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Analysis of protein folding through the combination of transition path theory and informative low-resolution representations

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The biologically active conformation of a protein is maintained by the interactions among those residues involved in native contacts, but in the course of the folding process amino acids can be involved in transient native as well as non-native interactions, which drive the molecule towards its folded state. Reconstructing how these interactions evolve is key to understanding the folding process; however, no technique is currently available to do so in a general and unsupervised manner.
We here present a method that highlights the most functionally relevant residues of a protein at each stage of its folding pathway. To do so, we jointly leverage two distinct techniques: transition path theory (TPT), to decompose the folding pathway in a sequence of steps according to the committor function; and the mapping entropy optimization workflow (MEOW), which highlights, at each step, the subset of residues that play the most relevant structural, energetic, and functional role.
We validate this method by applying it to a benchmark yet nontrivial case, namely miniprotein chignolin, showing that the combination of TPT and MEOW provides novel information on the molecule's folding pathway that is nonetheless coherent with well-established results. This approach, which is of general applicability, complements existing analysis methods and paves the way to an increasingly detailed comprehension of protein folding.

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