

Progress in macromolecular crystallography

The importance of crystallography was recently highlighted by the declaration by UNESCO of the Year of Crystallography 2014. This presented a good occasion to recall the advances of macromolecular crystallography achieved since its birth, more than half a century ago. This branch of structural biology is very highly interdisciplinary and encompasses elements of physics, chemistry, biology, and medicine, relying to a large extent on advanced computing. Indeed, the experiments are based on physics of diffraction of X-rays from protein and nucleic acid crystals, which are obtained biochemically or by genetic engineering from biological materials. The results are largely relevant to medical and pharmaceutical applications.

Max Perutz, a pioneer of macromolecular crystallography, spent 22 years on solving the crystal structure of hemoglobin, a red component of blood, and explained how this protein acts as carrier of oxygen from lungs to all other body tissues. With his coworkers he established grounds for various methods that are used until now by all protein crystallographers. However, these methods were enormously advanced within last about 50 years. This progress is in large part due to advancements in related sciences. X-ray diffraction experiments can now be performed at synchrotron or X-ray laser facilities instead of sealed tube sources first introduced by Röntgen. The proteins can be obtained in sufficient amounts by genetic engineering instead of from the original biological material. Many processes, such as protein and nucleic acid purification, crystallization and handling can be precisely done by automatic robots instead of relying on mundane human efforts. Last but not least, the amazing successes of macromolecular crystallography could not be achieved without the enormous progress in the capacity and speed of computers, which did not even exist when Perutz started his investigation of hemoglobin. A majority of the effort in solving crystal structures of macromolecules is spent on performing various elaborate computer calculations. The extensive use of computer graphics permits the display and manipulation of structural models in three dimensions, which is indispensable for detailed interpretation of the interactions between various reactive molecules.

The achievements of macromolecular crystallography have been in the forefront of science in general, as documented by a large number of Nobel Prizes. In 1962 Perutz and Kendrew were so honored by their work on oxygen-carrying proteins, hemoglobin and myoglobin. In the same year Crick, Watson, and Wilkins received Nobel Prizes for elucidation of the structure of DNA that explained how genetic information is passed between generations of all living organisms. Several years and Nobel Prizes later, in 2009, Yonath, Steitz and Ramakrishnan were awarded the Nobel Prize for determining the structures of ribosomes, which are organelles present in all cells of bacteria, plants and animals where all proteins essential for life are synthesized. In 2012 Kobilka and Lefkowitz received the Nobel Prize for the elucidation of the structure of the G-protein-coupled receptors (GPCR), signal carriers through the cell membrane, a class of multiprotein complexes, which are the target of large number of medical drugs. It can be mentioned that the development of drugs active against AIDS was highly reliant on the availability of crystal structures of proteins from the HIV virus.

Crystallography is the principal method for evaluation of three-dimensional structures of proteins and nucleic acids and their complexes. Almost 120,000 structures of macromolecules are currently stored in the Protein Data Bank, of which 90% were solved by X-ray crystallography. Due to their high medical relevance, macromolecular crystallographic laboratories are active not only in academic institutions, but also in many pharmaceutical companies. This branch of science continues to blossom and many further achievement, perhaps worthy Nobel Prizes, may be expected in the future.

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