AMYLOID DISEASES AND NANOSCIENCE: THE KINETICS OF FIBRILLAR PEPTIDE EVOLUTION

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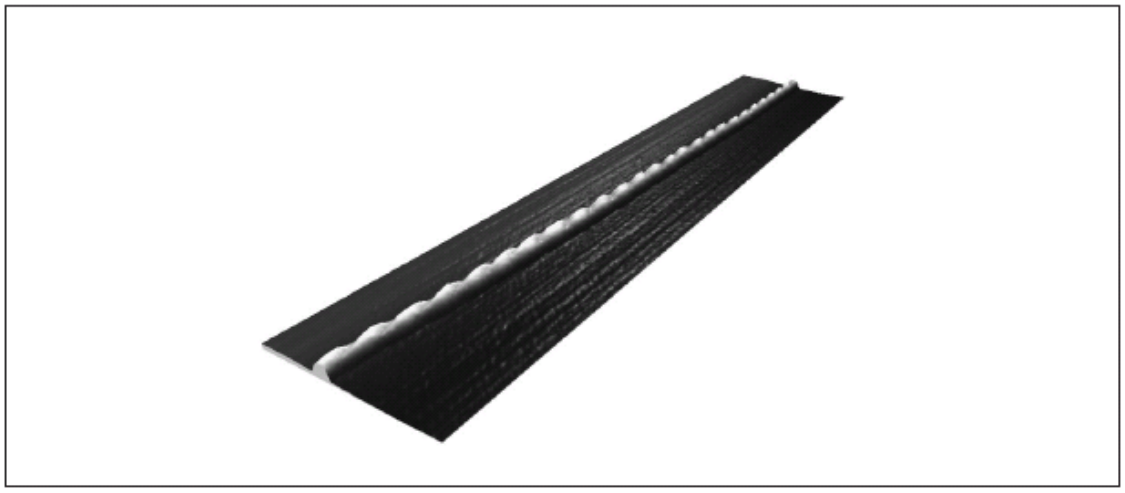
Amyloid fibrils, nanoscale filaments of polypeptides and proteins, are commonly observed in a range of human diseases such as Alzheimer's and Type II diabetes and as such represent an alternative folded state that polypeptide molecules can assemble into. They have a common structure consisting of a core of elongated beta strands and sheets held together by hydrogen bonding. Atypical fibril has a diameter of up to 10nm and a length ranging up to a few microns. Fundamental to an understanding of the kinetics of nucleation and growth of Amyloid fibrils is a requirement to quantify their mechanical properties; a challenge for which the AFM is ideally suited. We used two techniques in order to quantify a range of fibril mechanical properties. The first involved suspending a fibril of insulin across a nanoscale groove etched into a silicon surface with a focused ion beam. Force-distance curves were then recorded at different points along the fibril length that, along with dimensional measurements, allowed us to determine a number of mechanical properties. Asecond method was then used to independently confirm these measurements based on an analysis of the average magnitude of the thermally induced fluctuations from a rigid state. Fibrils deposited on to mica were imaged by tapping mode in the AFM. By using a worm-like chain model developed for the statistical analysis of semiflexible polymers we were able to independently estimate the rigidity of the fibrils. The values for mechanical properties obtained using this method were in excellent agreement with those obtained from the AFM bending experiments determining the strength of the fibril to be 0.6 ± 0.4 GPa, comparable to that of steel (0.6 - 1.8 GPA), and the mechanical stiffness to be 3.3 ± 0.4 GPa, comparable to that of silk. Adetailed analysis of the solution state growth kinetics indicated that internal fracturing of fibrils with a rate constant of 1.7 (1.3 10-8 s-1 is of fundamental importance in the proliferation of amyloid fibrils and therefore for understanding the progression of their associated pathogenic disorders.



AFM image of an insulin fibril with diameter ~6nm