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

Farbod Mahmoudinobar, Zhaoqian Su and Cristiano L. Dias

New Jersey Institute of Technology, Department of Physics, University Heights, Newark, New Jersey, 07102-1982

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 (ΔG), entropy (ΔS), enthalpy (ΔH), and heat capacity (ΔC). These quantities remain mostly unknown for amyloid fibrils due to experimental challenges. We find that the addition of a non-polar peptide ($A\beta_{16-21}$) to the fibril is dominated by the entropic energy ($-T\Delta S$). Also, ΔC of $A\beta_{16-21}$ 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.

*fm59@njit.edu