Detection of Optimal Structures in Homology Modeling Using Various Sequence Fitness Scores

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ABSTRACT:

Numerous protein toxins demonstrate potential for use as biological threat agents. Computational methods for determining the structures of these toxins can greatly assist in the design of therapeutics to counter their effects. Homology modeling is one such method where the structure of a target protein is predicted based on its sequence similarity to template proteins of known structure. We are devising algorithms based on homology modeling to optimize structure prediction using several sequence fitness scores. The bit score accounts for statistical parameters in a residue substitution matrix to measure the sequence similarity. We use two different energy potentials, the DFIRE-AA statistical potential and the generalized born (GB) physical potential, to score the conformation of a target sequence threaded onto template structures. We apply a correlation-based method on these scores relative to the root-mean square distance between structures to distinguish more native-like conformations. Finally, we are optimizing functions of normalized scores to predict the optimal structures. We are testing these algorithms on three sequences: the SH3 domain of chicken alpha spectrin, lysozyme, and myoglobin, and will compare the results to the known structures.

KEYWORDS: protein structure prediction, homology modeling, statistical energy potentials, physical energy potentials

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