A celebration of structural biology

The Protein Data Bank (PDB) is the primary data resource for structural biology. On its 50th anniversary, we celebrate the future of this ever-growing field.

The structural biology community is celebrating a true milestone: the 50th anniversary of the PDB. In 1971, the PDB was established as the central archive for experimentally determined macromolecular structure data. In these five decades it has become an integral resource for the structural biology community and has been instrumental in driving not only basic biological research but also drug discovery and development efforts. As the name suggests, proteins and protein complexes constitute the majority of structures in the PDB, but it has also become the standard structure repository for other macromolecules, including DNA, RNA and glycans. As the first open-access digital data resource in biology, the PDB has been a real trendsetter by serving as an inspiration for other open-access data sharing platforms, standardized data formats and practical visualization platforms.

The field of structural biology has seen tremendous growth over the decades as new technologies and methods have come into prominence. Newer techniques continue to push the limits of achievable atomic resolution and observable structural size and complexity. We thought this anniversary was the perfect opportunity to celebrate this progress and to take stock of upcoming trends and future directions. In collaboration with *Nature Structural & Molecular Biology* (also see their editorial), we invited a number of researchers—developers as well as expert users—working with various structural biology methods to comment on the current challenges in their field and their vision for the future.

Kicking off our focus issue is a Comment from Jasmine Young and colleagues, detailing the role of biocurators in maintaining the wwPDB and supporting the scientific community. For *Nature Structural & Molecular Biology*, Helen Berman writes about the community efforts—some that predate the inception of the PDB, others that have continued over the past 50 years—that were instrumental in shaping the resource as community needs evolved.

Historically, X-ray crystallography was the dominant method for structure elucidation, followed by nuclear magnetic resonance. The past decade, however, has seen tremendous advances in alternative approaches that are further increasing our capability to explore previously intractable molecules. In particular, serial femtosecond crystallography using X-ray free-electron lasers enables structure determination using crystals ranging in size from a few micrometers to a few hundred nanometers. These experiments can also capture intermediate structural states and structures of radiation-sensitive proteins, increasing the breadth of our understanding of protein function. In this issue, Aina Cohen discusses the future of macromolecular crystallography, new X-ray sources and time-resolved methods. New methods are also enabling exciting studies of biomolecular dynamics. Dorothee Kern discusses the need for better approaches to quantitatively probe the conformational dynamics and the functional energy landscapes of macromolecules.

Cryo-electron microscopy (cryo-EM), formerly a specialized, low-resolution technique, now allows high-resolution structure determination by directly imaging molecules without the need to crystallize them first. This has an added benefit of allowing researchers to study more complex assemblies and membrane proteins that typically elude crystallization. Kutti R. Vinothkumar highlights new developments in cryo-EM and considerations for establishing new facilities. Rhiju Das discusses developments in cryo-EM and how the technique is uniquely placed to help elucidate RNA-only 3D structures, which have so far been understudied. This issue also features a Review of sample preparation methods in cryo-EM by Peter Peters and colleagues. Cryo-electron tomography is an emerging technology that allows us to image molecules in their native cellular environment at nanometer resolution and solve molecular structures. Xueming Li discusses the practical and technical details of such studies while Michael Wozny and Wanda Kukulski describe the cellular complexity and the spatial and temporal context that may be elucidated by this technology.

Computational structure prediction and modeling have routinely provided structure and dynamics information complementary to experiment, often at time scales difficult to explore experimentally. Dmitry Korkin and colleagues discuss the need for improvements in de novo structure prediction approaches. In particular, they present an analysis of how de novo predicted structures of the SARS-CoV-2 viral proteins have fared in terms of accuracy when compared to experimentally determined structures. Integrative approaches, combined with advanced computational methods, are allowing structural biologists to model protein structures on much larger scales than possible with any one technique. Alexandre Bonvin highlights how integrative structure modeling helps bring together information from different sources to assemble the pieces of a complex molecular machine. Information from methods such as cross-linking mass spectrometry and deep mutational scanning provide key information about structure and interactions. The PDB also is gearing up for the future by developing guidelines and standards for deposition and reporting of integrative structural models. Zaida Luthey-Schulten describes how whole-cell models that aim to combine not only structural but experimental molecular biology data will enable systems-level integrative modeling. Although still in the early stages, whole cell computational simulations would ultimately allow a holistic understanding of cellular processes.

Nature Structural & Molecular Biology features a piece by David Goodsell discussing art as a tool for science and for structural biology in particular, in which artistic rendering of three-dimensional images of molecules have been both inspirational and necessary for hypothesizing the shape, size and complementary interactions of biomolecules. This joint focus also features a special cover! *Nature Structural & Molecular Biology* and *Nature Methods* have split a painting from Goodsell depicting the transport of an antibody-filled vesicle through the cross-section of a B cell and the release of antibodies from another vesicle into blood plasma. There are many facets within the field of structural biology, and often results from different approaches and techniques need to be brought together to make the higher level biological 'picture' apparent. Putting these covers together completes this picture. ❐

Published online: 7 May 2021
https://doi.org/10.1038/s41592-021-01163-x