process, but our theory is based on stochastic energetics, which is thermodynamics in fluctuating small world.

Here, I will show energetics of single active diffusion trajectories, where the instantaneous diffusion coefficient (IDC) as a new diffusion analysis quantity is derived. Considering decomposition of energy dissipation in a non-equilibrium steady state, we can make implication of the IDC clear. An advantage of our theory is to be able to discuss the meso scale energetics from only single-particle tracking data without measuring response.

2379-Pos Board B516
Analysis of Amino Acid Properties in Interaction Surfaces of Decoys Generated by Re-Docking Scheme
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Rigid-body docking processes generate many protein complexes (decoys) for searching near-native decoys (NN-decoys) in post-docking processes with analyzing various pairs of surfaces on two input proteins, using properties of electrostatics and desolvations between two molecules or proteins. Many powerful docking computer softwares were developed and were used for resolving various categories of problems, for example, analysis of protein interaction networks or drug design. Rigid-body docking process is popular and useful in such works. However, there are some unfortunate cases, which could not obtain NN-decoys. Then, we developed Re-docking scheme using interaction fingerprints (IFPs). Re-docking scheme is the process of iterating rigid-body docking for generating more NN-decoys. After initial-docking, we classify decoys into several interaction surfaces. Thereafter, other docking processes are performed with more fine searching limited in every interaction surfaces classified. We could obtain NN-decoys even if no NN-decoys in initial-docking process [Uchikoga et. al. (2013) PLOS ONE 8:e69365]. Then, we approach a problem of prediction of protein-protein interactions by using IFPs, which gives us properties of physico-chemical interactions because IFPs are composed of interacting amino acid pairs [Uchikoga & Hirokawa (2010) BMC Bioinform. 11:236]. By using IFPs, we can obtain these properties easily and trace interaction surfaces in docking processes. In this work, docking search spaces become to be seen by using amino acid properties involved in molecular surfaces of many decoys, generating by Re-docking scheme. Then, we would like to discuss about understanding interaction mechanisms.

2380-Pos Board B517
Inferencecam: Mapping of Single-Molecule Dynamics using Bayesian Inference
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Single-molecule imaging has become ubiquitous in biophysics, biology, biochemistry and biotechnology, covering a large range of in vitro and in vivo applications. This ever-growing field now requires new and reliable statistical tools for data analysis. This is especially true for high-density single-molecule tracking methods that yield massive amounts of data and invite the use of statistics-based methods for analysis. Of particular importance is the extraction of dynamic properties (such as diffusion and transport parameters) and the ability to map these properties at different spatial scales (up to the full extent of the cell).

Bayesian analysis is a powerful method that has recently garnered interest in the treatment of single-molecule trajectories. Previously, we have shown that it provides an efficient means for estimating the relevant physical parameters that characterize the motion of individual molecules. Of particular importance, we have shown that interaction fields (which are systematically neglected in most approaches) play a paramount role in the long-term dynamics of biomolecules. With this motivation, we present InferenceMAP, an interactive software tool that uses a powerful Bayesian technique to extract the parameters that describe the motion of individual molecules from single-molecule trajectories. The main features of our tool include:

- A versatile calculation platform for estimating dynamic parameters, including the ability to specify relevant prior probabilities.
- Adaptive meshing methods to conform to different temporal and spatial scales.
- The ability to generate vast three-dimensional landscapes of single-molecule dynamics

We present relevant applications inside lipid rafts, glycan receptors, and HIV assembly platforms.

2381-Pos Board B518
Neuroimage: A Novel Highly Efficient Tool for Image Processing of in vivo Neural Networks
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Simulation of biological neural networks has been of great interest in the last years with well-established simulation tools like NEURON being constantly developed on, while tools for image processing of experimental neuron data are still lacking. We present an image processing tool that takes confocal fluorescence microscopic 2D data of a neural network and converts it into a NeuroML file containing the network morphology. Thereby the network data is ready to be imported into neuroConstruct or any NeuroML compliant tool, where the network then can be visualised, manipulated and simulated using a broad range of already available simulators and cell models.

We investigate a neural network of in-vivo neuron cells extracted from mouse brain tissue and grown on a semiconductor substrate. Besides obtaining the positions of somata and axons together with their network topology we identify so-called micro tubes which are built for future experiments seeking to measure the action potentials of axons going through them. Our image processing is used here to analyse the preparation process, in particular the positioning of cells on the substrate and success rate of axons growing through micro tubes. Furthermore the tool offers the interface for subsequent simulation in neuroConstruct and NEURON.

Simulation of a simple electrophysiological input and output will be presented and will allow comparison with future experimental data.

