

What is structural biology?

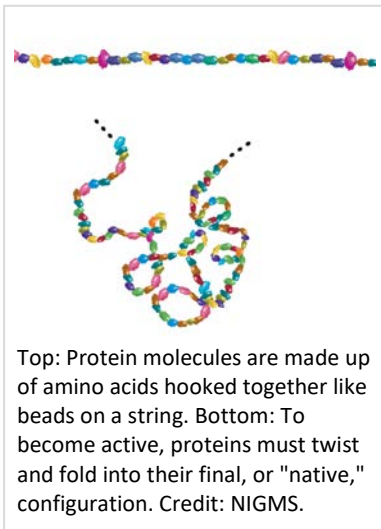
Structural biology is the study of how biological molecules are built. Using a variety of imaging techniques, scientists view molecules in three dimensions to see how they are assembled, how they function, and how they interact. That has helped researchers understand how the thousands of different molecules in each of our cells work together to keep us healthy. Structural studies have also shown how misshapen molecules make us sick, and as a result, these studies have prompted new treatments for many diseases.

What are molecules?

Molecules are groups of two or more atoms held together by chemical bonds. Molecules include DNA, RNA, proteins, carbohydrates (sugars), and lipids (fats). Structural biologists are particularly interested in proteins because they do so much of the work in the body. Increasingly, biologists are investigating large molecules made up of combinations of RNA and proteins, called RNA-protein complexes.

What are proteins?

Proteins are molecules that contribute to virtually every activity in the body. They form hair and fingernails, carry oxygen in the blood, allow muscles to move, and much more.



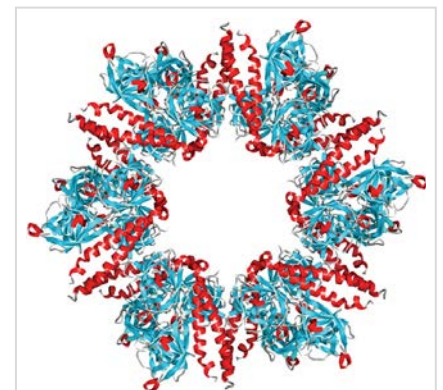
Top: Protein molecules are made up of amino acids hooked together like beads on a string. Bottom: To become active, proteins must twist and fold into their final, or "native," configuration. Credit: NIGMS.

What are proteins made of?

Proteins are made of long strands of small molecules called amino acids. There are 20 amino acids found in nature. Each protein contains a unique combination of a few dozen to many thousands of amino acids. Some proteins consist of multiple amino acid strands wound together.

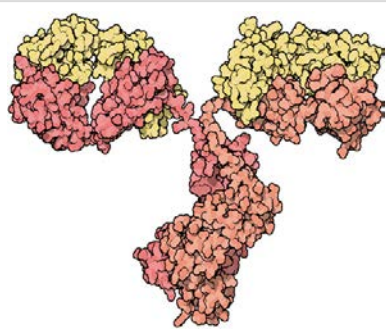
How does a protein get its shape?

Even though proteins are strings of amino acids, they do not remain in a straight line. The strands twist, bend, and fold into specific shapes. The way they fold depends in part on the way the amino acids interact with each other. Some sections of proteins form standard "motifs": corkscrew-like coils called alpha helices and flat sections called beta sheets.



A mix of alpha helices (red; curled ribbon forming a six-sided star) and beta sheets (blue; thinner, tangled strands). Credit: RCSB Protein Data Bank.

Researchers can easily determine a protein's amino acid sequence. The trick has been figuring out how and why the proteins fold. Scientists are beginning to solve that puzzle with research into how amino acids interact, and they are using powerful new computer programs that help predict protein motifs. Researchers are even starting to design their own brand-new proteins that perform specific jobs. This new work helps scientists understand not only how proteins fold but also how they misfold and malfunction in diseases such as Alzheimer's and cystic fibrosis. Knowing more about these processes might allow researchers to design new treatments.



An image of an antibody, an immune system protein that rids the body of foreign material, including bacteria. Credit: David S. Goodsell, The Scripps Research Institute.

Why does a protein's shape matter?

