A Novel Framework for De Novo Protein Design and its Applications

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Poster (2:20 PM)

A new de novo design framework based on approximate binding affinity calculations is introduced. The framework consists of two stages: a sequence selection stage and a binding affinity calculation stage. The sequence selection stage produces a rank-ordered list of amino acid sequences with the lowest energies by solving an integer programming sequence selection model [1]. The second stage employs Monte Carlo simulations to predict the structures [2] of the sequences from stage one and to perform docking simulations [3] between the new sequences and the target protein. Finally, rotamerically-based ensembles of the structures for each new peptide, the target protein, and the peptide-protein complex are generated and used to calculate an approximate binding affinity [4], which is used as ranking metric for the designed sequences.

This new framework was applied to a complex of C3c with compstatin variant E1. The computational studies elucidated key positions in the sequence of compstatin that greatly affect the binding affinity. Positions 4 and 13 were found to favor Trp, while positions 1, 9 and 10 are dominated by Asn, and position 11 consists mainly of Gln.

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