Using thermodynamics to understand
the molecular forces driving peptides to amyloid-like fibrils

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Protein aggregation into fibril-like structures is the common ground of amyloid diseases that include Alzheimer’s, Parkinson’s and type 2 diabetes. Thus, understanding the molecular forces driving peptides to amyloid-like fibrils may lead to new drug design strategies to prevent protein aggregation diseases. Parameters that regulate molecular mechanisms of fibril formation/dissociation can be studied by thermodynamic analysis of the process. This work is inspired by protein folding for which thermodynamics played a key role in determining molecular mechanisms of this transition. Our goal is to provide insights into the molecular driving forces of fibrils through thermodynamic studies. Here, we use all-atom molecular dynamics simulations to compute thermodynamic quantities related to addition/dissociation of a peptide to/from a fibril. An umbrella sampling protocol combined with replica exchange molecular dynamics is used to compute potential of mean force (PMF) as a function of distance between peptide and center-of-mass of the preformed fibril. The temperature dependence of the PMF is used to calculate changes in thermodynamic properties of the system. In particular, we compute changes in free energy ($\Delta G$), entropy ($\Delta S$), enthalpy ($\Delta H$), and heat capacity ($\Delta C$). These quantities remain mostly unknown for amyloid fibrils due to experimental challenges. We find that the addition of a non-polar peptide ($\text{A}_\text{B}_{16-21}$) to the fibril is dominated by the entropic energy ($-T\Delta S$). Also, $\Delta C$ of $\text{A}_\text{B}_{16-21}$ fibril dissociation is positive consistent with expected exposure of non-polar residues to water. To provide insights into effects of the amino acid sequence on fibril formation, we will also discuss thermodynamic changes of a polar fibril.

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