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Towards Large-Scale Validation of Protein Flexibility Using Rigidity Analysis

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Abstract
Proteins are dynamic molecules involved in virtually every chemical process in our bodies. Understanding how they flex and bend provides fundamental insights to their functions. At the atomic level, protein motion cannot be observed using existing experimental methods. To gain insights into these motions, simulation methods are used. However such simulations are computationally expensive.

Rigidity analysis is a fast, alternative graph-based method to molecular simulations, that gives information about the flexibility properties of molecules modeled as mechanical structures. Due to the lack of convenient tools for curating protein data, the usefulness of rigidity analysis has been demonstrated on only a handful of proteins to infer several of their biophysical properties. Previous studies also relied on heuristics to determine which choice of modeling options of important stabilizing interactions allowed for extracting relevant biological observations from rigidity analysis results. Thus there is no agreed-upon choice of modeling of stabilizing interactions that is validated with

experimental data.

In this thesis we make progress towards large-scale validation of protein flexibility using rigidity analysis. We have developed the KINARI software to test the predictive power of using rigidity analysis to infer biophysical properties of proteins. We develop new tools for curating protein data files and for generating biological functional forms and crystal lattices of molecules. We show that rigidity analysis of these biological assemblies provides structural and functional information that would be missed if only the unprocessed data of protein structures were analyzed. To provide a proof-of-concept that rigidity analysis can be used to perform fast evaluation of in silico mutations that may not be easy to perform in vitro, we have developed KINARI-Mutagen. Finally, we perform a systematic study in which we vary how hydrogen bonds and hydrophobic interactions are modeled when constructing a mechanical framework of a protein. We propose a general method to evaluate how varying the modeling of these important inter-atomic interactions affects the degree to which rigidity parameters correlate with experimental stability data.