1739-Pos Board B649
In Silico Investigation of Mutability of Spermine Synthase
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Spermine Synthase (SMS) is an enzyme which controls spermidine/spermine concentrations, both of which are polyamines playing an important role for cell development. Recently we have investigated the effect of missense mutations (G56S, V132G and I150T) known to cause Synder-Robinson Syndrome (SRS) on SMS stability and dynamics. Here we extend our study to predict the mutability of these clinically observed sites. For this purpose, we substitute *in silico* the wild type residue at each site (G56, V132 and I150) with all other 19 amino acids and calculate the effect of stability and ionizations states of SMS. We show that mutations at site 150 are expected to greatly disrupt wide type function regardless of the amino acid substitution. Such site is termed intolerable site and is characterized with very low mutability. In contrast, site V132, despite being at the dimer interface is predicted to tolerate mutations and to be quite mutable. The G56 site is in the middle of the spectra, since some of the mutations are predicted to have significant effect on dimer stability, which in turn is crucial for the function of SMS. The performed analysis shows that mutability depends on the detail of the structural and functional factors and can not be predicted based on conservation of wild type properties alone. This work was supported by awards from NLM/NIH, grant numbers 1R03LM009748 and 1R03LM009748-S1.

1740-Pos Board B650
Properties of Lipid a Bilayers Analyzed by Molecular Dynamics Simulations
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Lipopolysaccharide (LPS), responsible for the toxicity of Gram-negative bacteria, is made up of three regions: the O antigen, the core, and the innermost lipid A. Lipid A is the lipid component whose hydrophobic nature allows LPS to anchor to the bacteria outer membrane. Utilizing the latest C36 CHARMM lipid and carbohydrate force field, we have constructed a lipid A molecule of *E. coli*. Various bilayer systems were then constructed six different conditions: 1) $CaCl_2$ at 80% water and at 303K or 323K, 2) KCl at 80% water at 303K or 323K, and 3) KCl at 40% water at 303K or 323K. We are currently running molecular dynamics simulations of these systems. The simulation results will be discussed in terms of how different temperatures, ratios of water molecules to lipids, and charged ions affects the lipid A bilayer properties such as surface area, ion location, chain order, bilayer thickness and shape, and the carbohydrate conformations. The results from these simulations will be also compared with available experimental data. This work will be the basis of the future simulations of the complex glycolipid simulations such as LPS, and membrane protein simulations in more native bilayer environments.

1741-Pos Board B651
Structure Prediction and Simulations of the Major Outer Membrane Protein of Chlamydia
Muhammad S. Noon, Joseph B. Lim, Alexander D. MacKerell Jr., Jeffery B. Klauda.
Chlamydia trachomatis is an obligate intracellular human pathogen which can cause trachoma, conjunctivitis, infection of urogenital system and lymphogranuloma-venereum in humans. Preventive measures have recently focused on production of vaccine using the variable domain (VD) extracellular loops of the major outer membrane protein (MOMP). MOMP's crystal structure has not been determined, but serious efforts have been made to propose its structure and function experimentally and theoretically. Our objective is to utilize this information to obtain a consistent secondary and tertiary structure. MOMP functions as general diffusion porin having β-barrel structure. We predict 16 β-stranded transmembrane sheets, and variable domains at proper positions, consistent with available experimental data. Having no sequence similarity of MOMP with other porin proteins, a threading technique was utilized for structure prediction with the outer membrane porin protein (2OMF) of E.Coli as a template. Using hand-threading, MOMP sequence was aligned along the structure of 2OMF. The Modeler program was used to build a final structure (pre-refined). We selected a fragment with five β-sheets and loops containing VD-3 and VD-4. This fragment was further refined (post), using simulations, to get full length β-sheets in a realistic Chlamydial membrane. Our current objective is to continue molecular dynamics (MD) simulations to check the consistency of these (pre- and post-refined) fragments. Implicit water simulations of both refined fragments resulted in loss of secondary and tertiary structure, while MD simulations of post-refined fragment in Chlamydial membrane were stable. This implies that vaccine development requires delivery vehicles that are lipid-like to maintain the stability of these protein fragments. Moreover, future MD simulations of both fragments in a Chlamydial membrane will improve our understanding of stable loop conformations and guide experimentalists in developing a peptide-based vaccine.

