139i Investigating Molecular and Phase Stability of Protein Solutions by a Coarse-Grained Modeling Strategy

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Understanding the environmental factors that reduce the stability of native-state proteins and induce non-native protein aggregation processes in solution is a challenge of great practical and technological importance. Protein aggregation has been linked to numerous human pathologies such as Alzheimer's and Huntington's diseases. It also leads to premature degradation of pharmaceutical formulations, severely restricting the available strategies for purification, storage, and delivery of therapeutic drugs. In this talk, we will discuss new simulations of a recently developed coarse-grained model [1] for protein solutions. The simulations employ a novel implementation of transition matrix Monte Carlo techniques introduced earlier (see, e.g., [2]) to probe how environmental stresses such as protein concentration, temperature, and hydrostatic pressure can induce unfolding and phase separation. Our results suggest that both single-molecule protein stability and the global phase behavior of protein solutions can be quite sensitive to basic protein sequence information (e.g., hydrophobic content). We will discuss these results in the context of experimental data, and we will also describe how this type of coarse-grained model [1] can give general insights into aggregation processes and phase behavior of complex fluids in aqueous solution.

[1] J. K. Cheung and T. M. Truskett. Biophys. J., in press (2005).

[2] V. K. Shen and J. R. Errington, J. Chem. Phys. 122, 064508 (2005).