Predicting folding rates of two-state proteins: Analysis of rate-limiting long range contacts

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Inter-residue interactions are one of the most important factors responsible for the native state formation of proteins. Long-range order\(^1\) is one of the most successful descriptor in relating the three-dimensional structure of two-state proteins with their folding rates. Long-range order highlights the importance of long-range contacts (residues that are far in sequence and closer in the 3D structure) in predicting folding rates across three major structural classes of proteins. In the present work, rate limiting long-range contacts were classified into various bins based on the sequence separation distance between the contacting residues, and the role of these bins were analyzed for their importance in predicting the folding rates for a set of 40 two-state proteins belonging to the three major structural classes (all-\(\alpha\), all-\(\beta\) and mixed). For all alpha and mixed structural class proteins maximum correlation is obtained only when long-range contacts from all the sequence separation bins were included in the calculation. Rate-limiting contacts for both of these structural classes seem to be present through out in all bins with the most important contacts present in their last bin. For all beta structural class maximum correlation is obtained when long range contacts only from the first three sequence separation bins were included in the calculation and hence the rate-limiting contacts for the all beta structural class were present in the first three bin intervals itself. Our present method is validated by predicting the folding rates for a standard set of 22 two-state proteins and the results showed an excellent agreement between experimental and predicted folding rates.

Reference:


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