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Thermodynamic stability of polar and non-polar amyloid fibrils

FARBOD MAHMOUDINOBAR, ZHAOQIAN SU, CRISTIANO L. DIAS, New Jersey Inst of Tech — Protein aggregation into fibril-like structures is the hallmark of amyloid diseases that included Alzheimer's, Parkinson's and type 2 diabetes. An understanding of the molecular forces driving fibril formation may provide insights into strategies to prevent these diseases. Thermodynamics has played an important role in unraveling the molecular mechanisms of different conformational changes in proteins, e.g., protein folding. However, equilibrium thermodynamic quantities of amyloid fibrils are not easily accessible experimentally and they remain largely unknown. In this work, we discuss results from all-atom molecular dynamics simulations in which we measured equilibrium thermodynamic quantities related to addition/dissociation of a peptide to/from a fibril. We will highlight differences in the thermodynamic properties of polar and non-polar fibrils. Simulations were performed using an umbrella sampling protocol combined with replica exchange molecular dynamics to compute potential of mean force (PMF) of peptide addition as a function of temperature. The temperature dependence of the PMF is used to compute changes in entropy, enthalpy and heat capacity of peptide addition. We find that the non-polar fibril becomes more stable with increasing temperature and its stability is dominated by entropy. In contrast, the polar fibril becomes less stable with increasing temperature while it is stabilized by enthalpy. These behaviors are consistent with the nature of the interactions in their dry core and they highlight the importance of side chains accounting for stability of amyloid fibrils.

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