SOUTENANCE de THESE

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« Are thermophilic proteins rigid or flexible? An in silico investigation »

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Abstract :

Understanding the relation between protein flexibility, stability and function remains one of the most challenging, open questions in biophysical chemistry. For example, proteins need to be flexible to facilitate substrate binding but locally rigid to sustain substrate specificity. Exemplary cases are enzymes from thermophilic organisms that thrive at elevated temperatures. These proteins are stable and functional at a high temperature regime but generally lack activity at ambient conditions. Therefore, their thermal stability has been correlated, through what's known as the corresponding states paradigm, to enhanced mechanical rigidity. The generality of this view, however, has been questioned by a number of experimental and computational studies.

In the present study, we employ the "gold standard" of computational techniques, namely Molecular Dynamics simulations, in order to identify microscopical characteristics that distinguish thermophilic from mesophilic proteins, elaborating in particular on the rigidity paradigm mentioned above. We focus on two characteristic study-cases, two homologous monomeric G-domains of a hyperthermophilic and a mesophilic elongation factor and two homologous, thermophilic and mesophilic, tetrameric malate dehydrogenases. Our findings overall show that, indeed, protein rigidity is not the only way to achieve an enhanced thermal stability while they support the view that optimal activity of mesophilic proteins at ambient temperature is fine-tuned at the expense of their stability at high temperatures. Finally, some of our findings could inspire new strategies in the design of thermostable proteins.