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Dr. Petra Fromme received her BS and MS in biochemistry from the Free University of Berlin, received her Ph.D. in chemistry and did her habilitation in physical chemistry at the Technical University of Berlin. She was an Assistant and Associate Professor at the Max Volmer Institute before joining Arizona State University as a full Professor in the School of Molecular Sciences. She is an affiliated member of the Department of Physics, and is member of the graduate faculty in the Plant Biology and Biological Design graduate programs. She was awarded the Paul V Galvin Professorship in 2012 and named as Regents' Professor in 2015. She was appointed by ASU President Michael Crow as the director of the Biodesign Center for Applied Structural Discovery in 2014. Her research interests are in studying the structure-to-function relationship of membrane proteins involved in bioenergy conversion and infectious diseases. She was an integral part of a team of ASU researchers and international colleagues that developed the technique of serial femtosecond nanocrystallography for analyzing proteins using high-intensity X-ray Free Electron Lasers (XFEL). She has vast experience unraveling the structure and function of photosystem I and II proteins and ATP synthase, which are each crucial for solar energy conversion in our biosphere and her work is now also focused on medical important membrane proteinin infectious diseases and cancer. She has published over 150 articles and is internationally recognized as a leader in photosynthesis, protein macromolecular crystallography using synchrotrons and protein nanocrystallography using XFELs.

Introduction

Structural biology unravels the molecular basis of the biology of the cell. Knowledge of the structure and dynamics of proteins and their complexes is the key to understanding their functions and evolution as well as to modulating their functions. As a result, structural biology also has many applications in biomedicine and biotechnology. This issue reviews some of the major recent technical advances in structural biology.

Single molecule diffraction with XFELs, Barty

X-ray structure determination by single particle diffraction has motivated the development of X-ray Free Electron Lasers (XFELs). However, breakthrough discoveries in structural biology with XFELs are still based on crystals, which diffract in the ultra-bright femtosecond X-ray beam before they are destroyed. Barty describes single molecule X-ray diffraction that may be able to characterize structure and dynamics at physiological temperatures, thus revolutionizing structural biology. The challenges that have to be overcome to make single particle X-ray diffraction possible are also discussed.

Single particle cryo-EM, Nogales

Structures of single molecules can be determined in vitreous ice under cryogenic conditions by cryo-electron microscopy (EM). Images result from interaction between the sample molecules and electrons. 3D structure determination is based on class averaging of a large number of randomly oriented molecules, followed by single particle 3D structure reconstruction. Nogales describes recent technological advances that have dramatically increased the resolution limit of cryo-EM, by using a human transcription preinitiation complex as an example. The remaining challenges and limitations of cryo-EM are also discussed.

Micro-ED, Gonen and Nanenga

Microcrystal Electron Diffraction (micro-ED) is a new technique that is based on electron diffraction of small 3D nanocrystals. A rotational series of electron diffraction patterns is taken at ultra-low doses from a single frozen crystal that contains approximately 1 million unit cells; up to 90 electron diffraction patterns can be collected from each crystal. Despite the extremely low dose rate, high resolution diffraction patterns can be obtained. Gonen and Nannenga discuss the development of micro-ED, data collection and processing, as well as challenges and future improvements.

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Andrej Sali received his BSc degree in chemistry from the University of Ljubljana, Slovenia, in 1987; and his PhD from Birkbeck College, University of London, UK, in 1991, under the supervision of Professor Tom L. Blundell, where he developed the MODELLER program for comparative modeling of protein structures. He was then a postdoc with Professor Martin Karplus at Harvard University as a Jane Coffin Childs Memorial Fund fellow, studying lattice Monte Carlo models of protein folding. From 1995 to 2002, he was first an Assistant Professor and then an Associate Professor at The Rockefeller University. In 2003, he moved to University of California, San Francisco, as a Professor of Computational Biology in the Department of Bioengineering and Therapeutic Sciences, Department of Pharmaceutical Chemistry, and California Institute for Quantitative Biosciences (QB3). He was a Sinsheimer Scholar (1996), an Alfred P. Sloan Research Fellow (1998), an Irma T. Hirschl Trust Career Scientist (2000), the recipient of the Zois Award of Science Ambassador of Republic of Slovenia (2007), and elected a Fellow of International Society for Computational Biology (2014). He has been an Editor of Structure since 2002. He develops and applies computational methods for determining and modulating structures and functions of proteins and their assemblies.

SAS, Trewhella

Small-angle scattering (SAS) experiments using either X-rays or neutrons can characterize the coarse shapes of proteins and their complexes in solution. Trewhella describes applications of this approach, focusing on the contributions of SAS to integrative structure determination, where shape information from SAS data can be complementary to other types of structural information, such as distances from NMR spectroscopy and component structures from X-ray crystallography. Neutron scattering with contrast variation is highlighted as a particularly informative variant of a SAS experiment. To maximize the impact of SAS data, scientists are developing common representations, validations, and archives for the SAS data and SAS-based models.

Native MS, Robinson

Native mass spectrometry (native MS) can measure the stoichiometry and topological arrangements of protein complexes. Robinson describes recent technical advances using case studies that demonstrate the relevance and impact of the method, with a focus on the determination of the native stoichiometry of large protein complexes. The strong synergy of native MS with other structural biology methods is highlighted; for example, native MS can facilitate sample preparation for X-ray crystallography and cryo-EM.

FRET, Seidel et al.

Single molecule Förster Resonance Energy Transfer (FRET) probes macromolecular structure and dynamics. Seidel *et al.* review recent methodological developments in integrative structure modeling of proteins by satisfying spatial restraints on networks of FRET pairs. A workflow is presented that optimizes and automates experiment planning and modeling based on the FRET data. The workflow is illustrated by accurately resolving three protein conformers based on a realistically simulated single-molecule experiment. This integrative approach can be expanded by incorporating additional data from complementary spectroscopic and imaging techniques.

Molecular dynamics, Sansom et al.

Molecular dynamics simulations can provide atomic details of motions of proteins on the millisecond time scale. Sansom *et al.* review the application of molecular dynamics to membrane proteins and their interactions with specific lipids, at both atomic and coarse-grained resolutions. Larger-scale simulations reveal crowding and clustering of proteins in the lipid bilayer, resulting in slow and anomalous diffusional dynamics. Current methods allow near atomic resolution simulations of such systems as small membrane organelles and enveloped viruses, revealing key aspects of their structure and functionally important dynamics.

PDB, Berman et al.

The global Protein Data Bank (PDB) was the first open-access digital archive in biology that arguably shaped the structural biology of today. Berman *et al.* describe the history and evolution of the PDB, including the ways in which structural data and information are collected, curated, validated, archived, and disseminated by the Worldwide Protein Data Bank organization. The activities of the PDB are guided by the standards and policies established by the structural biology community. These standards and open access to the PDB have been instrumental in the development of structural biology, including structural bioinformatics, as well as in maximizing the impact of structural biology on biology.

Conclusion

The methodological developments described in this issue allow structural biology to push the envelope in several directions, including towards larger systems, systems that are heterogeneous and/or dynamic, samples that consist of single molecules, and systems that cannot be described based on data from a single method. The resulting structures are increasingly more accurate, precise, complete and efficiently determined. As a result, structural biology contributions to biology and medicine will continue to expand.