucose is the preferred sugar that is metabolized and is also a stimulus that controls the expression level of some quarter of the yeast's genes. Interestingly, yeast can measure the level of extracellular glucose through its various sensors, but not directly how much glucose it's importing. Two of these sensors, Snf3 and Rgt2, detect the concentration of extracellular glucose and accordingly regulate the transcription of the passive hexose transporters (HXTs) that are essential for glucose uptake in yeast. Here, we show that when the transcription of HXTs is controlled independently of the two sensors, surprising behaviors in the cell's growth rate are observed. In particular, both increase in glucose uptake rate (GUR) and the extracellular glucose concentration can each lead to substantial decrease in cell's growth rate. We therefore show that the growth rate of the cell in batch cultures is not just a function of how much glucose the cell eats, but also depends on how much glucose the cell senses outside. We attribute these growth rate behaviors to an imbalance between availability and consumption of glucose. By studying a *snf3Δ*, *rgt2Δ* mutant, the two sensors are shown to have an additional role in determining the growth rate than just through the transcriptional control of the HXTs. Furthermore, we have discovered that when just one of the main hexose transporters (HXT1~4, and HXT6) is present in a cell, glucose-sensitive post-transcriptional controls of that HXT other than the known endocytosis mechanism exist. Finally, we use an analytical model to reveal constraints placed on the synthesis of each HXTs to ensure proper scaling of GUR with extracellular glucose concentration.

1548-Pos Board B392

Modeling Intercellular MAPK Signaling in an Epithelial Wound Healing Assay

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Recent experiments in epithelial wound healing have demonstrated the necessity of MAPK activation for coordinated cell movement after damage. This MAPK activity is characterized by two wave-like phenomena. One MAPK ''rebounding wave'' that originates immediately after injury, propagates deep into the cell layer, and then regresses back to the wound interface. The second MAPK wave is a slow developing, sustained wave that propagates from the wound interface. Experimentalists have suggested that the first wave is originated by reactive oxygen species (ROS) generated at the time of injury. We develop a mechanistic diffusion-convection model that produces the observed behavior by taking advantage of the coupling between ligand (e.g. EGF) and ROS species in the activation of the MAPK cascade. In our model, the second wave is initiated, and sustained by the stresses induced by the slow cell movement toward the injury. We explore the bi-stability of the model in connection with the bi-stability of the MAPK cascade. In particular, we look for traveling wave solutions of the model and their properties under various regimes.

1549-Pos Board B393

Modeling cAMP-cGMP Crosstalk in the Cardiac Myocyte

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While the role of nitric oxide (NO) in regulating cardiac function through vascular smooth muscle relaxation has been characterized over the past 15 years, NO's effects in the cardiac myocyte have yet to be resolved. The addition of NO to these cells has been reported to cause a biphasic response; NO either increases or decreases cardiac contractility depending on its concentration. Proposed mechanisms for this response include a number of factors, ranging from direct nitrosylation of the ryanodine receptor by NO to modulation of the beta-adrenergic signaling pathway by NO-induced cGMP. This latter interaction is supported by experimental data showing a concomitant biphasic response of the L-type calcium current.

In order to elucidate the mechanisms underlying the biphasic response of the L-type calcium current to NO, we have developed a model combining descriptions of cAMP production via the beta-adrenergic signaling pathway and cGMP production via a NO signaling pathway. The cAMP-cGMP crosstalk model couples the production of cGMP by guanylyl cyclase to the beta-adrenergic signaling pathway via cGMP-activated and cGMP-inhibited cAMP phosphodiesterases (PDEs.) Integrative regulation of cAMP concentration will ultimately regulate the L-type calcium current, via altered activation of protein kinase A.

We hypothesized that the opposing behavior of these two cGMP-regulated cAMP PDEs leads to the biphasic effects on L-type calcium current seen experimentally.

To test this hypothesis, a model was formulated from existing models describing cGMP synthesis and beta-adrenergic control of L-type calcium current. These two pathway models were coupled using enzyme kinetic data describing the PDEs. Simulations from the model combining these two pathways show that the interplay between these two cGMP-regulated cAMP PDEs gives rise to the biphasic response of the L-type calcium current. Supported by R33HL87345.

1550-Pos Board B394

Cdc14-release Oscillation is Separable from Cell-cycle Progression, and Modulated by Clb-Cdk

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A free-running Cyclin oscillator suggests that the oscillation of Cyclin dependent kinase(Cdk) activity can lead to periodicity of cell-cycle events. In budding yeast S. cerevisiae mitotic Cyclin activity is primarily antagonised by the phosphatase Cdc14 which is released from nucleolus in late mitosis and becomes active to promote exit from mitosis. We devised a quantitative assay to study the effect of B-Cyclin on Cdc14 localization. By introducing physiological concentration of nondegradable Clb2-kd into the cell, we found that Cdc14-localization status became oscillating and uncoupled from cell-cycle progression. The frequency of this oscillation is controlled by Clb2-kd concentration, and saturated at twice the frequency of a normal cell-cycle. This observation suggests that cell-cycle progression may be controlled synergistically by kinase and phosphatase oscillators. We proposed a model for the cell-cycle-independent Cdc14 oscillation being a negative feedback oscillator involving the activation of APC-Cdh1 by Cdc14 and the subsequent degradation of polo kinase.

1551-Pos Board B395

Modeling Extrinsic Apoptosis Regulatory Network Pathways Using A Rules-based Framework

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We describe a systems approach to combine mathematical modeling and experimental measurement in the study of apoptosis in mammalian cells. The apoptotic signal is an important all-or-nothing mechanism which must be tightly regulated in the cell. Our focus will be on the role of pro and anti-apoptotic proteins in the extrinsic apoptosis signaling pathway leading to the formation of pores at the mitochondrial membrane by BAK and BAX proteins. This network is a prototypical cue-signal-response-feedback pathway of high biomedical importance. Construction of mathematical signal transduction models that recapitulate key features of signaling pathways as they exist in cells is currently very difficult, in large part because few tools are available to assemble, validate and update large dynamical models. We aim to implement novel methodologies based on ''rules-based'' techniques to allow for a flexible treatment of this complex network model. The calibration of such a model and application to ongoing experimental work in our laboratory is an important aspect of this work. We report our ongoing work on this subject paying particular attention to the rules-based building framework, the calibration steps and the use of experimental data for model calibration and validation.

1552-Pos Board B396

A Graded Response of a Transcription Factor to Increasing Doses of External Stimuli: A Thermodynamic Framework Describing the Behavior of NF-kB

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A paradigm in transcriptional regulation is that a graded increase in transcription factor (TF) concentration is ''digitally'' translated into an on/off transcriptional response by means of cooperative TF binding to adjacent DNA binding sites. Such paradigm stems from the analysis of TFs operating in developmental processes, notably embryonic segmentation, that require the definition of sharp borders separating different body regions.

Here we show that NF-kB, a key TF responsible for the expression of genes implicated in the inflammatory and immune responses, is an ''analogical'' transcriptional regulator. We demonstrate that increasing doses of inflammatory stimuli lead to gradually increasing concentrations of NF-kB in the cell nucleus, which in turn are translated into gradually increasing levels of transcriptional activity of NF-kB target genes. Differently to what observed in developmental systems, we show that the number of NF-kB binding sites in