A protein's structure allows it to perform its job. For instance, antibodies are shaped like a Y. This helps these immune-system proteins bind to foreign molecules such as bacteria or viruses with one end while recruiting other immune-system proteins with the other. DNA polymerase III is donut-shaped. This helps it form a ring around DNA as it copies its genetic information. And proteins called enzymes have grooves and pockets that help them hold onto other molecules to speed chemical reactions. Misfolded, or misshapen, proteins can cause diseases. They often stop working properly and can build up in tissues. Alzheimer's disease, Parkinson's disease, and cystic fibrosis are examples of diseases caused by misfolded proteins.

What kinds of proteins are there?

There are many different kinds of proteins. For example, many proteins are enzymes that aid biochemical reactions. Others have shapes or specific functions that help cells hold their shape and move, as described in the previous answer. Another type, called transporter proteins, are embedded in the cell's outer membrane and form channels that help vital substances such as sodium or potassium pass into or out of the cell.

How do scientists use protein structures to develop new drugs?

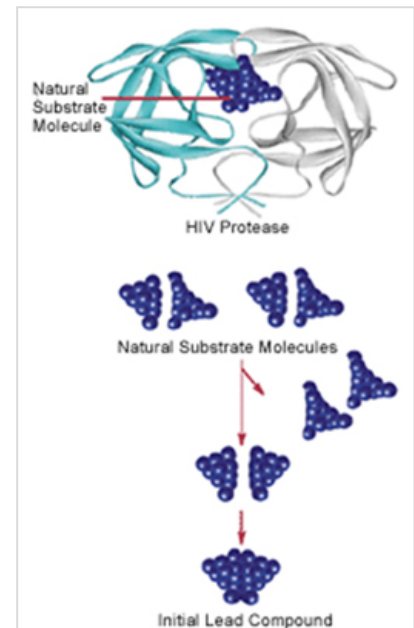
Drugs typically work by either blocking or supporting the activity of specific proteins in the body. Using an approach called structure-based drug design, scientists can make a template for a protein and use that blueprint for creating new medicines. They start with a computerized model of the protein structure they're interested in studying. For example, the computer model would allow researchers to examine how two proteins work together. Then, if scientists want to turn off one protein, they would try to design a molecule that would block or alter that interaction.

What's an example of a medicine developed using structure-based drug design?

Researchers used structure-based drug design to develop some anti-HIV drugs. HIV protease is an enzyme that keeps the virus alive. Knowing its structure allowed researchers to determine the kinds of molecules that could stop HIV protease from working. Scientists used computer models to fine tune molecules that could halt virus production. This work led to medicines called protease inhibitors.

How do scientists determine protein structures?

Researchers use several imaging techniques to determine the structure of proteins and other complex molecules. Cryo-electron microscopy (cryo-EM) allows scientists to "see" individual proteins as well as larger structures such as molecular complexes (groups of proteins that combine and function as a unit), viruses, or organelles (specialized structures within the cell that perform specific functions). X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy also make it possible for researchers to view proteins. To date, researchers have used these techniques to unravel the structure of more than 122,000 proteins. The Protein Data Bank stores these structures and gives scientists access to them. They are accessible at the [RCSB Protein Data Bank](https://www.rcsb.org/).



Knowing that HIV protease—an enzyme that breaks down HIV—has two symmetrical halves, pharmaceutical researchers initially attempted to block the enzyme with symmetrical, naturally occurring small molecules. They made these by chopping in half molecules of the natural substrate, then making a new molecule by fusing together two identical halves of the natural substrate. Credit: NIGMS.

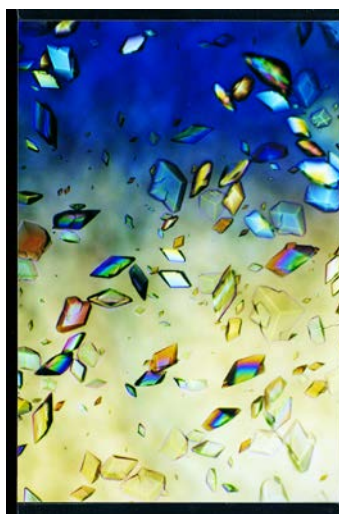
What is cryo-EM, and how does it work?

In cryo-EM, researchers rapidly freeze a cell, virus, molecular complex, or other structure so that water molecules do not have time to form crystals. This preserves the sample in its natural state. Scientists use an electron microscope to blast the frozen sample with an electron beam. This creates a two-dimensional projection of the sample on a digital detector. By creating hundreds of projections of the sample from many different angles and then taking the average of these angles, scientists generate a three-dimensional model of its structure. Recent advances in cryo-EM provide highly detailed images of proteins and other biological structures, including larger structures such as RNA-protein complexes.



