LTHREADER: PREDICTION OF LIGAND-RECEPTOR INTERACTIONS USING LOCALIZED THREADING

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Identification of ligand-receptor interactions is important for drug design and the treatment of diseases. Difficulties in detecting these interactions using high-throughput experimental techniques motivate the development of computational prediction methods. We propose a novel threading algorithm, LTHREADER, which generates accurate local sequence-structure alignments and integrates statistical and energy scores to predict interactions within ligand-receptor families. LTHREADER uses a profile of secondary structure and solvent accessibility predictions with residue contact maps to guide and constrain alignments. Using a decision tree classifier and low-throughput experimental data for training, it combines information inferred from statistical interaction potentials, energy functions, correlated mutations and conserved residue pairs to predict likely interactions. The significance of predicted interactions is evaluated using the scores for randomized binding surfaces within each family. We apply our method to cytokines, which play a central role in the development of many diseases including cancer and inflammatory and autoimmune disorders. We tested our approach on two representatives from different structural classes (all-alpha and all-beta proteins) of cytokines. In comparison with the state-of-the-art threader RAPTOR, LTHREADER generates on average 20% more accurate alignments of interacting residues. Furthermore, in cross-validation tests, LTHREADER correctly predicts experimentally confirmed interactions for a common binding mode within the 4-helical long chain cytokine family with 75% sensitivity and 86% specificity. For the TNF-like family our method achieves 70% sensitivity with 55% specificity. This is a dramatic improvement over existing methods. Moreover, LTHREADER predicts several novel potential ligand-receptor cytokine interactions.

Supplementary website: http://theory.csail.mit.edu/lthreader