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The power of hard-sphere models for proteins: Understanding side-chain conformations and predicting thermodynamic stability[1] ALICE QINHUA ZHOU, COREY O'HERN, LYNNE REGAN, Yale University — We seek to dramatically improve computational protein design using minimal models that include only the dominant physical interactions. By modeling proteins with hard-sphere interactions and stereochemical constraints, we are able to explain the side-chain dihedral angle distributions for Leu, Ile, and other hydrophobic residues that are observed in protein crystal structures. We also consider inter-residue interactions on the distribution of side-chain dihedral angles for residues in the hydrophobic core of T4 lysozyme. We calculate the energetic and entropic contributions to the free energy differences between wildtype T4 lysozyme and several mutants involving Leu to Ala substitutions. We find a strong correlation between the entropy difference and the decrease in the melting temperature of the mutatants. These results emphasize that considering both entropy and enthalpy is crucial for obtaining a quantitative understanding of protein stability.

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