Proteins in a crowd under heat and pressure

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In order to function, many proteins fold into a well-packed structure, and yet the folded phase must remain sufficiently flexible. It is unclear how proteins satisfy these contradictory constraints, especially in the crowded environment of a cell. I will present the theoretical and computational work from my group, which is in collaboration with experimentalists from the Gruebele group, addressing this challenging issue. We propose that these properties can coexist by tuning where the protein operates within its temperature-pressure-crowding phase diagram. Phase diagrams may contain 'critical points' where the difference between any two phases disappears, such as when liquid and water vapor become indistinguishable. We show that a protein can also have such a critical point. The enzyme phosphoglycerate kinase (PGK), which is involved in producing the 'energy molecule of the cell,' turns out to have a very crowding-sensitive critical point, above which the protein forms new structures. To paint a complete picture of the critical point for this protein, we expand upon the conventional temperature-pressure folding phase diagram by adding a third dimension: the degree of crowding (or volume-exclusion) from surrounding macromolecules. From simulations, we observe an intricate phase diagram, which contains a critical point that moves to lower a temperature as the crowding increases. We complement our simulation results by deriving a new thermodynamic equation of state that includes the critical line in the entire 3-dimensional phase diagram. To test our computational model, we observe folding transitions of PGK by fluorescence experiments, which validate the predicted critical point behavior. Our findings suggest that being near a critical point at physiological conditions would be advantageous for enzymatic function because a protein may sample widely different conformations without passing a costly thermodynamic barrier.

Panopto recording.