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gREST prediction of substrate bindings to stereoselective enzymes

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Molecular Dynamics (MD) simulations are increasingly used to predict protein-ligand bindings. Advances in enhanced sampling algorithms enable us to perform ms-scale simulations, rapidly raising the predictive power. Here, we apply the generalized replica-exchange with solute tempering method, gREST [1], which is a generalization of REST/REST2 [2], for the prediction of substrate bindings of stereoselective enzymes, Fsa2 and Phm7 [3]. Two enzymes catalyze [4+2] cycloadditions to form enantiomeric products. The gREST simulations extensively sampled possible binding poses otherwise elusive in conventional simulations, predicted the binding models consistent with the site-directed mutagenesis experiment. Intriguingly, the substrate bound to each of enzymes exhibits largely different flexibility, suggesting the distinctive mechanism behind these stereoselective reactions.

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