Molecular modelling of flexible enzymes: Binding affinity prediction, insights into biocatalytic selectivity and antidote design

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Predicting ligand binding to Cytochrome P450 liver enzymes is relevant considering their important roles in e.g. drug metabolism and adverse drug reactions (ADRs). However, computing binding affinities or free energies is difficult for P450s due to their flexibility and because substrates can often bind in multiple orientations. Here we will present our efforts to develop a Molecular Dynamics (MD) and Linear Interaction Energy based approach for efficient binding free energy calculation. In addition I will show how we use MD simulations and free energy calculations to understand selectivity in biocatalysis by in-house mutants of bacterial Cytochrome P450 BM3, and to support the design of a serine protease variant as possible antidote for anticoagulents.