Theory, Experiment, and Computations: A Synergistic Approach to Research

Thursday, 8:30 a.m. in MS&E 0113

Acetylcholine Promotes Binding of a-Contoxin MII at a_3b_2 Nicotinic Acetylcholine Receptors, **SOMISETTI V. SAMBASIVARAO[1], JESSICA ROBERTS[2], VIVEK S. BHARADWAJ[1], JASON G. SLINGSBY[1], CONRAD ROHLEDER[1], CHRIS MALLORY[3], JAMES R. GROOME[2], OWEN M. McDOUGAL[3]*, and C. MARK MAUPIN[1]*** ([1]Chemical and Biological Engineering Department, Colorado School of Mines, 1500 Illinois Street, Golden, CO 80401; [2]Department of Biological Sciences, Idaho State University, 650 Memorial Drive, Pocatello, ID 83209; [3]Department of Chemistry and Biochemistry, Boise State University, 1910 University Drive, Boise, ID 83725; cmmaupin@mines.edu).

α-Conotoxin MII (α-CTxMII) is a 16-residue peptide with the sequence GCCSNPVCHLEHSNLC, containing Cys2--Cys8 and Cys3--Cys16 disulfide bonds. This peptide, isolated from the venom of the marine cone snail *Conus magus*, is a potent and selective antagonist of neuronal nicotinic acetylcholine receptors (nAChRs). To evaluate the impact of channel--ligand interactions on ligand-binding affinity, homology models of the heteropentameric $\alpha_3\beta_2$-nAChR were constructed. The models were created in MODELLER with the aid of crystal structures of the *Torpedo marmorata*-nAChR (*Tm*-nAChR, PDB ID: 2BG9) and the *Aplysia californica*-acetylcholine binding protein (*Ac*-AChBP, PDB ID: 2BR8) as templates for the α_3- and β_2-subunit isoforms derived from rat neuronal nAChR primary amino acid sequences. Molecular docking calculations were performed with AutoDock to evaluate interactions of the heteropentameric nAChR homology models with the ligands acetylcholine (ACh) and α-CTxMII. The nAChR homology models described here bind ACh with binding energies commensurate with those of previously reported systems, and identify critical interactions that facilitate both ACh and α-CTxMII ligand binding. The docking calculations revealed an increased binding affinity of the $\alpha_3\beta_2$-nAChR for α-CTxMII with ACh bound to the receptor, and this was confirmed through two-electrode voltage clamp experiments on oocytes from*Xenopus laevis*. These findings provide insights into the inhibition and mechanism of electrostatically driven antagonist properties of the α-CTxMIIs on nAChRs.

Impact of Ionic Liquids on the Structure of Cellulose, **VIVEK BHARADWAJ*,TIMOTHY SCHUTT, COREY KINSINGER, TIMOTHY ASHURST, and C. MARK MAUPIN** (Chemical and Biological Engineering Department, Colorado School of Mines, 1613 Illinois St., Golden, Colorado, 80401, USA; vbharadw@mymail.mines.edu).

Ionic liquids (ILs) are effective solvents for the dissolution of cellulosic biomass due to their ability to solvate cellulose, which is hydrophobic and therefore has limited solubility in aqueous environments. Molecular Dynamics (MD) simulations and NMR spectroscopy have been utilized to investigate the molecular-level interactions that facilitate the IL enabled dissolution of cellulose. The impact of various water-IL mixtures on the configuration of the sugar ring (e.g. chair or boat) were investigated in addition to the energetics of solvation. It is found that the presence of ILs stabilizes the skewed boat ring configuration in addition to modifying the geometry around the glycosidic bond (i.e. φ and ψ dihedrals). These changes in geometry are believed to favorably impact the hydrolysis of the glycosidic bond. An enhanced understanding of how ILs facilitate solvation and hydrolysis of the β(1-4) linkage in cellulose may lead to more efficient processing of cellulosic biomass for the production of renewable biofuels and value added chemicals/materials.

Using α-Conotoxin Molecular Scaffolds to Inform the Discovery of Potent and Selective Receptor Ligands toward the Treatment of Parkinson's Disease, **OWEN M. McDOUGAL** (Department of Chemistry and Biochemistry, Boise State University, 1910 University Drive, Boise, ID 83725; owenmcdougal@boisestate.edu).

Conotoxins are small cystiene rich peptides that are both potent and selective for binding macromolecular receptors in mammalian systems. Alpha-conotoxins specifically target nicotinic acetylcholine receptors (nAChRs) and have been explored for usage as therapeutic drugs for ailments including Parkinson's disease, Schizophrenia, and Tourette's Syndrome. Significant effort has been expended to understand the interaction between α-conotoxins and complex dopaminergic neuronal nAChRs. Experimental challenges are encountered to understand these dynamic, membrane bound, ligand gated ion channels. The emergence of computational tools with ever expanding breadth of capabilities has enabled the investigation of these intricate systems. Using a blend of computational applications and experimental verification of predictions, new insights into conotoxin binding paradigms will be presented.

