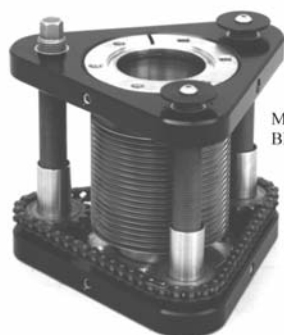


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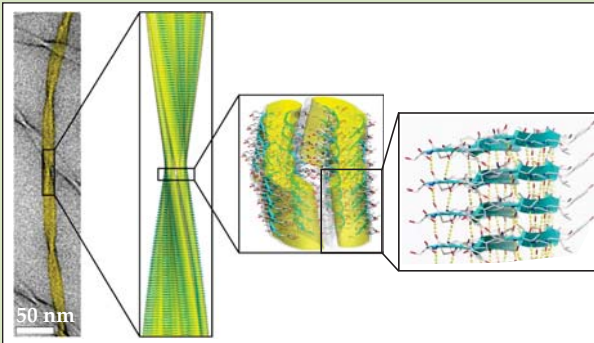
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An atomic view of an amyloid fibril

Protein folding, the spontaneous transformation of a linear chain of amino acids into a functional three-dimensional shape, is critical to life as we know it. Protein misfolding, by contrast, can lead to disease. Many of our most feared diseases, including Alzheimer's and Parkinson's, are associated with a particular misfolding phenomenon, in which many copies of a misfolded protein assemble into long, tough, unbranched strands called amyloid fibrils. Curiously, the amino-acid sequences of amyloid-forming proteins don't seem to have much in common, and even proteins not associated with any disease have been coaxed into forming amyloid fibrils in the lab.

The fibrils' molecular structure has long been a mystery. They don't dissolve or form regular crystals, so they can't be analyzed by solution-based nuclear magnetic resonance (NMR) or x-ray crystallography. But some features of the structure are known. As early as 1968, it was observed that a key amyloid structural motif was the β sheet, an array of short peptide chains, called β strands, lined up side by side.¹ In 2005 David Eisenberg (UCLA) and colleagues reported that short peptide molecules—just four to seven amino



acids long—could be made to assemble into amyloid-like microcrystals that were amenable to x-ray diffraction. They found that the β sheets were always arranged into closely bound pairs, like adjacent pages of a book, but that the sheets' relative orientation—face to face

or face to back, right-side up or upside down—depended on the specific amino-acid sequence.² Around the same time, advances in solid-state NMR allowed that technique to offer details of small-scale amyloid structure. (See the article by Clare Grey and Robert Tycko, PHYSICS TODAY, September 2009, page 44.)

Now an international team led by Christopher Dobson of the University of Cambridge in the UK has, for the first time, determined the atomic-resolution structures of entire amyloid fibrils, made from an 11-amino-acid peptide.³ The researchers obtained the structures by combining data from five techniques that view the fibril at different but overlapping length scales. Solid-state NMR gave them high-resolution structures of the β -sheet pairs, which were oriented face to back. The rightmost panel of the figure shows one such pair of vertically oriented sheets, viewed nearly edge on, with each of its constituent β strands represented by a thick teal arrow. Cryoelectron microscopy gave them a larger-scale map of each fibril's electron density. By superimposing the NMR structure on the electron-density maps, they found that each fibril was composed of four, six, or eight β -sheet pairs, arranged in a rectangular array. (The middle two panels show a fibril comprising six such pairs, with its cryoelectron microscopy electron-density envelope shown in yellow.)

Although not as informative as x-ray crystallography, x-ray fiber diffraction offered constraints on key distances in the β sheet's repeating structure. Transmission electron microscopy (leftmost image) and atomic force microscopy provided images of whole fibrils and fibril populations—and confirmed that the fibrils came in three discrete sizes.

The researchers expect that fibrils made from longer amino-acid sequences would be subtly different in some of their structural details. But on the smallest scale, the β sheets are held together by hydrogen bonds between the peptide backbones, which are common to all proteins. That universality helps to explain why so many different proteins form amyloid fibrils.

Johanna Miller

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