2382-Pos Board B519
Integrative Modeling Approaches to Interpret High-Resolution cryo-EM Reconstructions
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Modeling 3D-EM reconstructions with computational tools currently enables the interpretation at near-atomic resolution of different functional states of macromolecules, thereby deciphering the functional mechanism of biologically relevant complexes. Recent advances in cryo-EM, such as direct electron detectors, specimen preparation, image processing, and data automation, are increasing the number of determined structures, particularly at high (≤5 Å) resolutions. Here, several new integrative approaches are presented to retrieve structural information from these accurate reconstructions by incorporating modeling constraints from complementary biophysical techniques (crystallography, SAXS, FRET, etc.) or any other source of structural information (cross-linking, mutagenesis, prediction data, etc.). First, a two-step integrative approach was developed to unravel the topology of helical bundles using cryo-EM maps, distance restraints, and secondary structure predictions. This method unambiguously localized all helices of a key unassigned proteasome hexahelix and provided a topologically correct model that was later confirmed by crystallography. Second, our normal mode based flexible fitting algorithm, iMODFITY, was accelerated and adapted to deal with high resolution cryo-EM maps and other experimental constraints. Third, a fast loop-closure algorithm (RCD) was combined with integrative fitting strategies for modeling loops into unfilled densities. We strongly believe that these tools will facilitate the interpretation of the incoming high-resolution maps.

2383-Pos Board B520
Energy Tabulation Strategies for Accelerated Monte Carlo Simulation at Multiple Length Scales
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We have constructed novel coarse-grained models based on dividing biomolecular systems into rigid fragments and constructing six-dimensional tables of the interaction energy between them as a function of their relative displacement and orientation. The approach can be used for simulations on two length scales: conformational sampling within a macromolecule (e.g., protein) and interactions between elements of a multi-molecular complex (e.g., viral capsid). For conformational sampling of proteins, we tabulate interaction and solvation energies for small rigid fragments, obtained from an underlying atomistic force field. By applying potential energy smoothing techniques to these tables, we are able to improve sampling of these proteins, while maintaining secondary structure without added restraints. We use a similar tabulation strategy, based
on an underlying coarse-grained model, to study interactions among hepatitis B capsid subunit dimers, treating each entire dimer as a rigid fragment. The tables reduce the computation time of the capsid simulations by 2-3 orders of magnitude, potentially enabling the study pathways for the assembly of capsids using more realistic models than previously possible.

2384-Pos  Board B521
G-LoSA: An Efficient Computational Tool for Local Structure-Centric Biological Studies
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Molecular recognition such as ligand binding and protein-protein interaction (PPI) is a fundamental way for biological molecules to play their functional roles. These specific interactions are involved in the local regions of the molecules, rather than global structures. Therefore, accurate characterization of local structures in protein is needed to better understand biological mechanisms and to rationally design effective drugs. G-LoSA, a recently developed local structure alignment tool, has the advantages of not only predicting the ligand binding sites with high accuracy, but also identifying a single template ligand that is highly similar to the target ligand. Here, we present an improved version of G-LoSA aiming at extending its applicability to broad local structure-centric biological studies. The method generates all possible alignments between two local structures by iterative maximum clique search and fragment superposition and then determines the final optimal alignment by a G-LoSA alignment scoring function, GA-score. GA-score is a length-independent and physico-chemical property-based scoring function to measure structural similarity between two local structures. G-LoSA outperforms its previous version in identifying ligand templates and also shows robust performance in detecting similar ligand binding pockets and PPI interfaces from the benchmark sets. Finally, we introduce its application to in silico fragment-based drug design. As demonstrated by this work, G-LoSA is a promising computational tool that can be universally applied to diverse local structure-centric biological studies.

2385-Pos  Board B522
Multi-Scale Deep Neural Network Microscopic Image Segmentation
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With digital technology and fast imaging speed, huge amount of microscopic images are produced in biomedical research every day. A key procedure in processing and analyzing the images involves recognition and segmentation of features, patterns, or regions that are of interest to the researchers. Such work is often manually done by humans, which is very time-consuming and thus impractical when image data are massive. Traditional image segmentation algorithms have difficulty in identifying high-level features (e.g. a particular morphology of a cell type or an organelle). Plus, many microscopic images, especially super-resolution STED images, are highly noisy. The analysis of noisy images poses an even higher challenge to traditional algorithms. Compared with computer algorithms, humans are incredibly good at identifying high-level features. Machine learning, which let computer learn human behaviors, is thus a suitable solution. Deep learning is a set of emerging machine learning methods that is being successfully applied in many applications, such as face recognition and speech recognition. It has also been used to process specific types of microscopic images.

