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Molecular origins of Protein-Protein Interactions: Dynamic Flexibility of Interface TUSHAR MODI, BANU OZKAN, Arizona State Univ — Timely orchestrated protein-protein interactions underlie cellular functions. Thus, understanding molecular origins of protein interactions is crucial, particularly estimating changes in binding free energies upon mutations. Current methods rely on 3-D structure of the protein complexes, ignoring conformational dynamics. Here using the SKEMPI data set, containing thermodynamic and kinetic parameters for protein-protein interactions forming complexes and mutants, we develop a novel approach that measures the changes in conformational dynamics at protein interfaces using the dynamic flexibility index (DFI). DFI quantifies flexibility of each position by computing its fluctuation response profile to perturbations exerted on chain, encompassing conformational dynamics. We perform molecular dynamics simulations of wild type and mutant for 21 cases, and then compute change in flexibility of the interface upon mutations using DFI analysis. Strikingly, the total change in DFI shows a strong correlation with change in binding free energies with a correlation coefficient of R=-0.72, suggesting that mutations leading to an increase in flexibility result in decrease in binding energies. Overall, this new approach gives insight into functional impact of mutations through chain flexibility.

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