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Amyloid fibrils: formation, replication, and physics behind them

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The assembly of normally soluble proteins into long fibrils, known as amyloids, is associated with a range of pathologies, including Alzheimer's and Parkinson's diseases. A large number of structurally unrelated proteins form this type of fibrils, and we are in a pursuit of physical principles that underlie the amyloid formation and propagation. We show that small disorders oligomers, which are increasingly believed to be the prime cause for cellular toxicity, serve as nucleation centers for the fibril formation. We then relate experimentally measurable kinetic descriptors of amyloid aggregation to the microscopic mechanisms of the process. Once formed, amyloid fibrils can catalyse the formation of new oligomers and fibrils in a process that resembles self-replication. By combining simulations with biosensing and kinetic measurements of the aggregation of Alzheimer's Aβ peptide, we propose a mechanistic explanation for the self-replication of protein fibrils, and discuss its thermodynamic signature. Finally, we consider the design of possible inhibitors of the fibril self-replication process. Mechanistic understandings provided here not only have implications for future efforts to control pathological protein aggregation, but are also of interest for the rational assembly of bionanomaterials, where achieving and controlling self-replication is one of the unfulfilled goals.