case we examined the sodium- dependent glucose co-transporter of Vibrio parahaemolyticus (vSGLT) which mediates galactose transport into the cytoplasm of vibrio parahaemolyticus bacteria. According literature, kinetic of co-transporter has between 5 and 6 states or conformations, but in this case the unbinding of substrates is studied by inward-facing conformation, also known as state release model of co-transporter. We performed a computational study to analyze the global movements of a vSGLT transporter, and we compared our computational results with those found in previous experimental reports. Normal modes analysis with an Elastic Network Model (ENM) was used to explore the changes in global movements between vSGLT in the presence or absence of the ions they transport (Na^+, galactose). ENM has been shown to be a useful computational tool for predicting the dynamics of membrane proteins in many applications. The lowest normal modes generated by the ENM provide valuable insight into the global dynamics of biomolecules that are relevant to their function.

1428-Pos Board B496

Predicting Small Molecule-Binding to DNA with Computational Docking and Empirical Entropic Contributions

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DNA interacts with small molecules, from water to endogenous reactive oxygen and nitrogen species, environmental mutagens and carcinogens, and pharmaceutical anticancer molecules. Understanding and predicting the physico-chemical interactions of small molecules with DNA is key not only for the comprehension of molecular-level events that lead to carcinogenesis and other diseases, but also for the rational design of drugs that target DNA. We recently validated a popular docking method that includes a physics-based free energy function and a Lamarckian Genetic Algorithm, for the prediction of small molecule geometries upon physical binding to DNA. We noticed that quite often the binding site closest to the experimental geometry was not the one with the lowest free energy but the one found with the highest frequency among all computational simulations. An empirical conformational entropy term based on the docking frequency was added to the free energy function in order to improve the binding site predictions. We found that in two small molecule-DNA systems the inclusion of the vibrational entropy term decreased significantly the root-mean-square-deviation of the lowest free energy geometry compared to the experimental crystallographic structure. Including the entropy term preserved the successful prediction of the binding geometry compared to the crystallographic structure for a third small molecule-DNA system. These, as well as any results we obtain from applying the methodology to additional small molecule-DNA systems, will be presented and discussed.

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Towards In-Silica Screening of Molecule Permeation through Outer Membrane Channels in Gramm-Negative Bacteria

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The demand of new drugs for combating multidrug-resistant bacteria appears more urgent for Gram-negative bacteria: the presence of the outer membrane, which hinders the access of molecules to internal targets, renders the development of anti-infectives more challenging. Today neither a robust screening method for permeation nor defined physical/chemical rules governing permeation through the outer membrane are available. By assuming diffusion as the physical mechanism of the transport of molecules through the channels, we suggest a simple quantitative model for the free energy profile of the molecule-pore interaction. The major penetration barrier has an entropic origin and comes from the steric constraints in the channel. It strongly depends on the average dimension of the pore and that of the molecule as well as on their fluctuations. The macroscopic electrostatic interactions modulate the steric barrier and may either compensate or increase the latter locally. The final tune of the total free energy profile is attributed to the specific interactions like hydrogen bonds, hydrophobic, etc. The diffusional flux of molecules through channels is calculated then with the analytic solution to the Nernst-Planck-type equation provided the chemical potential difference at the sides of the membrane is known. Being based on the clear physical conception, the parameters of the model may be obtained from the all-atom MD simulations for a membrane channel and the molecules separately. Alternatively, the model may be considered as a scoring function for fast quantification of the pore permeability for molecules with the parameters fit to the available experimental data. This, in particular, opens up the possibility for the computational screening of virtual libraries of possible modifications of an antibiotic in order to improve its permeability through the membrane.

1430-Pos Board B498

On the Robustness of SAC Silencing in Closed Mitosis

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Mitosis equally partitions sister chromatids to two daughter cells. This is achieved by properly attaching these chromatids via their kinetochores to microtubules that emanate from the spindle poles. Once the last kinetochore is properly attached, the spindle microtubules pull the sister chromatids apart. Due to the dynamic nature of microtubules, however, kinetochore-microtubule attachment often goes wrong. When this erroneous attachment occurs, it locally activates an ensemble of proteins, called the spindle assembly checkpoint proteins (SAC), which halts the mitotic progression until all the kinetochores are properly attached by spindle microtubules. The timing of SAC silencing thus determines the fidelity of chromosome segregation. We previously established a spatiotemporal model that addresses the robustness of SAC silencing in open mitosis for the first time. Here, we focus on closed mitosis by examining yeast mitosis as a model system. Though much experimental work has been done to study the SAC in cells undergoing closed mitosis, the processes responsible are not well understood. We leverage and extend our previous model to study SAC silencing mechanism in closed mitosis. We show that a robust signal of the SAC protein accumulation at the spindle apparatus can be achieved. This signal is a nonlinear increasing function of number of kinetochore-microtubule attachments, and can thus serve as a robust trigger to time the SAC silencing. Together, our mechanism provides a unified framework across species that ensures robust SAC silencing and fidelity of chromosome segregation in mitosis.

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Computational Analysis of the Mechanism of the Ubiquitin Conjugating Enzyme Ubc13

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Post translational modification (PTM) is a process by which proteins are chemically altered after they have been assembled. In one such PTM, lysine ubiquitination, the small protein ubiquitin is added to the lysine of a target protein via a thioester aminolysis reaction. This reaction is catalyzed by a series of enzymes. The second enzyme in this cascade, E2, which is covalently linked to ubiquitin, transfers ubiquitin to the target lysine. The accepted mechanism for ubiquitination is a stepwise mechanism that creates an oxyanion intermediate. This intermediate is hypothesized to be stabilized by an ''oxyanion hole.'' In Ubc13, the E2 enzyme under investigation here, there is an asparagine side-chain that is hypothesized to serve as the oxyanion hole. However, the validity of the accepted mechanism has come into question and because recent studies have suggested a structural role for this residue. In our study, molecular dynamics was used to examine the hydrogen bonding environment of the active site in two structures of Ubc13 and determine the likelihood for the formation of the oxyanion hole. Furthermore, a combination of metadynamics, a rare-events sampling method, and hybrid quantum mechanics/molecular mechanics (QM/MM) was used to find potential reaction pathways and to then calculate their relative barrier heights.

1432-Pos Board B500

Physical Binding of a Tobacco-Specific Carcinogen (NNK) Metabolite to the Human TP53 Gene with Ramifications for DNA Damage and Mutations

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The most prevalent and carcinogenic of the tobacco-specific nitrosamines is 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). NNK is a potent carcinogen that causes numerous types of cancers, most commonly lung adenomas and adenocarcinomas. The diazonium ion formed through the enzymatic metabolism of NNK by cytochrome P450s, can bind chemically to DNA (DNA damage). These adducts, if not repaired, can cause mutations that lead to tumorigenesis. We do not have a complete understanding of the binding of the diazonium ion to DNA which is important for future preventative strategies of NNK-associated cancers. The focus of this research is to computationally model and understand the physical interactions between the NNK diazonium