Proceedings of the ASME 2008 Summer Bioengineering Conference (SBC2008)
June 25-29, Marriott Resort, Marco Island, Florida, USA

SBC2008-192239

HOW CONCENTRATION AND CROWDING IMPACT PROTEIN STABILITY: INSIGHTS FROM A COARSE-GRAINED MODEL

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Much of the current understanding of the protein folding problem derives from studies of proteins in dilute solutions. However, in many systems of scientific and engineering interest, proteins must fold in concentrated, heterogeneous environments. Cells are crowded with many molecular species, and chaperones often sequester proteins and promote rapid folding. Proteins are also present in high concentrations in the manufacture, storage, and delivery of biotherapeutics. How does crowding generally affect the stability of the native state? Are all crowding agents created equal? If not, can generic structural or chemical features forecast their effects on protein stability?

To investigate these and related questions with computer simulations, one requires models sophisticated enough to describe three parts of the folding problem: the intrinsic free energy of folding of a protein in solvent, the main structural features of the native and denatured states, and the connection between protein structure and effective protein-protein interactions. The model must also be simple enough to allow for the efficient simulation of hundreds to thousands of foldable protein molecules in solution, which precludes the use of atomistically detailed descriptions of the proteins, the solvent, or any co-solutes.

We recently developed a coarse-grained modeling strategy that, while still basic, satisfies these criteria. It is not optimized to describe any specific protein solution. Rather, it is a general tool for building a qualitative understanding of experimental trends regarding how concentration or crowding impact the thermodynamic stability of globular proteins. To date, the approach has been used to study how protein concentration affects the folding transition [1], how solution demixing phase transitions (e.g., liquid-liquid phase separation) couple to protein denaturation [2], and how surface anisotropy of the native proteins relates to their unfolding and self-assembly behaviors in solution [3]. In this talk, I will discuss this multi-scale modeling strategy and some key insights that it has produced thus far.

REFERENCES

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