ChemMapper: a versatile web server for exploring pharmacology and chemical structure association based on molecular 3D similarity method

Jiayu Gong¹,†, Chaoqian Cai¹,†, Xiaofeng Liu²,* Xin Ku³, Hualiang Jiang², Daqi Gao¹ and Honglin Li¹,²,*.†

¹School of Information Science and Engineering, ²Shanghai Key Laboratory of New Drug Design, State Key Laboratory of Bioreactor Engineering, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China and ³Department of Proteomics and Bioanalytics, Center of Life and Food Sciences Weihenstephan, Technische Universität München, Freising 85354, Germany

ABSTRACT

Summary: ChemMapper is an online platform to predict polypharmacology effect and mode of action for small molecules based on 3D similarity computation. ChemMapper collects >350,000 chemical structures with bioactivities and associated target annotations (as well as >3,000,000 non-annotated compounds for virtual screening). Taking the user-provided chemical structure as the query, the top most similar compounds in terms of 3D similarity are returned with associated pharmacology annotations. ChemMapper is designed to provide versatile services in a variety of chemogenomics, drug repurposing, polypharmacology, novel bioactive compounds identification and scaffold hopping studies.

Availability: http://lilab.ecust.edu.cn/chemmapper/

Contact: xfliu@ecust.edu.cn or hlli@ecust.edu.cn

Supplementary information: Supplementary data are available at Bioinformatics online.

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1 INTRODUCTION

Recent advances in systems biology and chemical biology exhibit great challenges to the current drug discovery paradigm that drugs selectively bind with one or two targets and show that most drugs interact with multiple targets, namely, polypharmacology (Keiser et al., 2009; Paolini et al., 2006). On the other hand, identification of new hit compounds and optimization of lead compounds targeting specific proteins or exhibiting desired pharmacological effects are still playing a pivotal role in conventional drug discovery projects in the form of virtual screening and scaffold hopping. In this context, there is an urgent request for developing new strategies to acquire knowledge of the complete pharmacology profile and bridge the chemical and pharmacological spaces to improve the success rates of current drug discovery research, including reducing the side effects and increasing the regulatory effects on the complete networks (Keiser et al., 2009).

One of the emerging scenarios to address this question is the application of molecular similarity searching on basis of the well-known similar property principle, namely, similar structures may have similar bioactivity and the same potential drug targets, which is expected to relate the pharmacology space by chemical structural similarity information (Johnson et al., 1990). According to this principle, small molecule similarity had been used to identify off-targets for a long period (Boehm et al., 2008). The 2D similarity methods have been widely used in various online tools, like Similarity Ensemble Approach (SEA) (Keiser et al., 2007), SuperPred (Dunkel et al., 2008) and ChemProt (Kim Kjaerulff et al., 2013), which relate protein pharmacology and disease networks by fingerprint-based ligand similarity, and FtreesWeb (Rarey and Dixon, 1998), which adopts graph theory to encode molecular 2D descriptions to perform virtual screening against large chemical databases. Also, numerous online servers using 3D similarity methods are also emerging, like Superimposé (Bauer et al., 2008), which provides two different 3D superimposition algorithms and three different databanks for screening, and wwLigCSRre (Sperandio et al., 2009), which is built on top of CSR algorithm that searches for the maximal common substructure between two sets of unordered coordinates to screen focused chemical libraries. Recently, a direct comparison of 2D and 3D methods for on- and off-target prediction reveals that the benefit of 3D over 2D was obvious for prediction of polypharmacology and drug pairs that shared high 3D similarity but low 2D similarity (i.e. a novel scaffold) were shown to be much more likely to exhibit pharmacologically relevant differences in terms of specific protein target modulation (Yera et al., 2011).

