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Exploring the Free Energy Landscape of Amyloid-beta Peptides in Different Environments Using Metadynamics

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The Amyloid-Beta (Aβ) peptide is an Intrinsically Disordered Protein (IDP) whose aggregation process at the neuronal membrane is considered a central event associated with the onset of Alzheimer's disease (AD). Aβ is a 39-42 amino acid long peptide, and the ratio of its alloforms Aβ40-to-Aβ42 is believed to play a role in AD development. Due to the transient secondary structures of Aβ, the exploration of its conformational space under physiological conditions remains challenging and calls for high-resolution studies. Here, to explore the complex free energy landscape of the Aβ40 and Aβ42 monomers and their changes due to different environments, we have conducted ten-microsecond Well-Tempered Metadynamics simulations. In particular, we studied Aβ structural transitions in different solvents: water, hexafluoroisopropanol (HFIP), and dimethyl sulfoxide (DMSO); the latter two represent useful models for investigating how the properties of the environment influence the tendency of Aβ to sample specific secondary structures. Our results show that in water, both Aβ40 and Aβ42 mainly sample disordered conformations with a non-negligible β-sheet content. Conversely, HFIP promotes α-helix formation, while DMSO, primarily acting as a hydrogen bond acceptor, favors protein unfolding, particularly of β-sheet structures.