Virtual screening performance and core-hopping potential of common pharmacophore hypotheses derived from Phase's novel pharmacophore feature-based shape alignment

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Motivated by very fast shape-alignment algorithms and the continuing need for pharmacophore modeling support in ligand- and structure-based discovery projects, we have developed a novel approach to generating common pharmacophore hypotheses by using feature-based shape alignments. We quantify the performance of this new method with a unique hypothesis-ranking metric in several retrospective virtual screening experiments. Using the DUD-E dataset, we examine the effect that the number and diversity of the active ligands employed in hypothesis creation have on the hypotheses' enrichment and core-hopping potential. We then compare the results to pharmacophore hypotheses that have been derived solely from protein-ligand complexes. Finally, using a dataset of aligned ligands taken from PDB complexes, we quantify the new common pharmacophore method's ability to generate interpretable hypotheses.