Multi-Scale Simulations Yield Insight into Protein Diffusion and Stability in Crowded Environments

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Abstract

Proteins inside the living cell are exposed to a highly crowded and heterogeneous environment, which may substantially affect their properties and, consequently, their function. Recent experimental evidence indicates that both the diffusivity and the stability of a protein can be altered by tuning its interactions with the crowded environment. To gain a detailed understanding of these effects, microscopic insights from molecular simulations are strongly desired; however, the wide spread of the time- and length scales involved in macromolecular crowding poses a significant challenge for conventional simulation approaches. Here we combine lattice Boltzmann molecular dynamics with all-atom replica exchange simulations into a computational framework that allows us to investigate protein diffusion and stability in crowded solutions. We employ our computational scheme to examine how the stability of a protein is modulated by distinct states of local packing occurring in the crowded solution. Furthermore, we show how our molecular simulations allow rationalizing the results of fast relaxation imaging (FReI) measurements of protein stability in crowded conditions.

Keywords: multiscale simulations, molecular dynamics, macromolecular crowding, protein diffusion, protein stability

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