Frank DiMeo

MacCHESS

A COLLISION OF PHYSICS AND BIOLOGY

Understanding the Fundamental Process of Life

Synchrotron-generated x-ray radiation has had a major impact on our understanding of many of the most fundamental processes of life. Among the earliest group of researchers to take advantage of synchrotron radiation in addressing biological questions was a community of scientists called structural biologists. These biologists use the diffraction of x-ray radiation from protein crystals to determine the three-dimensional shapes of proteins. This experimental approach, commonly referred to as x-ray crystallography, has proven to be extremely valuable, because by knowing the shape of a protein in three dimensions, it then becomes possible to understand how the protein functions. Given that proteins are responsible for virtually every activity required for the normal functions of cells (the basic building blocks of life), this is extremely valuable information. Perhaps even more important, however: by knowing the three-dimensional shape of a protein, researchers can better understand exactly what goes wrong when its shape or structure changes. Such changes, which occur because of a mutation in the gene that codes for the protein, often alter the normal cellular function of the protein and are responsible for a large array of pathological disorders and diseases.

Proteins and Protein Complexes

During the past 10 years, the application of synchrotron radiation to the solution of protein structure has undergone a steady and impressive evolution: from the determination of the three-dimensional structures of individual proteins to the more challenging structures of protein complexes (proteins typically function in cells by binding to and altering the activity of other proteins), to the even more formidable undertaking of solving the structures of large complexes consisting of many proteins. These ever expanding achievements in x-ray crystallography are providing answers to the most important questions in biology, including how the brain functions, how we develop from single cells to the nearly incomprehensible array of cells that comprise a human being, and why we age and eventually die. There is no other place where these remarkable accomplishments are more prominently on display than at the macromolecular crystallography resource at Cornell's MacCHESS.

MacCHESS can be proud of a number of truly spectacular successes throughout its history and continuing right up to the present. Among these are the recent accomplishments of Tom Steitz and colleagues from Yale University in determining the

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Jon Reis

Brian Crane

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three-dimensional structures of the macromolecular complex that is responsible for assembling the basic components of genes (polymerases), as well as the macromolecular factory (ribosomes) that takes these genes and translates them into proteins. Another outstanding example comes from the work of Rod MacKinnon and his students from the Rockefeller University, who produced the first picture of the protein complexes, called ion channels, that are responsible for controlling the flow of potassium across the outer membranes of cells. Perhaps equally remarkable has been the successful determination of the structures of various viruses, the biological culprits that are responsible for a number of human maladies ranging from the common cold to AIDS. This work was pioneered at MacCHESS by Michael Rossman from Purdue University, beginning several years ago, and has more recently resulted in extraordinary progress in the understanding of the fundamental workings of viruses, thanks to the x-ray crystal structures produced at MacCHESS by Steve Harrison and his colleagues from Harvard University.

SR and New Directions in Biology

The continuing merger between physics and biology is also leading to an interesting phenomenon in the scientific community. An ever-increasing number of investigators who lack rigorous training in the physical sciences or structural biology are now taking great advantage of synchrotron radiation to chart new directions in biology and the biomedical sciences. Indeed, Rod MacKinnon represents a prototype of such an investigator, as his prior training was in medicine. It was the generous early support of Sol Gruner, director of CHESS, and the MacCHESS staff that enabled MacKinnon, a physician, to launch his landmark experiments using synchrotron radiation to solve the structures of ion channels and paved the way for what would become extraordinary accomplishments.

For a number of years, the overarching interests of my research group at Cornell, Molecular Medicine/Chemistry and Chemical Biology, have been understanding and identifying the regulatory cues that dictate whether cells grow normally or become cancerous. During efforts to assemble the genes and proteins that regulate how cells grow, however, it became clear that detailed structural information on how these proteins function and bind to their signaling partners was absolutely essential. Aided by the MacCHESS staff and facility, students from our laboratory gained the necessary training to solve the three-dimensional structures of a number of proteins and protein complexes relevant to cancer. This information is now elucidating new strategies for therapeutic intervention.

Cornell has many examples of how exciting new advances in biology and the possibilities for novel therapeutic approaches are emerging from taking advantage of MacCHESS. Quan Hao, director of MacCHESS, and his colleagues are solving the three-dimensional structures of proteins that play essential roles in the immune response and are obtaining information that may relate to AIDS. The laboratories of Brian Crane and Steven Ealick, Chemistry and Chemical Biology, are using synchrotron radiation to obtain structural information about proteins that are essential to the basic survival of bacteria, providing what is certain to be extremely valuable information for designing new drugs to combat pathogenic organisms.

Watching Cellular Machines Work

The future holds even more exciting possibilities. Scientists can now dream of seeing single protein molecules go through their many molecular rearrangements, which occur on a time scale of fractions of seconds and culminate in essential biological activities. Researchers may even anticipate being able to watch the massive protein complexes that function as cellular machines produce the signals that form the very essence of life. With the application of new methods to harness and utilize energy—for example, through the development of the ERL—these experiments, which a few years ago seemed several decades beyond reach, will soon become reality.

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