computational protein-protein docking approaches can provide a useful alternative to address this issue. We present a novel protein docking algorithm, VDOCK, based on the use of 3D Zernike descriptors (3DZD) as regional features of molecular shape. The key motivation of using these descriptors is their invariance to transformation, in addition to a compact representation of local surface shape characteristics. In our previous works we have shown that 3DZD are suitable for comparing global/local protein surface shape and surface physicochemical properties to quantify their similarity. Here we apply 3DZD for quantifying surface complementarity. Docking decoys are generated using geometric hashing, which are then initially screened by a shape-based scoring function that incorporates buried surface area and 3DZD. The benchmark studies show that 3DZD are not only efficient in identifying shape complementarity for bound docking cases but superior to other existing methods in accommodating a certain level of flexibility of the protein surface in unbound docking cases, taking advantage of 3DZD's controlable resolution of the surface description. In the next stage, generated docking decoys are evaluated using a physics-based scoring function. The weighting factors to combine these terms are trained using several different target metrics on a large dataset of docking decoys. Additional information and steps for selecting models are also employed, which include protein-protein interaction site predictions and optimization of global and side-chain conformations.

2394-Pos

A Physics-Based Iterative Method to Extract Distance-Dependent All-Atom Potentials for Protein Structure Prediction

Shengyou Huang, Xiaoqin Zou.
Dalton Cardiovascular Research Center, Department of Physics and Astronomy, Department of Biochemistry, and Informatics Institute, University of Missouri, Columbia, MO, USA.

One of the challenges in protein structure prediction is the development of an accurate scoring function that yields a global minimum free energy for the native state. Although the knowledge-based scoring function has proven to be a successful scoring approach to protein structure prediction, there exists a hurdle in deriving knowledge-based potentials. Namely, the ideal reference state is inaccessible. In this work, we have developed a general physics-based iterative method to extract distance-dependent all-atom potentials for protein structure prediction. Our method circumvented the long-standing reference state problem. The derived scoring function was extensively evaluated with three diverse test sets, and showed significant improvement over other well-known scoring functions. The results suggest the efficacy of our scoring function for protein structure prediction.

2395-Pos

Using Molecular Simulations to Screen for Antibiotics with Enhanced Permeation Properties through Bacterial Pores

Eric Hajjar[1], Amit Kumar[1], mahendran Kozhinjampara[2], Andrey Bessonov[2], Mathias Winterhalter[2], Paolo Ruggerone[1], Matteo Ceccarelli[1].
[1]University of Cagliari, Department of Physics, Cagliari, Italy, [2]Jacobs University Bremen, Bremen, Germany.

Gram-negative bacteria are protected by an outer membrane and to function, antibiotics have to diffuse through outer membrane channels, or porins, such as OmpF. Previously, we revealed the complete permeation pathways of β-lactams antibiotics, such as ampicillin, using all atom accelerated molecular dynamic simulations and found remarkable agreement with experimental results(1). Here we follow the paradigm for selecting antibiotics with better permeation properties via computer simulations. In-depth analysis of the simulations revealed the key determinants for the diffusion of ampicillin through OmpF: a subtle balance of interactions at the constriction region of the channel compensates the loss of entropy of the antibiotic and facilitates its diffusion. The simulations were then repeated using porins mutated in their key interacting residues, such as Asp113, and the drastic changes found in ampicillin permeation confirmed our hypothesis. Guided by these results, we then predict that an antibiotic that would interact differently with OmpF, such as penicillin-G that lacks the ampicillin positive group, would translocate faster. This is confirmed by the calculation of the effective energy barriers for translocation, and importantly, we are able to validate the predictions by a wide range of experiments using electrophysiology, spectroscopy and swelling assays techniques. We conclude by drawing, the complete inventory of the rate-limiting interactions and map them on both the porin and antibiotics structure. Finally we show how our multi-scale approach can help rational antibiotics design and screening as we extend it to (i) novel antibiotics of pharmaceutical and therapeutical interest and (ii) homology modeled porins from novel pathogenic strains which shows interesting antibiotic resistance profiles.

1. Hajjar, E., et. al. Bridging time and length scales: from macroscopic flux to molecular mechanism of antibiotics diffusion through porins. Biophys. J. (minor revisions).

