



## Developing Computational Methods for Enzyme Design

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As part of an ongoing project to develop methods for the computational design of enzymes, docking programs were evaluated based on three criteria: 1) Does the docking program predict binding of the correct substrate? 2) Does the docking program correctly predict that the enzyme binds more strongly to a transition state analog than to the ground state? 3) Does the docking program predict that the enzyme binds the product less strongly than the substrate? The study focused on the performance of the Molegro Virtual Docker (MVD) program and the docking program FRED. The enzyme chorismate mutase, which catalyzes the reaction of chorismate into prephenate, and a variety of mutants were explored, since the quantitative experimental data about binding of substrate, transition state and product are known, and 3D structures of the proteins are available. The interactions of chorismate mutase enzyme and various point mutations, with chorismate, a transition state analog, and prephenate were tested. Initial comparisons of docking results with available kinetic data display no correlation between docking scores and the presence or absence of bonds known to be necessary for catalysis versus the rate of catalysis or  $K_M$ . The respective binding affinities calculated for chorismate, a transition state analog inhibitor, and prephenate display the correct trend, but the differences between binding affinities are found to fall within the error range of the program for the prediction of binding affinities. Thus the programs calculate the magnitudes of docking correctly but not precisely enough to numerically differentiate between different poses.