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Exploring the Free Energy and Conformational Landscape of Peptides Upon Aggregation and Amyloid Formation

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Using various physical-chemical tools and perturbation parameters, the effects of temperature, pressure as well as lipid interfaces and confining geometries on the various stages of the aggregation and fibrillation reaction of amyloidogenic peptides have been studied. First we show data on the experimentally derived static structure factor obtained for the protein insulin which has been analyzed with a statistical mechanical model based on the DLVO potential. The data reveal that the protein self-assembles into equilibrium clusters already at low concentrations in the pre-nucleation phase. Then, mechanistic details about the nucleation process and concurrent aggregation pathways of insulin and more disease related amyloidogenic peptides, such as IAPP and PrP, and the differential stability of the aggregate structures formed are discussed. Also solvational perturbations, accomplished by the addition of various salts and cosolvents have been explored. They exert pronounced and diversified effects on the unfolding, non-native assembly and fibril formation, which ultimately manifest in morphological variations of mature aggregates and fibrils. Finally, the presence of lipid interfaces and soft-matter confinement will be discussed, which drastically change the aggregation pathway as well as the kinetics of peptide aggregation. Using various model membrane systems, the influence of different membrane characteristics on the lipid-protein interaction has been revealed.