We have designed a multi-scale convolution neural network for segmenting noisy microscopic images. Images at original resolution and down-sampled images at multiple scales are fed to the network for information extraction. The purpose of adopting this multi-scale architecture is to obtain local fine resolution while maintain larger field of views, which gives network low classification error rate while maintain reasonable processing speed. The network has been tested on segmentation of mitochondria labeled with mitotracker. Network separate image pixels into two categories: “background” and “mitochondria”. Training and testing of the network is done with standard back-propagation algorithm, with human labeled segmentation data. Preliminary result shows the trained network well outperformed multiple traditional image segmentation methods.

2386-Pos  Board B523
Using Rules & Pathway Databases to Create Quantitative Mechanistic Models in Virtual Cell
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Recent technological advances have resulted in an accumulation of experimental data and a growing interest in using this data to build quantitative models of biological processes. The traditional approach to build such models involves manual formulation of model hypothesis and data search. This is becoming inadequate due to the degree of complexity in the models and the great variety of data available. In particular, for understanding and modeling the dynamics of protein-protein interactions, the mechanisms of interactions have to be described at the level of protein sites, the parts of proteins that are responsible for protein-protein interactions, such as protein phosphorylation sites and interaction domains. The rule-based approach provides modelers with an opportunity to efficiently use such information. However, despite the high relevance of the site-specific details of protein-protein interactions for understanding system behavior, rule-based models incorporating these details are not very common, because of difficulties in mining and using this information for modeling. To address this need, we developed 2 new capabilities within the Virtual Cell modeling and simulation framework. The first one is BioNetGen@VCell, which enables the user to create rule-based models and combine rules and reactions in a single interface. The other, PathwayCommons@VCell, enables the user to easily extract information from external pathway databases and create computational models of pathways. We describe the technology underlying these tools and present an example model that makes use of them.

2387-Pos  Board B524
A Statistical Overview of Experimentally Defined Anisotropic Displacement Parameters (ADP) Currently Deposited in the RCSB PDB
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The potential of X-ray crystallography to provide information for protein dynamics has not yet been extensively investigated. In addition to atom XYZ coordinates, typical PDB files provide the temperature factor, also referred to as isotropic B-factor, which describes the magnitude of atomic fluctuations. Currently, approximately 5% (~5500 unique pdb files) of the structures deposited in the RCSB PDB are high resolution (~< 1.4 Å). These high resolution structures generally provide an additional line for each atom entry, with the second containing a symmetric tensor with six integers that describes an ellipsoidal, instead of spherical, distribution of electron densities. Importantly, this asymmetric distribution of electron density reflects the anisotropic movement of the atomic nuclei. A diagonalization of this 3x3 tensor yields three eigenvalues (W1, W2, and W3), which define the distribution of electron density along those three prominent axes. The degree of anisotropy is defined as the ratio of W1 to W3 and varies between 0 (extremely anisotropic, like a rod or a pancake) and 1 (a sphere). Our preliminary analysis over the ADPs derived from ~1500 high resolution structures revealed that interestingly, the backbone carbon atoms are more anisotropic than the Cα and Cβ atoms. The Cα atoms show the lowest degree of anisotropy, and proceeding out along the side chain from Cα to C-e, the degree of anisotropy gradually increases. We also analyzed the trend of isotropic B-factors. Indeed, the value of isotropic B-factors increases outward from the backbone C to the C-e atom. In summary, we performed a statistical analysis over the ADPs of structures in the RCSB PDB, with the aim to obtain useful information in order to gain a better understanding of the physical basis of ADP.

2388-Pos  Board B525
Prediction of Functionally Linked Interface (FLIP) Regions in Residue Interaction Network (RIN) Models of Protein Structures
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Various cellular processes involve participation of proteins as monomers or oligomers. The formation of the oligomers is often related to their structural stability and interaction capabilities. Here, we continue our work on the characterization of the physico-chemical patterns of amino acid residues involved in quaternary interactions that form Functionally Linked Interfaces of Proteins (FLIPs). Proteins are represented as a network with residues as nodes and proximity between residues (both bonded and non-bonded interactions) being the edges (a residue interaction network or RIN). Our previous studies of RINs have shown that FLIPs can be distinguished from Functionally uncorrelated Contacts (FunCs) with ~74% accuracy, indicating residues show organizational differences in the interfaces of FLIPs and FunCs. In the current work, we identify threshold values of network centrality features that predictively distinguish FLIP, FunC, and non-interface regions of RINs.