Citation: CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e105; doi:10.1038/psp.2014.1

www.nature.com/psp

ORIGINAL ARTICLE

VNP: Interactive Visual Network Pharmacology of Diseases, Targets, and Drugs

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In drug discovery, promiscuous targets, multifactorial diseases, and "dirty" drugs construct complex network relationships. Network pharmacology description and analysis not only give a systems-level understanding of drug action and disease complexity but can also help to improve the efficiency of target selection and drug design. Visual network pharmacology (VNP) is developed to visualize network pharmacology of targets, diseases, and drugs with a graph network by using disease, target or drug names, chemical structures, or protein sequence. To our knowledge, VNP is the first free interactive VNP server that should be very helpful for systems pharmacology research. VNP is freely available at http://cadd.whu.edu.cn/ditad/vnpsearch.
CPT Pharmacometrics Syst. Pharmacol. (2014) **3**, e105; doi:10.1038/psp.2014.1; published online 12 March 2014

INTRODUCTION

Drug discovery and development is a highly complex, lengthy, and expensive process, which starts from understanding molecular mechanisms of diseases, proceeds through selecting therapeutic targets, and leads to discovering drug leads and optimizing drug candidates.[1–4] Diseases are usually multifactorial,[5] in which multiple targets are affected and have to be targeted for successful treatment outcomes. Target proteins are always promiscuous[6] with small molecular drugs. "Dirty" drugs may bind to many different molecular targets or receptors in the body and so tend to have a wide range of effects and possibly negative side effects.[7–11]

Several research groups curated different databases for storing information of diseases, targets, and drugs. Online Mendelian Inheritance in Man contains information on all known mendelian disorders and >12,000 genes.[12] However, there is a lack of the disease-related target and drug information. DrugBank database combines detailed drug (i.e., chemical, pharmacological, and pharmaceutical) data with comprehensive drug target (i.e., sequence, structure, and pathway) information.[13] In DrugBank, the therapeutic indication descriptions (for example, "Used in combination with prednisone for the treatment of metastatic, castration-resistant prostate cancer") of drugs are listed, which needs further manual curation for specific diseases. BindingDB is a public, Web-accessible database of measured binding affinities, focusing chiefly on the interactions of proteins considered to be drug targets with small, drug-like molecules.[14] The disease information of the targets and drugs are not yet provided. Therapeutic Target Database is a database containing information about the known and explored therapeutic proteins and nucleic acid targets, diseases, pathway information, and the corresponding drugs.[15]

The above-mentioned databases provide valuable resources for drug discovery. Currently, the potentially useful knowledge among diseases, targets, and drugs are still hidden in the text descriptions. CIDeR (multifactorial interaction networks in human diseases) provides a systems biology tool to integrate disease-associated factors focusing on metabolic and neurological diseases.[16] Using systems or network[4,10,17,18] tools to investigate the structure and dynamics of molecular networks is a novel paradigm of drug discovery.

RESULTS

Disease-Target-Drug Database

Disease-Target-Drug Database (http://cadd.whu.edu.cn/ditad/) stores known connections among diseases, targets, and drugs approved by the US Food and Drug Administration. Each record has a drug target, which is also used as a bridge to link diseases and drugs. Currently, there are >1,000 diseases, >500 protein targets, and >4,000 drugs (including >2,500 herb medicines and 1,500 chemical drugs) curated with tens of thousands of connections among them. The diseases and drugs are curated from the "Pharmacopoeia of People's Republic of China, version 2010, three columns" (http://en.wikipedia.org/wiki/Pharmacopoeia_of_the_People%27s_Republic_of_China), compiled by the Chinese Pharmacopoeia Commission (http://www.chp.org.cn/cms/about/). The target information is from the Therapeutic Target Database.[15] To our knowledge, there are no visual and interactive Web-based tools available elsewhere to explore the network pharmacology complex relationships.

Visual network pharmacology

Visual network pharmacology (VNP) is specially designed to visualize the complex relationships among diseases, targets, and drugs, which mainly contains three functional modules: drug-centric, target-centric, and disease-centric VNP. Users can search the database using disease, target, or drug name strings; chemical structures and substructures; or protein sequence similarity and then obtain an online interactive network view of the retrieved records. In the obtained network view, each node is a disease, target, or drug, and each edge is a known connection between two of them.

