TOWARDS THE ATOMISTIC SIMULATION OF FIBRIL FORMATION

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By extended atomistic simulations in explicit solvent and bias-exchange metadynamics, we studied the aggregation process of 18 chains of the C-terminal segment of amyloid-beta, an intrinsically disordered protein involved in Alzheimers disease and prone to form fibrils. Starting from a disordered aggregate, we are able to observe the formation of an ordered nucleus rich in beta sheets. The rate limiting step in the nucleation pathway involves crossing a barrier of approximately 40 kcal/mol and is associated with the formation of a very specific interdigitation of the side chains belonging to different sheets. This structural pattern is different from the one observed experimentally in a microcrystal of the same system, indicating that the structure of a "nascent" fibril may differ from the one of an "extended" fibril.

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