BASED ON THE LOCAL SEQUENCE SIMILARITY METHOD FOR PREDICTION OF AMINO ACID POSITIONS RELATED TO THE PROTEIN-LIGAND SPECIFICITY

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Motivation and aim: Detection of the residues responsible for ligand specificity is applied in protein engineering and discovery of new drug targets. However, many existing methods require the precise superposition of functionally specific residues in aligned sequences. This is not always possible in the case of diverged protein family. We applied original method SPrOS (Specificity Projection On Sequence) to detect amino acid positions associated with ligand specificity of proteins belonging to the same family.
Methods and algorithms: The method SPrOS allows detecting the amino acid residues specific to user-defined groups. SPrOS compares the sequence segments from the studied protein and proteins from the training set. Contrary to other segment-comparison approaches extracting the string motifs, SPrOS calculates the scores for single positions by the similarity of their surroundings. We tested our method on the sequences of protein kinases classified by interaction with small molecular compounds known as the promising leads for drug development.
Results: The prediction of ligand-specific positions was performed on kinases with known 3D structure. The significant specificity estimates were obtained for residues located in ATP-binding cleft, which is a known binding-site for kinase inhibitors. The impact of several found residues is confirmed by the published experimental studies. Filtering out the close homologues of the test protein at the sequence comparisons, we were able to locate specific residues with the more precision.
Conclusions: We showed the applicability of our method for recognition of the amino acid residues associated with ligand specificity. The method was successfully applied to complicatedly partitioned protein family when functional classification differs from phylogeny. Based on inspecting the 3D structures, we suggest that predicted positions determine specific interaction by directly contacts with the ligand molecule.
Available: http://www.way2drug.com/spros/

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References
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