Predicting flexibility and motions of proteins using rigidity theory

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Abstract:

It has long been recognized that protein structural flexibility is as crucial for protein function as its structure. Some biological data (NMR ensembles, multiple configurations, HD exchange) can provide experimental insight. We can model the molecule like an engineered structure of fixed units (atoms with their bond angles as rigid units, bonds as potential hinges) plus biochemical constraints coming from the geometry (hydrogen bonds, hydrophobic interactions). This generates a 'molecular graph' in the theory of combinatorial rigidity. Drawing on graph theoretic algorithmic methods for bar-body frameworks (the 6|V| - 6 pebble game), as well as the 25 year old molecular conjecture, a basic algorithm on the molecular graph makes flexibility/rigidity predictions for the molecular structure. The predictive algorithm is embedded in an online FIRST server at flexweb.asu.edu, along with an extension FRODA to model the initial motions of the molecule.
Our recent work has extended this basic model and the pebble game algorithm to predict hinge motions of proteins, as well as some preliminary predictions for 'allostery' - where binding on one portion of a large molecule changes the shape or binding at a distance 'active site' of the molecule. We also have a new approach and guidance on how to use the pebble game/FIRST and solvent accessibility information to give a prediction on rigidity/flexibility and hydrogen-deuterium exchange rates of structural protein ensembles.