Pharmacophores, Pharmacosteres, Flexibility and Fast Feature Multiplets

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Chemical structures reflect the way chemists put molecules together, but they do not directly reflect how molecules interact with proteins. This is fortunate, since the very large number of structures that are synthetically accessible would destroy any hope of rationalizing structure/activity relationships were it not for the fact that different substructures interact with protein residues in a relatively limited number of ways. In fact, complementary ionic, aromatic, hydrophobic and hydrogen bonding features can account for most of the stability of ligand-protein complexes, with the balance attributable to an even more generalized shape complementarity. Hence, the particular disposition of specific interactions in 3D space (the pharmacophore) and the overall shape of the interacting surfaces (the pharmacostere) can be used to characterize any particular binding site. The flexibility of most molecules of pharmaceutical interest complicates things, as does the flexibility of the proteins to which they bind. Ligand and protein each exist in a conformational space with a nominal dimensionality equal to the number of rotatable bonds that it contains. In practice, however, the torsions about each rotatable bond are highly interdependent, which greatly reduces the effective dimensionality. Moreover, certain protein motions can compensate for motions in the ligand. Matching ligands up to binding sites is still a daunting task, but decomposing pharmacophores and pharmacosteres into their constituent triplets, quartets and other multiplet subsets has proven itself a powerful way to approach the problem.