

FROM INTEGRATIVE STRUCTURAL BIOLOGY TO CELL BIOLOGY

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Zoom Details

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ABSTRACT

Integrative modeling is an increasingly important tool in structural biology, providing structures by combining data from varied experimental methods and prior information. As a result, molecular architectures of large, heterogeneous, and dynamic systems, such as the ~52 MDa Nuclear Pore Complex, can be mapped with useful accuracy, precision, and completeness. Key challenges in improving integrative modeling include expanding model representations, increasing the variety of input data and prior information, quantifying a match between input information and a model in a Bayesian fashion, inventing more efficient structural sampling, as well as developing better model validation, analysis, and visualization. In addition, two community-level challenges in integrative modeling are being addressed under the auspices of the Worldwide Protein Data Bank (wwPDB). First, the impact of integrative structures is maximized by PDB-Dev, a prototype wwPDB repository for archiving, validating, visualizing, and disseminating integrative structures. Second, the scope of structural biology is expanded by linking the wwPDB resource for integrative structures with archives of data that have not been generally used for structure determination but are increasingly important for computing integrative structures, such as data from various types of mass spectrometry, spectroscopy, optical microscopy, proteomics, and genetics. To address the largest of modeling problems, a type of integrative modeling called metamodeling is being developed; metamodeling combines different types of input models as opposed to different types of data to compute an output model. Collectively, these developments will facilitate the structural biology mindset in cell biology and underpin spatiotemporal mapping of the entire cell.

ABOUT SPEAKER



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Andrej Sali is Professor at the Research Collaboratory for Structural Bioinformatics Protein Data Bank, the Dept of Bioengineering and Therapeutic Sciences, the Quantitative Biosciences Institute (QBI), and the Dept of Pharmaceutical Chemistry, UCSF, USA received his BSc degree in chemistry from the University of Ljubljana, Slovenia, in 1987, working on the sequence-structure-function relationship of stefins and cistatins under the supervision of Professor Vito Turk; and his PhD from Birkbeck College, University of London, UK, in 1991, developing the MODELLER program for comparative modeling of protein structures under the supervision of Professor Tom L. Blundell. He was then a postdoc with Professor Martin Karplus at Harvard University as a Jane Coffin Childs Memorial Fund fellow, studying protein folding. From 1995 to 2002, he was an Assistant/Associate Professor at The Rockefeller University. In 2003, he moved to University of California, San Francisco, as a Professor of Computational Biology in the Dept of Bioengineering and Therapeutic Sciences, Dept of Pharmaceutical Chemistry, and California Institute for Quantitative Biosciences (QB3). He was recognized as Sinsheimer Scholar (1996), an Alfred P. Sloan Research Fellow (1998), an Irma T. Hirschl Trust Career Scientist (2000), the Zois Award of Science Ambassador of Republic of Slovenia (2007), a Fellow of International Society for Computational Biology (2014), Jubilee Professor of Indian Academy of Sciences (2017), Bijvoet Medal recipient (2018), and member of National Academy of Sciences of USA (2018). He has been an Editor of Structure since 2002. He is also a Founder of Prospect Genomix that merged with Structural Genomix (2001); and of Global Blood Therapeutics (2012). His lab develops and applies modeling methods for computing structures of biomolecular assemblies that are consistent with all available information from experimental methods, physical theories, statistical inference, and prior models. This integrative approach maximizes accuracy, precision, and completeness of the resulting models. The Integrative Modeling Platform (IMP) has been used to determine the several macromolecular assemblies including the 550-protein yeast Nuclear Pore Complex, the 19-protein 9S subunit of the 26S proteasome. This research was also a major contributing factor to the establishment of PDB-Development, the nascent worldwide Protein Data Bank archive for integrative structures. Finally, the integrative modeling approach is being expanded to the mapping of biomolecular networks and spatiotemporal modeling of entire cellular neighbourhoods.