GeoFold: A mechanistic model to study the effect of topology on protein unfolding pathways and kinetics

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Abstract:

Protein unfolding is modeled as an ensemble of pathways, where each is a tree of intermediate states and branches in the tree represent additional degrees of conformational freedom. Using a known protein structure, the program (GeoFold) generates a directed acyclic graph of linked elemental subsystems, each modeling a partitioning of a substructure into two incompletely partitioned states. Denaturation of the system proceeds by defining a free energy barrier height based on the principle that exposed surfaces are solvated before the configurational entropy is expressed. To simulate unfolding on the graph, rates are calculated for each elemental substructure at each time step using transition state theory. The model exhibits two-state behavior with respect to temperature and denaturant and shows the expected linear relationship of overall folding rate with denaturant. Predicted unfolding rates are compared with experimental values for fifteen well-studied proteins. Strengths and deficiencies of the model are discussed.

1. Kinetically stable (KS) proteins can be identified by differential resistance to SDS denaturation

- High-throughput method for isolating all KS proteins in a cell lysate
- Removal of SDS during PAGE separation on a narrow gel
- The gel strip is immersed in boiling 1% SDS
- SDS-PAGE separation

2. KS proteins in E. coli have recurrent structural themes

- Selected seqs from E. coli lysate 2D gel

3. GeoFold models folding as a series of splittings of three types: break, pivot and hinge

4. GeoFold generates a kinetic model for a protein

5. UnfoldSim runs a kinetic simulation

6. High traffic unfolding pathways may be dissected and visualized

7. Unfolding rates can be measured as k_s ln[2]/t_{1/2}

8. Simulated k_s agree with experimental k_s for KS and non-KS proteins

9. Unfolding pathways can be summarized using contact maps

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Stages of protein unfolding are represented using a tree structure. The geo-fold graph shows the relationship between different stages of unfolding, with nodes representing states and branches indicating transitions. The model allows for the simulation of unfolding pathways and the calculation of unfolding rates. Contacts between residues are critical in determining the stability and dynamics of proteins. The simulation can be used to predict unfolding rates and compare them with experimental data, providing insights into the mechanisms of protein unfolding.