Cryo-EM can be used to determine the structures of large molecular complexes such as the origin recognition complex (ORC). The ORC recognizes and binds DNA to start the process that copies the cell's genetic material prior to cell division. Credit: Huilin Li, Brookhaven National Laboratory, and Bruce Stillman, Cold Spring Harbor Laboratory.

What is X-ray crystallography, and how does it work?



Structural biologists create crystals of proteins, shown here, as a first step in X-ray crystallography, which can reveal detailed, three-dimensional protein structures. Credit: Alex McPherson, University of California, Irvine.

X-ray crystallography shoots a beam of X-rays through a tiny solid crystal made up of trillions of identical protein molecules. The crystal scatters the X-rays onto an electronic detector, similar to the way images are captured in a digital camera. A computer gauges the intensities of the scattered X-rays to assign a position to each atom in the crystallized molecule. The result is a three-dimensional digital image. This method has been used to determine more than 85 percent of known protein structures.

What is NMR spectroscopy, and how does it work?

NMR spectroscopy works using the natural magnets—the nuclei of certain atoms—inside proteins. Those natural cellular magnets interact with a big magnet inside the NMR machine. The big magnet forces the protein's magnets to line up. Researchers then blast the sample with a series of split-second radio-wave pulses and observe how the protein's magnets respond. Scientists use several sets of these NMR blasts and combine the data to get a more complete picture



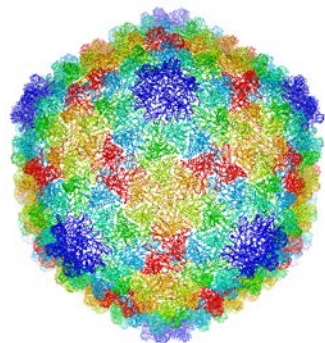
This is a machine used to do NMR spectroscopy. Most of these machines use magnets that are 500 megahertz to 900 megahertz. This magnet is 900 megahertz. Credit: Varian NMR Systems.

of the protein. Although X-ray crystallography can examine larger proteins than NMR is of the protein. Although X-ray crystallography can examine larger proteins than NMR is able to do, NMR technology can study proteins immersed in liquid solutions. In contrast, X-ray crystallography requires that proteins be organized into crystals.



New technology is beginning to allow researchers to progress from creating static pictures of proteins and other molecules to making movies of their actions.

Images provide snapshots of what these cellular elements are doing at specific points in time. Although they supply valuable information, these still pictures don't capture how proteins and other molecules inside cells are constantly moving and changing, folding and unfolding as they interact. Understanding this dynamic system is critical to unlocking how life works. In addition, there is a whole class of proteins, called intrinsically disordered proteins, that do not hold a specific shape. Their shape adapts to what's going on inside the cell, making it nearly impossible to take a still picture of them.



An atomic-scale model of a virus that infects the Salmonella bacterium. Credit: C. Hryc and the Chiu Lab, Baylor College of Medicine.

Scientists are now using powerful computer models to make molecular movies so they can see the full range of proteins in live action. By feeding in information from various imaging techniques about how amino acids and other building blocks interact, scientists can create moving pictures. Such movies help researchers understand how proteins work in their natural state and allow them to design highly specific drugs.

What does the future hold for structural biology?

Researchers on the frontier of structural biology are merging all of the imaging techniques—X-ray crystallography, NMR, Findings Magazine and cryo-EM. This allows them to create a more precise map of what proteins and other

molecules look like and how they interact. Scientists can create a single image that zooms in to see specific proteins and also zooms out to see how they interact within the larger cellular structure. In addition to combining existing techniques, scientists are developing ever more powerful methods. For example, new X-ray lasers allow insights into processes that occur in less than one tenth of a trillion of a second, much faster timescales than that captured by other sources of X-rays.

Scientists use super-efficient methods to determine protein structures more quickly than ever before. They also use sophisticated techniques to predict three-dimensional structures of proteins. And they use high-powered computer models to design and create new proteins not found in nature that have useful functions, such as discovering and combating disease. This work will continue to increase our understanding of the diverse roles molecules play in biology and to spur advances in medicine.

NIGMS is a part of the National Institutes of Health that supports basic research to increase our understanding of biological processes and lay the foundation for advances in disease diagnosis, treatment, and prevention. For more information on the Institute's research and training programs, see <https://www.nigms.nih.gov>.

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