Title:	Substrate Promiscuity: Ambiguity in Disguise
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Abstract: Enzymes have remarkable substrate specificity and selectivity required for their function. However, enzymes often catalyze non-cognate substrates or reactions referred to as promiscuity. Such secondary reactions serve as reservoirs for evolving novel enzymatic functions and could facilitate adaptations under environmental or genetic perturbations. The substrate promiscuity is the inherent ability of the enzyme to catalyze alternate substrate(s). Elucidating structural insights of substrate promiscuity would enable rational enzyme design. Previous studies have indicated the roles of various structural attributes, yet the mechanistic insights of promiscuity still remain elusive. The overall objective of the work is to investigate the structural and/or conformational basis of substrate promiscuity by analyzing curated sets of generalists (multiple substrates) and specialist (one substrate) enzymes. We carefully constructed a dataset of substrate promiscuous (generalist) and specialist enzymes that have experimentally determined structures bound to their cognate substrate or analogs. First, we examined the active site attributes of generalists/specialists to discern promiscuous enzyme features. Through multiple approaches, we found that active site features are ubiquitously shared features among generalist/specialist enzymes. Thus suggesting that features such as flexibility and hydrophobicity are commonly required for enzymatic functions and may not be distinguishable properties of promiscuous enzymes. Based on previous studies, we examined the role of conformational flexibility in accommodating alternate substrates. We performed long timescale (1.5 □s) equilibrium Molecular Dynamics (MD) simulations for 14 enzymes (7 of each specialist and generalist). We investigated whether enzymes' distinct active site conformations would have variable preferences for various substrates. The conformations were clustered using structure-based independent component analysis and assessed for the function of clusters using function variability measure. We observed that most promiscuous/specialist enzymes have distinct active site conformations; however, these show similar functional states (closer to an enzymatically active form). This suggests that distinct conformations states may not necessarily exhibit selective preferences for substrates; instead, subtle differences among conformations may enable the accommodation of alternate substrates. Apart from comparing the conformational diversity of active site residues, we investigated their connectivity to regions of high conformationally frustrated interactions(RHF), which have been implicated to have roles in protein function. Using three short MD simulations, we identified RHF residues and constructed a community network of residues based on correlated motions. The active site is modular, suggesting that correlated motions are essential for binding/catalysis. Notably, most RHF residues belong to or are linked to communities containing active site residues, indicating their influence on functional states. The present work proposes the view of substrate promiscuity as a continuum against the prevailing notion of distinct generalist and specialist enzyme classes. Through our analyses, we have provided insights into the structural and conformational aspects of substrate promiscuity of enzymes.

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