



For his pioneering work in the determination of atomic structure of a macromolecule by electron microscopy (EM). Henderson determined the first atomic structure of a 2-D protein crystalline array (bacteriorhodopsin) by EM. His identifications of the key bottlenecks for obtaining high-resolution EM structures has guided subsequent efforts to revolutionize single particle cryoEM for structural biology research at the atomic level.

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To know how a molecule works within a cell, scientists first need to figure out the complex arrangement of atoms that make up its structure. For decades, this has been done with X-ray crystallography: A protein is coaxed into crystal form, then blasted with X-rays that bounce off the atoms, forming patterns that guide researchers to the eventual structure. But many important molecules have resisted crystallization. And even after crystallization, X-ray diffraction may not reveal a molecule's structure. This is what happened with bacteriorhodopsin—a light-driven proton pump found naturally as 2-D crystals in the membrane of Archaea, which Henderson and colleague Nigel Unwin tackled in 1973.

They turned instead to electron microscopy. That technique usually requires a stain that can obfuscate details, and it had never before been used to determine the molecular detail of a protein. But Henderson and Unwin realized that by placing unstained 2-D crystals on a thin carbon support on a metallic grid, they did not need the stain and could figure out the protein's structure. Their map of bacteriorhodopsin, published in 1975, was a first for the field. Work over the next 15 years successfully identified and overcame the bottlenecks leading to determination of the high-resolution structure in 1990.

In the 1980s and 1990s, a new method emerged for determining protein structure: cryoEM. In this technique, proteins are flash-frozen by plunging into liquid ethane then imaged with electron microscopy. But due to limitations, cryoEM remained a niche method until Henderson and others developed better sensors for electron microscopes, as well as better software for the system. These developments have vastly improved cryoEM and the method has now replaced X-ray crystallography as the preferred technique for determining protein structures.