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Simulation of the Effects of Flanking Sequences on Polyglutamine Aggregation[1] JASON HAAGA, Lehigh University Department of Physics, SIDDIQUE KHAN, University of Pennsylvania Department of Medical Physics, JAMES GUNTON, Lehigh University Department of Physics — Huntington's disease is one of a set of nine progressive neurodegenerative diseases caused by the expansion of CAG sequence repeats. This results in affected proteins with abnormally long polyglutamine (polyQ) tracts, which beyond a pathological threshold length form toxic aggregates. Recent experimental studies suggest the sequences flanking the polyQ tract have a profound impact on the aggregation rates and morphologies. The 17 residues N terminus to the polyQ insert in the huntingtin protein (Htt) have been shown to accelerate aggregation, particularly the formation of insoluble fibrils. The proline-rich C terminal region has been demonstrated to slow the rate of aggregation. We propose a coarse-grain model of the polyQ tract, with and without its N and C terminal regions, and utilize Brownian dynamics simulation to examine the kinetics of aggregation.

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