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Novel computational methods to design protein-protein interactions[1] ALICE QINHUA ZHOU, COREY O'HERN, LYNNE REGAN, Yale University — Despite the abundance of structural data, we still cannot accurately predict the structural and energetic changes resulting from mutations at protein interfaces. The inadequacy of current computational approaches to the analysis and design of protein-protein interactions has hampered the development of novel therapeutic and diagnostic agents. In this work, we apply a simple physical model that includes only a minimal set of geometrical constraints, excluded volume, and attractive van der Waals interactions to 1) rank the binding affinity of mutants of tetratricopeptide repeat proteins with their cognate peptides, 2) rank the energetics of binding of small designed proteins to the hydrophobic stem region of the influenza hemagglutinin protein, and 3) predict the stability of T4 lysozyme and staphylococcal nuclease mutants. This work will not only lead to a fundamental understanding of protein-protein interactions, but also to the development of efficient computational methods to rationally design protein interfaces with tunable specificity and affinity, and numerous applications in biomedicine.

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