

P031 Cytochrome P450 selectivity prediction using molecular dynamics and the Linear Interaction Energy (LIE) method

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The LIE method can be used for binding affinity prediction of a set of compounds to a target protein in lead optimization. The method is based on the linear response approximation and calculates the ligand binding free energy as the weighted difference of the ligand-surrounding interaction energies between ligand bound to a solvated protein and in solution (equation 1).

$$\Delta G_{bind} = b\Delta_{protein-water}\langle V_{l-s}^{el} \rangle = a\Delta_{protein-water}\langle V_{l-s}^{VdW} \rangle \quad (1)$$

Two simulations are performed, one in water and one in solvated protein, and α and β are parameterized using a training set. The LIE method has also been previously applied for selectivity prediction by separately calculating the binding free energy of a ligand in two different proteins, requiring three simulations in total. Here we introduce a novel approach to predict selectivity of binding for a set of 15 thiourea containing compounds to different human cytochrome P450 subtypes. In this new approach only simulations of the ligand bound to the two proteins are required, resulting in the following LIE equation:

$$\Delta G_{bind} = b\Delta_{protein1-protein2}\langle V_{l-s}^{el} \rangle = a\Delta_{protein1-protein2}\langle V_{l-s}^{VdW} \rangle \quad (2)$$

This approach results in improved selectivity prediction as compared to calculations based on two separate LIE models. The RMS errors for the two models are 2.7 kJ/mol and 8.3 kJ/mol respectively, with the latter model displaying two large outliers.