PVA and functionalized nanoparticles. The last component will help to the structures with the cellular regeneration. In order to better understand this system, first the PVA properties will be studied to verify its functional use in this kind of structures. Computational techniques will be used to build the structures, study their properties and to simulate its behavior when interacting with other components. The objective of this study is to characterize the scaffolds for tissue engineering in terms of mechanical properties and descriptors that will help to predict its biodegradability. In silico experimental studies were used to characterize a descriptor that can be related with the biodegradability of the material, solvent accessibility, once the new tissue starts to grow over the scaffold material.

1597-Pos Board B548

Mapping Functional Group Requirements of Ligands at the Occluded Binding Pocket of β2-Adrenergic G-Protein Coupled Receptor using Site Identification by Ligand Competitive Saturation Simulations

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β2-adrenergic G-protein coupled receptor (B2AR) is an important therapeutic target for obstructive pulmonary diseases. The ligand binding pocket (LBP) in this and a number of other drug targets is deeply buried, offering significant challenges to computer-aided drug design approaches. Site Identification by Ligand Competitive Saturation (SILCS) is an in-situ fragment sampling method that maps the spatial distributions and approximate affinities of chemically diverse functional groups on a macromolecule through molecular dynamics (MD) simulations of the macromolecule in an aqueous solution of small molecules. Notable is the simultaneous inclusion of waters and protein flexibility such that the method accounts for ligand and binding site desolvation when mapping the affinity patterns of the different fragments (FragMaps). To probe an occluded LBP, a novel Grand-Canonical Monte-Carlo/MD (GCMC/MD) strategy is extended to the SILCS methodology. GCMC drives the small molecules and explicit solvent sampling of the occluded pocket, and the MD allows for the conformational sampling of the macromolecule in the presence of the small molecules, which is useful in identifying regions in the LBP that were inaccesible in the crystal conformation. Good agreement is obtained between the FragMaps and the positions of chemically similar functional groups of ligands observed in the crystal structures of B2AR. Ligand grid free energy (LGFE), an approximate estimation of binding affinity derived from FragMaps had good correlation with the experimentally measured binding affinity for diverse ligands. Clear differences were found in the FragMaps at the LBP across the activated and inactivated conformations of the B2AR. These differences were useful in determining the nature of a ligand that would preferentially bind to one of the two states and consequently guide drug design.

1598-Pos Board B549

Insights from All-Atom Molecular Dynamics Simulations of 40 Nucleosome Chromatin Fiber

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Gene expression is regulated, in part, by the organization of chromatin fiber, which is the next hierarchical level of chromatin compaction beyond the nucleosome. Due to the large size of the fiber - millions of atoms - computational studies investigating its organization have typically used coarse-grain simulations. Such simulations use customized, relatively unproven, force fields, and fail to elicit the finer details of the atom level structure. We use multiscale all-atom simulations of 40 nucleosome (over 1 million atom) chromatin fiber to study its structure and response to modifications such as post-translational modifications implicated in chromatin remodeling. The multiscale method used, Hierarchical Charge Partitioning (HCP), exploits the natural organization of biomolecules (atoms, groups, chains, and complexes), to speedup implicit solvent simulations of the fiber by over 2 orders of magnitude. The method uses the proven Amber force field to compute interactions between nearby atoms, while approximating interactions with distant components by a smaller number of charges that optimally reproduce the low order multipole moments of these components. We use the novel technique to gain insight into the organization of the more flexible regions of the fiber, such as linker DNA and histone tails.

1599-Pos Board B550

Computationally Projecting the Influence of Nucleic Acid on Pathways of Nucleation-Limited Virus Capsid Assembly

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Elucidating assembly pathways of complex macromolecular structures, such as virus capsids, is an important problem for understanding the many cellular processes dependent on self-assembly but also challenging given limited experimental technologies for observing such systems. We have previously addressed this problem through simulation-based data fitting, learning rate parameters of coarse-grained stochastic simulation models to match light scattering data from bulk assembly of purified coat protein in vitro providing an unprecedented view of the fine-scale reaction pathways that might have produced those data. A key question raised by such models, though, is how well they might reflect assembly under more natural cellular conditions where factors such as local concentration changes, non-specific crowding, and often the influence of nucleic acid during assembly become relevant. In the present study, we examine the latter issue, how using analytical models of various contributions of RNA folding to assembly would influence overall pathways and kinetics, primarily with reference to cowpea chlorotic mottle virus (CCMV). We find a surprising complexity and synergy of interaction effects. Energetic effects that gain or lower free energy tend to disrupt successful assembly relative to the in vitro model individually, while the full combination of positive and negative effects collectively promotes greatly accelerated assembly without loss of yield. Furthermore, it accomplishes this change in kinetics while substantially altering the ensemble of assembly pathways open to the system. These simulation results help us understand how RNA viral coat and genome may interact in assembly to promote rapid growth while avoiding kinetic traps expected from much prior theory, bringing us a step closer to the goal of understanding how viral assembly in the cell may differ from our current conception based largely on in vitro models.

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Docking to the Highly Flexible Estrogen Receptor Ligand Binding Domain via Mixed-Resolution Monte Carlo

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We report on a docking study using a new version of our mixed-resolution Monte Carlo (MRMC) software, which was previously employed for simple self-docking of estradiol to the ligand-binding domain of the estrogen receptor (ER). The MRMC software represents ligands and the binding site of a receptor in atomistic detail and the remainder of the protein coarse-grained, with the whole system fully flexible. The present cross-docking study examined dozens of ligands, both agonists and antagonists, in the context of both active and inactive conformations of ER. Because our MRMC software performs conformational sampling as part of the docking procedure, we are able to extract extensive information about pose stability and alternative poses, including ligand interactions with the nominally ''wrong'' conformation (e.g., antagonists with the active conformation).

1601-Pos Board B552

Towards the Simulation of a Complete ATP Synthase: Unravelling the Structural Basis of the Enzyme's Reversible Action

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The most prominent bioenergetic macromolecuar-motor in all life forms is ATP synthase that transforms an ion gradient existing across the cell membrane into the synthesis of ATP from ADP. Even with a wealth of available biochemical and structural information derived from numerous past and ongoing experiments, the exact mechanism of ATP synthase function remains unknown. Recently, crystallographers provided the first high-resolution view of ATP activity in Enterococcus hirae V1-ATPase. Employing a suite of transition path sampling methods, the sequence of conformational transitions involved in a functional cycle accompanying ATP hydrolysis have been investigated. The simulation suggests ADP unbinding is followed by ATP uptake which, in turn, leads to the torque generation step, i.e., rotation of the center stalk. The trajectory yields multiple intermediates, a couple of which have been isolated in independent crystallography experiments. The simulation further infers, in agreement with single-molecule experiments, that ATP binding is not the torque generation step. Finally, using data from four different high-resolution PDB structures a complete model of ATP synthase has been constructed. An evaluation of the elastic energy stored in the different ATP synthase subunits provides a structural basis for the reversible action of the synthase.

1602-Pos Board B553

SIN Mutations Alter Structure and Dynamics of Human Mononucleosomes

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ATP driven chromatin remodeling factors like SWI/SNF actively alter nucleosome structure and dynamics. Histone mutations have also been identified that alter nucleosome dynamics. These SIN (SWI/SNF INdependent) mutations