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Conformational Dynamics and Order of Compactness of α-Synuclein Induced via C-terminal Truncation

Abstract: C-terminal truncation of α-synuclein (α-Syn) has emerged as a critical modulator of its liquid-liquid phase separation and amyloid aggregation, processes that are closely linked to the pathology of neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD). While the functional implications of α-Syn truncation have been increasingly recognized, the molecular mechanisms by which C-terminal truncation alters α-Syn conformations remain poorly understood at the atomistic level. In this study, we systematically investigated the impact of progressive C-terminal truncation on α-Syn structure using molecular dynamics simulations across multiple force fields, including CHARMM36, CHARMM36-IDP, and AMBER99SB-ILDN. We simulated a series of truncation variants (residues 1–98 to 1–140) and compared their structural behavior to the full-length protein. In CHARMM36, truncated α-Syn variants that exhibited stable α-helical structures in the N-terminal and NAC regions gradually transitioned into short helices, β-sheets, and β-bridges during the simulation. The intrinsically disordered C-terminal region of the full-length protein interacted with the N-terminal helices, contributing to intrapeptide contacts. Truncation of this region disrupted these contacts, resulting in increased interpeptide interactions and enhanced helicity. Notably, the αS1–98 variant adopted a more compact conformation than αS1–140 in CHARMM36, a feature not consistently observed in other force fields. The performance of each force field is assessed from several structural parameters such as radius of gyration, root mean square deviation, percentage of secondary structure, and favorable conformations obtained for different force fields. Our findings suggest that C-terminal truncation significantly alters the conformational landscape of α-Syn, facilitating structural transitions associated with pathological aggregation. These results provide mechanistic insights into how truncation modulates α-Syn behavior and provide valuable insights for understanding its role in neurodegenerative disease progression.

Keywords: α-Synuclein, MD simulation, Free Energy Landscape (FEL), Contact Surface Area (CSA) **strong text

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