Contribution of water to protein folding and strategies for protein design

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The mechanisms of cold and pressure denaturation of proteins are matter of debate and are commonly understood as due to water-mediated interactions. Here, we study several cases of proteins, with a unique native state or intrinsically disordered, by means of a coarse-grain protein model in explicit solvent. We show, using Monte Carlo simulations, that taking into account how water at the protein interface changes its hydrogen bond properties and its density fluctuations [1, 2, 3, 4] is enough to predict protein stability regions with elliptic shapes in the temperature-pressure plane, consistent with previous theories.

Our results [5, 6] clearly identify the different mechanisms with which water participates to denaturation and allow us to develop an advanced computational design protocol for protein engineering [7]. In particular, we apply our design analysis to understand why proteins that are functional at ambient conditions do not necessarily work at extreme conditions of temperature T and pressure P, and why there are limits of T and P above which no protein has a stable functional state. We show that the hydropathy profile of proteins is a consequence of evolutionary pressure exerted by water [7]. This result can lead the way for engineering working proteins and drugs at extreme conditions and is potentially relevant in protein self-assembly [8].

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