Extracting knowledge from protein structure geometry

Protein structure prediction techniques proceed in two steps, namely the generation of many structural models for the protein of interest, followed by an evaluation of all these models to identify those that are native-like. In theory, the second step is easy, as native structures correspond to minima of their free energy surfaces. It is well known however that the situation is more complicated as the current force fields used for molecular simulations fail to recognize native states from misfolded structures. In an attempt to solve this problem, we follow an alternate approach and derive a new potential from geometric knowledge extracted from native and misfolded conformers of protein structures. This new potential, Metric Protein Potential (MPP), has two main features that are key to its success. Firstly, it is composite in that it includes local and nonlocal geometric information on proteins. At the short range level, it captures and quantifies the mapping between the sequences and structures of short (7-mer) fragments of protein backbones through the introduction of a new local energy term. The local energy term is then augmented with a nonlocal residue-based pairwise potential, and a solvent potential. Secondly, it is optimized to yield a maximized correlation between the energy of a structural model and its root mean square (RMS) to the native structure of the corresponding protein. We have shown that MPP yields high correlation values between RMS and energy and that it is able to retrieve the native structure of a protein from a set of high-resolution decoys.

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