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All-Atoms simulations of Huntingtin's N-terminal: solvent and membrane effects

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The Huntingtin protein has drawn considerable attention as its aggregation into amyloid fibrils is related to the Huntington disease, a neurodegenerative disease characterized by motor and emotional dysfunctonalities and the loss of cognitive functions. Of its 3000 plus residues, attention has focused mostly on the first exon of Huntingtin, composed of a amphipatic region of 17 amino acids (Htt17), a polyglutamine repeat domain (Q_N) and a proline rich domain (C_{38}), that modulates its aggregation and localization within the cell. The Htt17 segment is particularly important because it serves as a membrane anchor that could accelerate the fibrilation process.

Following recent solution and solid-state NMR experiments that unveiled Htt17's structure and orientation in micelles and POPC bilayer [1], we refine these experimental finds using a state-of-the-art approach combining molecular dynamics (MD), Hamiltonian replica exchange (HREX) and Metadynamics (MetaD). We focus primarily on the characterization of the dynamics and thermodynamics of Htt17 in solution and in a phospholipid bilayer.

In solution, we find that Htt17 samples a broad ensemble of alpha-helix, coil and two-helix bundle structures in agreement with NMR chemical shifts. The addition of the Q_N domain shifts the helical propensity from the amino terminus to the carboxy terminus. Finally, the addition of a polyproline domain stabilizes the helical conformation. Many of the observed structural features could play a crucial role in the aggregation or in the interaction with the membrane [2].

In the phospholipid bilayer, we find that Htt17 could be more structured than the proposed NMR model. Htt17 leads to local deformation of the membrane due to the extension of the neighbor phospholipid acyl chains to cover its nonpolar surface These deformations were shown to promote dimerization of the inserted peptide and could favor the formation of large aggregates [3].

1. Michalek, M. et al. (2013). Biophysical journal, 105(3), 699-710
2. Côté, S. et al. (2015). Biophysical Journal, 108(5), 1187-1198
3. Binette, V. et al. (2016). Biophysical Journal (In press)

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