1742-Pos Board B652
Development of a Novel Algorithm for Identifying Transcription Factor Binding Motifs in the Genome DNA Sequences
Ryo Nakaki, Masaru Tateno.
Finding of transcription factor binding motifs (TFBMs) is essential for identifying the detailed transcriptional regulation networks. In this study, we developed a novel algorithm for identifying the TFBMs by using the genome DNA sequence. We compared the accuracy of our algorithm with that of the conventional ones by exploiting ChIP-on-chip genome DNA sequence fragments, as test data, which were extracted by treatments to induce specific TFBMs of *S. cerevisiae* and human estrogen receptor (ER) expressed in human MCF-7 breast cancer cells. As a result of our calculation of the *S. cerevisiae* data, our algorithm identified 69 % known TFBMs from 65 datasets, each of which is corresponding to distinct TFBMs. In contrast, the conventional algorithms identified 63 % (BioProspector), 49 % (MDscan), and 52 % (MEME); here, the default parameter set was used for each identification system. Also, for ER elements (ERE), our algorithm exactly identified the position-specific scoring matrix (PSSM) using the human ER data, whereas the conventional algorithms did not. If single sequence repeats (SSLs) are removed from the ER data, BioProspector identified the PSSM of the human ERE. Accordingly, our system is expected to identify unknown TFBMs as well as known ones using genome DNA sequences without editing/tuning the parameter set used in our identification system. Further, identification of co-regulated known/unknown transcription factors is now going on by using experimental data obtained by DNA microarray techniques and the cap analysis gene expression (CAGE) systems.

1743-Pos Board B653
Correlating in Vitro Measurements of Protein-DNA Binding Affinities with in Vivo Repression and Impact on the Growth Rate of the Host Organism
Liskin Swint-Kruse, Michael Manley, Sudheer Tungtur, Hongli Zhan.
In order to fully decode the information of patient genomes, we must determine which protein polymorphisms alter function. One resource for addressing this question is the sequence set of naturally occurring homologs. Sequence comparisons easily identify conserved positions, which usually cannot be changed without consequence. However, the impact of changing nonconserved positions is less-easily predicted. We have devised a model system for testing computational identifications of important nonconserved positions and measuring the functional impact from amino acid substitutions at these positions. The model system is based on chimeric proteins of the LacI/GalR family; functional change can be detected as either altered in vivo repression or altered in vitro DNA binding properties. For this system to accurately model a naturally-evolving system, an observed change in repression must be large enough to impact the growth of the host organism. Here, we use a series of point mutations in an engineered LacI/GalR transcription repressor to correlate altered in vivo repression with thermodynamic measurements of DNA binding affinities and bacterial growth rates. Results will determine whether most changes in repression are due to changes in DNA-binding affinity for the in vivo operator DNA binding site, and will determine how large a change in repression is required to alter bacterial life cycles.

1744-Pos Board B654
Learning Gene Regulations from Multiple Knockout Data via an Efficient Dynamic Bayesian Network Reconstruction
Yu Bai, Mark Tong.
With the availability of KOMP mutant mice, RNAi and lower cost of whole genome microarrays and sequencing techniques, a new generation of multi-knockout comparative studies will be feasible and highly desirable in identifying genetic functional and interactive relationships. Nevertheless, given the large number of molecular factors occurring in a system level and varying with time, precise gene interaction identification is a formidable challenge. Many existing computational approaches are limited to static and/or relatively simple gene networks. Herein, we developed a new algorithm to discover time-dependent, complex gene regulations from multiple perturbation data. The approach is based on Dynamic Bayesian Networks (DBN) in conjunction with an improved Markov-Chain-Monte-Carlo (MCMC) sampling. DBN permits temporal pattern exploration and a system level data integration. We used a data-derived Proposal Matrix (DPM) that estimates the significance of gene relationships to guide MCMC search more efficiently. Further, we consolidated prior