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Toward a physical energy function for intra- and inter-protein interactions by combining structural knowledge with physical principles

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Toward a physical energy function for intra- and inter-protein interactions by combining structural knowledge with physical principles

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Understanding of how proteins fold, bind, and/or function requires an accurate energy function to describe water-mediated interaction between amino acid residues. A simple, effective method to obtain an approximate energy function is to extract it from known structures of proteins (called knowledge-based statistical potential). One natural consequence of this commonly-used statistical approach is that the outcome (the energy function) is strongly dependent on input (the structural database used to extract the energy function). For example,

the structural database of single-chain proteins and the interface database of dimeric proteins produced quantitatively different pair potentials for folding and binding studies. This is due to significantly different compositions of amino acid residues at the surface, core, and binding interface of proteins. In another example, the potential extracted from all-alpha protein structures was shown to be quantitatively different from that from all-beta protein structures. The database dependence of statistical energy functions, however, is unphysical. This is because the same physical interaction (water-mediated interaction between amino-acid residues) is responsible for protein folding and binding and for the formation of beta-strands and alpha helices. Here, we show that this problem can be solved by using a simple physical principle for energy extraction. The resulting physically more accurate energy function in turn leads to a significant leap in the accuracy for selecting native structures of proteins and protein-protein complexes from decoys and predicting loop conformation, stability changes upon mutations, and binding free energy of protein-protein/peptide complexes. Moreover, the new energy function provides a quantitative understanding for the burial of hydrophobic residues in protein interior. Results indicate that it is possible to extract the common physical interaction masked under different ``mixture'' of amino acid residues in different proteins and protein interfaces.