

## 11. A Unifying Motif of Intermolecular Cooperativity in Protein Associations

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*When examined at the molecular level, most biological processes entail protein associations. In thermodynamic terms, the binding process relies on a small fraction of interfacial residues called hot spots. As shown in this paper, these hot spots share a unifying molecular attribute: they provide a third-body contribution to intermolecular cooperativity. By intermolecular cooperativity we mean three-body interactions defined by two purely combinatorial rules based solely on structural analysis of protein complexes: a) one body belongs to a protein chain and the other two, to its binding partner, b) two of these bodies are paired by an (intra or intermolecular) electrostatic interaction whose dehydration is promoted by nonpolar groups in the third body. This characterization does not preclude the third body from being also engaged in an intermolecular hydrophobic interaction. Intermolecular cooperativity is essential to maintain the integrity of the protein-protein interface by preventing disrupting hydration of interfacial polar moieties. The molecular attribute characterizing the hot spots can be exploited in rational drug design since such regions may serve as blueprints to engineer small molecules disruptive of protein-protein interfaces.*