

Public Abstract

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Title:COMPUTATIONAL OPTIMIZATION ALGORITHMS FOR PROTEIN STRUCTURE REFINEMENT

Despite significant advancement being made during the recent past in predicting structure of proteins using computational methods, these techniques often cannot achieve sufficiently high level of accuracy to fully appreciate biological function and to serve as a reliable starting point for rational drug design efforts to develop novel therapeutics. Bringing these low-resolution models as close as possible to the native structure, called the protein structure refinement problem, however, has remained largely unsolved. Existing approaches in protein structure refinement suffer from two key challenges: (1) lack of consistency and (2) failure to produce meaningful degree of refinement.

This thesis is composed of three major contributions. First, we propose a consistent and efficient computational optimization protocol called 3Drefine. Next, we further improve the 3Drefine algorithm by developing an iterative version of the protocol, named i3Drefine. Finally, we present a novel conformation ensemble-based iterative refinement method, REFINEpro, aimed at producing pronounced degree of refinement. All of these methods were benchmarked in diverse and large-scale datasets and achieved consistent refinement in both global and local structural quality measures. In particular, i3Drefine was ranked as the best protein structure refinement server method in recent Critical Assessment of Protein Structure Prediction experiment. All of these methods are freely available to the scientific community in the form of software and web-servers.