Herein, we present a versatile web-based tool ChemMapper for exploring target pharmacology and chemical relationships against any given small molecules via SHAFTS, a fast 3D similarity method in which the 3D similarity calculation is driven by the hybrid information of molecular shape and chemotype features (Liu et al., 2011; Lu et al., 2011). ChemMapper assembles a large repertoire of bioactive chemical database annotated with target information and multiple screening databases from different catalogs of the chemical vendors. It facilitates identification...
of potential targets that may play a pivotal role in biological response to the drugs and other active chemicals, as well as the discovery of new hit compounds with similar pharmacology profiles but novel scaffolds. Moreover, ChemMapper can also be useful in the application of drug repurposing, as well as investigation of potential side effects related to the drugs and other active chemicals.

2 METHOD

2.1 Data set-up

The polypharmacology information for the bioactive compounds and biological annotations of the corresponding targets was gathered from various public databases, including ChEMBL (ChEMBL 14), DrugBank (version 3.0), BindingDB (December 2012), KEGG (May 2011) and PDB (November 2010). The chemical–protein interaction annotations were categorized as follows: protein name, UniProt access ID, species, biological functions, Gene Ontology (GO) annotations (molecular function and biological process involved) and activity data. Other non-annotated chemical structures are also incorporated for virtual screening from public databases like ZINC. The final database consists of nearly 350,000 molecular entries annotated for >20,000 proteins and >3 million compounds for virtual screening. Multiple 3D conformers were pre-generated for each compound to facilitate 3D similarity calculation (Supplementary Table S1).

2.2 Similarity metrics

ChemMapper uses SHAFTS as the 3D similarity calculation method. SHAFTS adopts a hybrid similarity metric combined with molecular shape and colored (labeled) chemical groups annotated by pharmacophore features, which is designed to integrate the strength of pharmacophore matching and volumetric overlay approaches. Previous studies proved SHAFTS is more efficient and accurate in ligand-based virtual screening than the common 2D fingerprint-based similarity and other 3D similarity methods (Liu et al., 2011; Supplementary Material).

3 WEB INTERFACE

ChemMapper accepts a chemical structure (sketched online or uploaded in multiple chemical structure file formats) as the query and provides two types of online calculation services: Target Navigator and Hit Explorer. The input 2D structure will be automatically converted into single 3D conformer. In the Target Navigator mode, the users are allowed to search either bioactive compound collections with corresponding target information (ChEMBL, DrugBank and BindingDB) or chemical substrates from the KEGG enzyme database. The results table can be filtered, re-ordered and grouped in terms of various rules (Supplementary Fig. S1a). A list of potential protein targets is returned ranked by the inference of chemical–protein association network whose edges weighed by the bioactivity of the similar compounds to the query (Supplementary Fig. S1b). The biological annotations for each target, including name, species, function and involved pathway, are displayed as well (Supplementary Fig. S1c). In the Hit Explorer mode, only the most similar compounds from various public chemical repositories to the query are returned, which presumably exhibit similar bioactivity or function. Alternatively, the users are able to upload their customized mini-database (in sdf or mol2 format) for virtual screening by 3D similarity calculation. In both mode, the overlay poses between the query and each target compound can be visualized. All the information in the result table can be downloaded in Comma Separated Values (csv) format as well. Two test cases (polypharmacology effect of loratadine and scaffold-hopping for EGFR inhibitors) relevant to the two modes are described in detail in the Supplementary Materials.

Comparing with 2D fingerprint-based similarity calculation, 3D similarity calculation is slower: a typical query to the ChEMBL (339,624 entities) in ChemMapper takes 12–24 h. A monitoring page is provided for bookmarking to redirect to the result page as the job finishes.

4 CONCLUSION

The goal of ChemMapper is to provide an online versatile framework for fast exploring the target pharmacology and chemical relationship via molecular 3D similarity methods. ChemMapper links bioactivity and target protein annotation data associated to small molecules to chemical 3D similarities, which can lead to novel perspectives and new applications to the old drugs and suggest new associations between the chemical and pharmacological spaces.

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REFERENCES


