Folding simulations of the Prion Protein with the native-centric Hydrophobic Potential

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Introduction: The Prion protein is related to the development of transmissible spongiform encephalopaties (TSE) through the conversion of its native conformation (nPrP) into a “scrapie form” (scPrP). This unusual behavior provides an interesting model for the general investigation of protein folding and the relation between amino acid sequence and tertiary structure.

Methods: We report initial results from Molecular Dynamics folding simulations of the Prion protein using a native-centric hydrophobic potential. A tunable amount of native information is provided by explicit constraints on atomic burials, as expressed by distances from the molecular center. A sequence-compatible amount of burial information was previously shown to successfully recover the structure of small globular proteins (Pereira de Araujo and Onuchic, PNAS 106:19001-19004, 2009).

Results: Simulations using the native form as initial conformation demonstrated an appropriate stabilization by native burials, with resulting trajectories displaying root mean square deviations from the native below $\pm2.5\AA$.

Trajectories beginning from random conformations tend to fall in a kinetic trap containing an incorrectly oriented helix.

Conclusion: Our preliminary results indicate that exact native burials will produce successful folding for sufficiently long trajectories, which will permit an investigation on the amount of required burial information. Eventual discrepancies with previous results would suggest topology to be involved in the peculiar folding behavior of the Prion protein. The effect of peptides known to inhibit the conversion can also be explored.