Simple, intuitive calculations of free energy of binding for protein ligand complexes

P. Cozzini (1), M.Fornabaio (2), A.Marabotti (2§), D.J.Abraham (4), G.E.Kellogg (4*), A.Mozzarelli (2,3*)

1Department of General and Inorganic Chemistry,
2Department of Biochemistry and Molecular Biology,
3National Institute for the Physics of Matter, University of Parma, 43100 Parma, Italy;
4Department of Medicinal Chemistry & Institute for Structural Biology and Drug Discovery, School of Pharmacy, Virginia Commonwealth University, Richmond, Virginia 23298-0133, USA.

The prediction of the binding affinity between a protein and ligands is one of the most challenging issues for computational biochemistry and drug discovery. While the enthalpic contribution to binding is routinely available with molecular mechanics methods, the entropic contribution is more difficult to estimate. We describe and apply a relatively simple and intuitive calculation procedure for estimating the free energy of binding for 53 protein-ligand complexes formed by 17 proteins of known three-dimensional structure and characterized by different active site polarity. HINT, a software model based on experimental LogPo/w values for small organic molecules, was used to evaluate and score all atom-atom hydropathic interactions between the protein and ligands. These total scores (HTOTAL), which have been previously shown to correlate with dGinteraction for protein-protein interactions, correlate with dGbinding for protein-ligand complexes in the present study with a standard error of ±2.4 kcal mol-1 from the equation dGbinding = -0.00123 HTOTAL - 6.941. A more sophisticated model, utilizing categorized (by interaction class) HINT scores, produces a superior standard error of ±2.0 kcal mol-1. It is shown that within families of ligands for the same protein binding site, better models can be obtained with standard errors approaching ±1.0 kcal mol-1. Also described are standardized methods for preparing crystallo-graphic models for hydropathic analysis. Particular attention is paid to the relationship between the ionization state of the ligands and the pH conditions under which the binding measurements are made. Sources and potential remedies of experimental and modeling errors affecting prediction of dGbinding are discussed.