is searched to detect local structures with similar geometry and physicochemical properties to a query structure regardless of sequence continuity and protein fold. Then, the ligands in the identified complexes are used as templates to predict a binding site and a ligand structure for the target protein. The performance of G-LoSA is validated against benchmark targets. G-LoSA is able to not only predict the ligand binding sites with high accuracy but also identify a single template ligand that is highly similar to the target ligand. In addition, our benchmark analyses show that an assembly of structural fragments from multiple template ligands can be used to design novel ligand structures specific to the target protein. This study clearly indicates that local-structure based binding-site prediction and ligand modeling have potential for *de novo* ligand design.

2080-Pos Board B99

A Multibody Atomic Statistical Potential for Predicting Enzyme-Inhibitor Binding Energy

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Accurate prediction of enzyme-inhibitor binding energy has the capacity to speed drug design and chemical genomics efforts by helping to narrow the focus of experiments. Here a non-redundant set of three hundred high-resolution crystallographic enzyme-inhibitor structures was compiled for analysis, complexes with known binding energies (ΔG) based on the availability of experimentally determined inhibition constants (k_i). Additionally, a separate set of over 1400 diverse high-resolution macromolecular crystal structures was collected for the purpose of creating an all-atom knowledge-based statistical potential, via application of the Delaunay tessellation computational geometry technique. Next, two hundred of the enzyme-inhibitor complexes were randomly selected to develop a model for predicting binding energy, first by tessellating structures of the complexes as well as the enzymes without their bound inhibitors, then by using the statistical potential to calculate a topological score for each structure tessellation. We derived as a predictor of binding energy an empirical linear function of the difference between topological scores for a complex and its isolated enzyme. A correlation coefficient (r) of 0.79 was obtained for the experimental and calculated ΔG values, with a standard error of 2.34 kcal/mol. Lastly, the model was evaluated with the held-out set of one hundred complexes, for which structure tessellations were performed in order to calculate topological score differences, and binding energy predictions were generated from the derived linear function. Calculated binding energies for the test data also compared well with their experimental counterparts, displaying a correlation coefficient of $r = 0.77$ with a standard error of 2.50 kcal/mol.

2081-Pos Board B100

Water Matters: Role of Water in the Binding Selectivity of β-Blockers to Human β-Adrenergic Receptors

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This work investigates the problem of selective binding of the chosen β-blockers towards human β1 and β2-adrenergic receptors (βARs). The selective blockade of the cardiac β1 has important medical applications. However, the current understanding of this prominent medical problem is still very limited. The recently published crystal structures of β1 and the β2 [1,2] offer an opportunity to understand the mechanism of β1-selective binding with atomic accuracy. Numerous computational studies have explored the binding pockets or conformational properties of these receptors through homology modeling, structure-based modeling, fragment-based screening and molecular dynamics simulations [3-5]. Yet, as far as the authors know, thus far there have been no computational studies focusing exclusively on the problem of the selective blockade of the β1 subtype. The computations carried out and reported here fill this gap. Surprisingly, our simulations show that water plays a fundamental role in the binding site of both βARs, being particularly important in determining the selectivity of binding.

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2082-Pos Board B101

The Role of First and Second Shell Interactions in Phosphate Binding Proteins

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The phosphate anion is involved in a wide range of processes ranging from cell signaling to energy storage in cells. It can interact with proteins in different modes, where its interactions range from being covalently bound to the protein to coordinating metal sites in enzymes. The motif for coordinating or binding the phosphate depends on its functional usage, e.g. a structural motif known as the P loop is often found. In this work, we survey phosphate-binding proteins with emphasis on the molecular recognition of the first- and second-shell interactions between anion and amino acid residues. To characterize the binding sites, we optimize the geometries by using density functional theory calculations. From the optimized geometries, we calculate the charge transfer and force constants between the first shell interactions and the phosphate moiety as well as the interaction between the first- and second shell of the protein. The results serve to describe the strength of the first shell interaction, where positive amino acids and metals are often observed. Results also show the importance of the second shell interactions to support the binding motif. Our approach can provide basic insight into the high specificity amino acid interactions with phosphate seen in phosphate binding proteins. This knowledge is of importance in understanding phosphate-binding proteins and in the development of biomimetic sustainable phosphate biosensors.

2083-Pos Board B102

On Parameter Identifiability in Non-Linear Biophysical Models

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The quantitative modeling of biological phenomena allows for a deeper understanding of underlying mechanisms as well as the determination of biophysical parameters. However, we note that in many systems, the unique identification of relevant parameters is not possible with common experimental methods. The parameters of a model are said to be identifiable if there a unique point in parameter space that leads to an optimal agreement with particular data. In common non-linear models, however, there is not a unique map from parameter space to data space, and the confusion resulting from this lack of parameter identifiability may be slowing progress in many fields of biophysics. We use a simple example model to show analytically that this problem often results from rank-difficient regression, i.e., there are an infinite number of ways for the model parameters to fit the data equally well. Further, we use the same model to show that the identifiability problem can be resolved if additional experimental data is included for model constraint. Unfortunately, most models of interest will not be amenable to analytical examination. We present a numerical method based on Markov chain Monte Carlo (MCMC) sampling which can be used for any data and any model and will allow the diagnosis of these issues. We provide example uses of MCMC to asses parameter identifiability in a variety of systems. This method is an important tool that provides the ability to assess parameter identifiability for a given model and various potential experimental manipulations. This new kind of power analysis will lead to more precise conclusion and more fruitful experimentation.