CHEMICAL ENGINEERING

DISTINGUISHED YOUNG SCHOLARS SERIES

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Trying to move a field forward: method development for membrane protein modeling in the past, the present and the future

ABSTRACT: Membrane proteins are involved in a variety of essential cellular functions, comprise about 30% of gene products, and are targeted by over 50% of drugs on the market. They are extremely difficult to study by experimental methodologies, which is highlighted by the limited number of structures in the Protein Data Bank (PDB), accounting for only 2% of deposited structures. Computational structure prediction, modeling and design are therefore critical in facilitating our understanding of membrane protein structure and function (Koehler Leman et al., 2015).

The number of membrane protein prediction tools is on the rise and the quality of these tools increases in accordance with the database size of membrane protein structures for derivation and testing. Most of these methods are stand-alone tools that require their own implementation of membrane-specific score functions and representation of the membrane bilayer. Further, the user is required to become familiar with each tool, its prediction accuracies and file format conversions. In contrast, adapting existing soluble protein tools for membrane proteins has enormous merit in the development of new computational approaches.

One extensive tool for structure prediction, docking and design is the software suite Rosetta. In addition to the variety of prediction tools that are readily available for biomolecular modeling, Rosetta also includes widely-tested energy functions for soluble environments, which are a combination of knowledge-based and physics-based terms. Rosetta is further used for large-scale, highly parallel, high-throughput applications. It is developed by a consortium of laboratories known as the Rosetta Commons, including hundreds of scientists worldwide and licensed by over 20,000 academic users as well as many pharmaceutical companies, enabling the development of drug therapies worldwide. Rosetta is therefore ideally suited for extension to improve membrane protein modeling.

A few years ago, we created an implementation of a general platform for membrane protein modeling in Rosetta, termed RosettaMP. After two years of iterations between design, implementation, and testing, we published the manuscript describing this framework in PloS Computational Biology (Alford, Koehler Leman et al., 2015). RosettaMP includes a representation of the membrane bilayer and connects to the previously established high- and low-resolution score functions for the hydrophobic environment in the membrane. We showed the advantage of RosettaMP by implementing four proof-of-concept applications describing protocols for high-resolution refinement, prediction of DDG's of mutation, protein-protein docking, and assembly of symmetric complexes, all in the membrane environment. While improvement of these protocols and extensive benchmarking for each of them is a time-consuming task, we could show that RosettaMP could be easily combined with existing Rosetta protocols to create completely novel applications. Current and next steps are to expand and advance this functionality by various protocols for membrane protein modeling, such as high-resolution refinement of large proteins that can also be used for refinement of protein structures into cryo-EM density maps, domain assembly, prediction of the effect of mutations, ligand docking, protein design, and others, each with its own benchmarked application. RosettaMP therefore opens up a vast range of possibilities for membrane protein modeling applications that never existed before, and that are only limited by our imagination. Since membrane proteins only yield sparse data for structure determination, my focus is also on incorporation and simultaneous use of a range of experimental data (from NMR, EPR, CryoEM, mass-spec, mutational and cross-linking assays) for membrane protein modeling. An integrated approach will inform further experiments and hence facilitate structure determination of these notoriously difficult-to-study proteins. These structures are the cornerstone for our understanding of membrane protein function, origins of disease, and ultimately drug development and many new exciting developments are yet to come.

BIOGRAPHY: Dr. Koehler Leman did her undergraduate studies both at the University of Edinburgh in Scotland, UK and at the University of Leipzig in Germany, where she received her Master's degree in Physics. Her PhD work in Chemical and Physical Biology at Vanderbilt University focused on method development for membrane protein structure elucidation both experimentally in the lab of Charles Sanders, as well as computationally with Jens Meiler. On the experimental side, she focused on paramagnetic tagging of membrane proteins for NMR spectroscopy, while on the computational side she developed methods for secondary structure prediction and transmembrane span prediction. For her postdoctoral time, Dr. Koehler Leman moved to Johns Hopkins University to the lab of Jeffrey Gray to immerse herself in method development in the Rosetta software, where she developed a general framework for membrane protein modeling, which has been the basis for most of her work for the past 6 years. After her time at Hopkins, she joined the lab of Richard Bonneau at NYU and the Simons Foundation to continue developing methods for membrane protein modeling in Rosetta. She is now one of the main method developers in the Rosetta community who focuses on developing and improving applications for membrane protein structure prediction, docking and design. In her talk, Dr. Koehler Leman will provide insights into how structural biology of membrane proteins has changed in the past 15 years and how her past experience shapes her approach to method development for maximum impact in this field.

LECTURE 4:00 - 5:00 (PAA) A110
Happy Hour in Benson Hall Lobby Following

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