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Accurate and Robust Mechanical Modeling of Proteins

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Abstract
Through their motion, proteins perform essential functions in the living cell. Although we cannot observe protein motion directly, over 68,000 crystal structures are freely available from the Protein Data Bank. Computational protein rigidity analysis systems leverage this data, building a mechanical model from atoms and pairwise interactions determined from a static 3D structure. The rigid and flexible components of the model are then calculated with a pebble game algorithm, predicting a protein's flexibility with much more computational efficiency than physical simulation. In prior work with rigidity analysis systems, the available modeling options were hard-coded, and evaluation was limited to case studies.

The focus of this thesis is improving accuracy and robustness of rigidity analysis systems. The first contribution is in new approaches to mechanical modeling of noncovalent interactions, namely hydrogen bonds and hydrophobic interactions. Unlike covalent bonds, the behavior of these interactions varies with their energies. I systematically investigate

energy-refined modeling of these interactions. Included in this is a method to assign a score to a predicted cluster decomposition, adapted from the B-cubed score from information retrieval. Another contribution of this thesis is in new approaches to measuring the robustness of rigidity analysis results. The protein's fold is held in place by weak, noncovalent interactions, known to break and form during natural fluctuations. Rigidity analysis has been conventionally performed on only a single snapshot, rather than on an entire trajectory, and no information was made available on the sensitivity of the clusters to variations in the interaction network. I propose an approach to measure the robustness of rigidity results, by studying how detrimental the loss of a single interaction may be to a cluster's rigidity. The accompanying study shows that, when present, highly critical interactions are concentrated around the active site, indicating that nature has designed a very versatile system for transitioning between unique conformations.

Over the course of this thesis, we develop the KINARI library for experimenting with extensions to rigidity analysis. The modular design of the software allows for easy extensions and tool development. A specific feature is the inclusion of several modeling options, allowing more freedom in exploring biological hypotheses and future benchmarking experiments.