Using peptide mutation and structural similarity to aid in drug development, **THOMAS LONG** (Departments of Computer Science and Chemistry and Biochemistry, Boise State University, 1910 University Drive, Boise, ID 83725; thomaslong@u.boisestate.edu).

Specific nicotinic acetylcholine receptor (nAChRs) subtypes have been implicated in a number of neurological disorders including Parkinson's Disease, Alzheimer's disease, and drug addiction. In an effort to discover drugs capable of mitigating the effects of such diseases, our group has developed a software-based approach to drug development which utilizes α-Conotoxin MII (α-CtxMII), a 16-residue peptide known to be a potent and selective antagonist of neuronal nAChRs. In our approach, a large peptide library composed of α-CtxMII analogs is created and virtually screened using a genetic algorithm that has been incorporated into the Dockomatic software package. The PubChem structural database is then searched for small molecules which are structurally similar to the top scoring α-CtxMII analogs. Since the PubChem structural database is composed of small molecules which have already been subjected to clinical testing, the result of the search is a set of drugs already approved for human use. We consider it to be a useful addition to modern drug discovery techniques

Comparison of the Microcirculation in the Human Conjunctiva in Healthy and Diabetic Patients, **WILLIAM L. DOW[1]*, FRANK G. JACOBITZ[1], and PETER CHEN[2]** ([1]Shiley-Marcos School of Engineering, University of San Diego, 5998 Alcala Park, San Diego, CA 92110, USA; [2]Department of Bioengineering, University of California, San Diego, La Jolla, CA 92093, USA; wdow@sandiego.edu).

The microcirculation includes the smallest arterioles, capillaries, and venules with vessel diameters ranging from 8 to 150

μm, and represents a region where active and passive exchanges of nutrients and metabolites take place. Epidemiologists study the microcirculation in detail and have identified associations between microvascular disorder and organ damage. It has been hypothesized that, by the time the most common symptoms of hypertension and diabetes are recognized and accurate diagnosis can be made, permanent damage has been done to blood systems (Schmid-Schönbein, 1999). A comparison between healthy and diseased states may lead to the identification of changes in the microcirculation that can be used to diagnose a variety of vascular related disorders (To et al., 2011, Cheung et al., 2010). The bulbar conjunctiva is an ideal site to evaluate the microvascular network non-invasively in humans where the arteriolar, capillary and venous components can readily be seen. Analysis of the conjunctiva microvasculature based on observation and limited quantitative analysis has proven to be successful in identifying the changes associated with diabetes, hypertension, sickle cell anemia, and other vascular related disorders (Smith et al., 2009, Cheung et al., 2010, Cheung et a., 2002). In this study, a simulation approach that includes measured morphometric data, projected mechanical properties, and dynamic information to model the conjunctiva vasculature of healthy and diabetic patients in implemented, allowing the theoretical prediction of disease states. The simulation results show that the diameter and mean pressure distributions of the healthy conjunctiva distinctly contrast those of the diabetic sample.

Augmenting NMR Crystallography through Fragment Methods, **JOSHUA D. HARTMAN** (Department of Chemistry, University of California Riverside, 900 Universisty Avenue, Riverside, CA 92521; jhart005@ucr.edu).

New developments in fragment-based electronic structure methods have brought improved accuracy to crystal structure prediction. Through significant reductions in computational demand, fragment-based chemical shielding calculations make MP2 level results tractable for chemically interesting organic crystals thereby creating new opportunities for combining chemical shielding calculations with NMR measurements to determine crystal structure. In the present work, we explore fragment approaches for NMR shielding in crystals and explore the effects of coupling fragment methods with an electrostatic embedding model based on atom-centered distributed multipole moments. Through coupling raw shielding tensor calculations with standard linear regression techniques we examine the ability of fragment methods with charge embedding to reproduce known experimental chemical shifts in molecular crystals and to discriminate between different molecular crystal polymorphs.

Creating Computational Models of Cellular Development through Machine Learning in a Visual Programming Environment, **NIC CORNIA*, TIM ANDERSEN, and JEFF HABIG** (Department of Computer Science, Boise State University, 1910 University Dr., Boise, ID 83725; niccornia@u.boisestate.edu, tandersen@boisestate.edu, jwhabig@gmail.com).

VPEvolve is a free and open source application that uses machine learning to develop computational models. Additionally, it utilizes a Visual Programming Environment (VPE) for the setup of the Genetic Algorithm (GA) used to generate the computational models. Specifically, the User Interface is designed to use glyphs or components and connections to represent the population flow through genetic operators as the GA is applied. These glyphs give the user an intuitive way to set the parameters for the GA, better visualization of the GA flow, and allow the user to customize the components and connections. This customization of components allows the user to select a group of components and connections and create a single glyph, which makes it easier to setup when similar sections of components and connections are often used. VPEvolve is currently being developed along side research being done in Bioinformatics to create models of cellular development based on the regenerative properties of planaria or flatworms. Since these models are difficult to produce by hand, GAs can be particularly useful to facilitate the process of model creation and also validation. VPEvole is a client-side application that allows the user to setup the parameters for the GA, uses a modeling platform such as CellSim, which performs the cellular development simulations, and presents the fitness values of the population to the user as the evolutionary search is performed.