Probabilistic Pharmacophore Matching

Boris Klebansky and Richard M. Fine

BioPredict, Inc.

Abstract

Many problems in computational chemistry can be reduced to finding a match of chemical features in three dimensions. Problems that can be tackled in this way include pharmacophore matching for small molecules as well as docking ligands into the active site of a protein. Here we apply a Markov Random Fields (MRF) computational engine to this problem. Pharmacophore match is performed as a graph match of a source pharmacophore to a target pharmacophore of the ligand and, in docking, to pharmacophore description of the active site. The pharmacophores are graphs, whose nodes are chemical entities and whose edges are associated distance constraints. The weighted graph-matching problem is expressed as an MRF model, whose solution minimizes its associated free energy function. The resulting solution is a maximal a posteriori (MAP) probability distribution that statistically describes optimal (in MAP) match of the pharmacophore into ligand or into protein active site. Individual low-energy placements of the pharmacophore are obtained by marginalizing the MAP distribution. MRFs can be combined, allowing simultaneous probabilistic match into multiple models (ensembles) of ligand conformations or protein active sites to account for ligand and protein flexibility or to represent protein families. This results in newly defined consensus pharmacophore that mix features of constituent models. To bias pharmacophore matches MRFs can incorporate sets of probabilistic beliefs, expressed as probabilistic prior distributions. We also describe how to combine the probabilistic pharmacophore matches to derive a consensus pharmacophore from a set of ligands.

We acknowledge grant support from NIH-GM071055.

bk@biopredict.com