**HitPick: a web server for hit identification and target prediction of chemical screenings**

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**ABSTRACT**

**Motivation:** High-throughput phenotypic assays reveal information about the molecules that modulate biological processes, such as a disease phenotype and a signaling pathway. In these assays, the identification of hits along with their molecular targets is critical to understand the chemical activities modulating the biological system. Here, we present HitPick, a web server for identification of hits in high-throughput chemical screenings and prediction of their molecular targets. HitPick applies the B-score method for hit identification and a newly developed approach combining 1-nearest-neighbor (1NN) similarity searching and Laplacian-modified naïve Bayesian target models to predict targets of identified hits. The performance of the HitPick web server is presented and discussed.

**Availability:** The server can be accessed at http://mips.helmholtz-muenchen.de/pro/hitpick.

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**INTRODUCTION**

Chemical biology experiments are increasingly used to search for chemical modulators of biological processes in cell-based and even whole-organism assays as illustrated by the thousands of phenotypic screenings stored in public repositories (Seiler et al., 2008; Wang et al., 2010). In these assays, the identification of the molecular targets of hits is essential to understand the molecular basis of the chemical activities in the bioassay. Recently, drug target prediction methods have been applied to the hits of cells (Young et al., 2008) and zebrafish (Lagmner et al., 2012) phenotypic screenings showing that computational approaches are suitable tools that facilitate the interpretation of the biological activity of chemicals.

Although diverse *in silico* methods have been proposed to identify hits (Makarenkov et al., 2007; Malo et al., 2006) and predict targets for chemicals [reviewed in (Kuhn et al., 2008)], only few of them are available as easy-to-use online tools (Keiser et al., 2007; Wang et al., 2012). To overcome this situation and assist in the analysis and interpretation of chemical phenotypic screens, we introduce HitPick, the first web server for hit identification and target prediction of chemical screenings. HitPick provides the functionality to detect bioassay hits using the B-score method and predicts targets of a chemical of interest using a new integrative approach that combines 1-nearest-neighbor (1NN) similarity searching and a machine-learning method. On cross-validation, the target prediction approach of HitPick performs better than each of the methods alone, achieving a sensitivity of 60.94%, a specificity of 99.99% and a precision of 92.11%.

**2 METHODS**

We apply the widely used B-score method for hit identification, which uses the median polish procedure to remove the bias in rows and columns in a plate (Malo et al., 2006). Hits are determined by a P-value cut-off of 0.05, and replicates of compounds will be considered as hits when all the replicates are identified independently as hits.

For target prediction, HitPick uses a newly developed approach that combines two methods based on 2D molecular fingerprints, namely, 1NN similarity searching (Schuffenhauer et al., 2003) and Laplacian-modified naïve Bayesian target models (Nidhi et al., 2006). For each query compound, the most similar compound from a dataset of known ligand–target interactions is determined by calculating the pairwise Tanimoto coefficient (Tc) (Willett, 1998). Then, Laplacian-modified naïve Bayesian target models generate a score for all known targets of the most similar compound (Nidhi et al., 2006), resulting in a list of ranked target predictions.

For the implementation of this approach, we used a set of 145 549 human chemical–protein physical interactions extracted from the STITCH 3.1 database (Kuhn et al., 2012). In this study, we restrict the target prediction to human proteins, as it is currently the species with the largest number of known drug targets, enabling thus more accurate predictions. In total, we obtained 99 572 compounds with unique SMILES strings with known interactions for which we generated 2D circular fingerprints based on the Morgan algorithm with feature invariants similar to the FCFP (Rogers and Hahn, 2010) using RDKit (http://rdkit.org). Using these molecular fingerprints, we created Bayesian models for 1375 proteins with at least three known ligands. For benchmarking, we randomly assigned 85% of the known ligands to the training set and the remaining 15% to the validation set. In total, the validation set contained 22 868 positive and 20 779 507 negative compound–target relationships, respectively.

To facilitate the analysis of experiments with many hits, the target prediction for screenings with >100 hits is carried out for a structurally diverse subset of 100 compounds obtained by applying the MaxMin-Algorithm (Ashton et al., 2002) implemented in RDKit.

The fingerprint creation for the STITCH compounds, building and application of Bayesian target-specific fingerprint models were implemented in a KNIME (http://www.knime.org) workflow making use of the chemoinformatic functionality provided by KNIME itself as well as by RDKit.

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HitPick reports only those targets per compound for which we can reliably estimate the precision. The precision depends on the similarity to the most similar compound in the set of known interactions as well as on the rank of the target’s score. Users can select different precision thresholds for the target prediction results as desired. Under a lower threshold, more chemicals will have predictions at the cost of a lower precision. In addition, an overview of the predicted targets is given in form of pie chart.

The processing time for hit identification depends on the size of the assay data. For bioassays containing less than 5000, 10 000 and 100 000 compounds, the web server returns the results in less than 1, 2 and 30 min, respectively. The target prediction takes ~5 min per batch of query.

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**Conflict of Interest:** none declared.