2396-Pos

Simulation Study of Stapled Alpha-Helical P53 Peptide Analogs:probing the Relationship between Structural Stability and Biological Potency

Udayan Mohanty[1], Zuojun Guo[1], Justin Nohere[2], Tomi Sawyer[2], Woody Sherman[3], Goran Krilov[1].
[1]Department of Chemistry; Boston College, Chestnut Hill, MA, USA, [2]Aileron Therapeutics, Inc., 840 Memorial Drive, Cambridge, MA, USA, [3]Schrodinger, Inc., 120 W 45th Street, 29th Fl.,, New York, NY, USA.

Reactivation of the p53 cell apoptosis pathway through inhibition of the p53-hDM2 interaction is known to be a viable approach to suppressing tumor growth in many human cancers and stabilization of the helical structure of p53 analogs via a hydrocarbon cross-link (staple) has been found to lead to increased potency and inhibition of protein-protein binding. However, details of the structure and dynamic stability of the stapled peptides and their relationship to the nature and location of hydrocarbon linker are not well understood. Here, we use extensive molecular dynamics simulations to study a series of stapled α−helical peptides over a range of temperatures in solution. The peptides are found to exhibit substantial variations in predicted helicities that are in good agreement with the experimental values. In addition, we find significant variation in local structural flexibility of the peptides with the position of the linker, which appears to be more closely related to the observed differences in activity than the absolute helical stability. These simulations provide new insights into the design of α−helical stapled peptides and could aid in the development of potent inhibitors of protein interfaces.

2397-Pos

Synthesis of Kynapcins and Telephoric Acids as Prolyl Endopeptidase Inhibitors of Anti-Dementia Drugs

Yean-Jang Lee[1], S.-Y. Lin[2].
[1]Changhua University of Education, Changhua, Taiwan, [2]Ta-Tsun Middle School, Changhua, Taiwan.

Prolyl endopeptidase (PEP), a serine protease, is known to cleave a peptide substrate on the C-terminal side of a proline residue. Additionally, the PEP activity of Alzheimer's patients has been found to be significantly higher than that of the normal person. Therefore, the search for PEP inhibitors as anti-dementia drugs, which may play a crucial role in curing Alzheimer's disease, has attracted significant attention from the synthetic, biological, and medicinal comunities. Recently, Song et al. reported that two novel PEP inhibitors, benzofuran dimer kynapcin-24 (**1**) (IC_{50}, 1.14 μM) and pentacyclic polyozellin, as well as related compounds, were isolated from Polyozellus multiflex Murr. On the other hand, although propeptin (IC_{50}, 1.1 μM) has inhibition similar to **1**, it is a hydrophilic and large molecular weight peptide, which may make it difficult to penetrate the blood-brain barrier. With the difficulty of propeptin as a PEP inhibitor and the promise shown by drugs such as **1**, The synthesis of kynapcin-24, which can be isolated from the Korean mushroom *Polyozellus multiflex* Murr, is achieved in 12% overall yield from commercially available 3,4-dihydroxybenzaldehyde by a route in which the longest linear sequence is only 14 steps. The key transformations in the synthesis are the Cu-mediated and Pd-catalyzed coupling reactions of benzofuranyl iodide **12** with stannane **15**, and 5-endo-dig iodocyclization of a phenol propargyl ether. In addition, telephoric acids have also synthesized in high yields. Finally, the molecular model was examined the interactions of proteins and ligands as well.

Apoptosis

2398-Pos

FCS Studies of the Pore Formation by Protein BAX in Lipid Membranes

Olena Ivashyna[1], Ana J. García-Sáez[2], Eric T. Christenson[1], Petra Schwille[2], Paul H. Schlesinger[1].
[1]Washington University School of Medicine, St. Louis, MO, USA, [2]Biotechnologisches Zentrum, Dresden, Germany.

BAX is a pro-apoptotic member of the BCL-2 protein family. At the onset of apoptosis, monomeric, cytoplasmic BAX is activated and translocates to the outer mitochondrial membrane, where it forms oligomeric pores. The biophysical mechanism of BAX pore formation and the structure of the BAX pore are not clear. To study the mechanism of BAX pore formation in lipid membranes we designed an *in vitro* system employing giant unilamellar vesicles (GUVs) and fluorescently labeled BAX combined with the single-molecule sensitivity technique, dual-focus scanning FCS. Use of scanning FCS in experiments, where two spectrally different populations of BAX molecules interact with