Three search examples are illustrated: a disease-centric network (**Figure 1**), retrieved by "Alzheimer's disease"; a target-centric network (**Figure 2**), obtained by "Muscarinic

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Received 6 November 2013; accepted 28 December 2013; advance online publication 12 March 2014. doi:10.1038/psp.2014.1

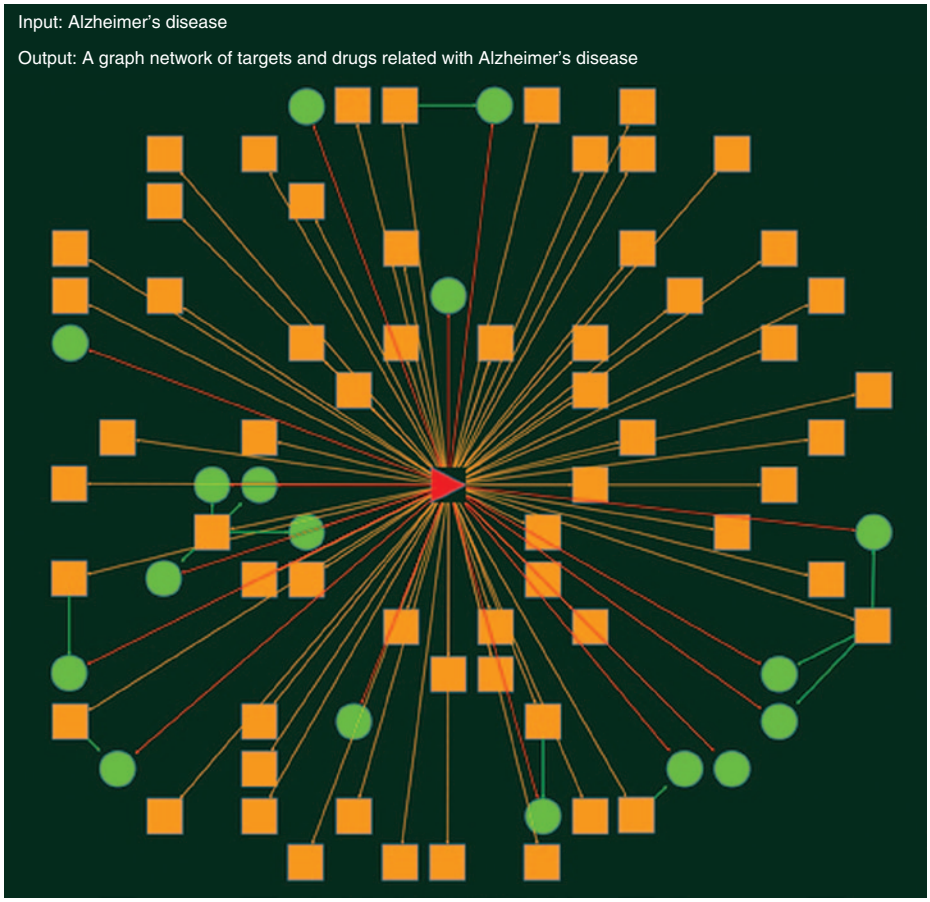

Figure 1 A disease-centric view of visual network pharmacology retrieved by the search term "Alzheimer's disease."

acetylcholine receptor"; and a drug-centric network (**Figure 3**), searched by chemical substructure (7-amino-3-cephem-4-carboxylic acid), in which red triangles, green circles, and yellow rectangles correspond to diseases, drugs, and targets, respectively.

In **Figure 1**, the input disease string "Alzheimer's disease" will find >50 proteins and >10 drugs. The graph provides an intuitive view to network the targets and drugs related with Alzheimer's disease. The connection degrees between targets and drugs are asymmetry, for instance, three drugs connecting to acetylcholinesterase. One drug is linked to alpha-2 adrenergic receptor.

In **Figure 2**, the query string "Muscarinic acetylcholine receptor" will obtain six targets. These targets are found connecting with >20 diseases and 50 drugs.

In **Figure 3**, the network view is obtained by chemical substructure "7-amino-3-cephem-4-carboxylic acid," represented as smiles string[23] "NC1C(=O)N2C1SCC=C2C(=O)O." There are >30 drugs containing the chemical substructure. These drugs are further mapped with six diseases and six targets. Furthermore, after clicking on any node on the graph, users will get a detailed list of the related records.

DISCUSSION

Network pharmacology analysis

In the VNP graphs, diseases are usually multifactorial, in which multiple targets/pathways have to be involved for the successful treatment outcomes and thus multiple drugs are usually developed for the same disease. Second, target proteins are always promiscuous with small molecular drugs and are related with different diseases. Third, some drugs are found interacting with several different molecular targets or receptors in the body, which might be the reason that the drugs have a wide range of effects and possibly negative side effects. Using the VNP, users can easily get a landscape of the related diseases, targets, or drugs in a dynamic and interactive way.

VNP has potential applications such as network analysis of drug combinations and drug repositioning. Hypertension is a typical disease with multiple mechanisms resulting from a complex interaction of genes and environmental factors. VNP provides a convenient tool to get an overview (**Supplementary Figure S1**) of the drugs and targets for the treatment of hypertension. The treatment of hypertension involves multiple mechanisms and thus several targets. The majority of people require more than one drug to control their hypertension, which includes thiazides, angiotensin-converting enzyme inhibitor, angiotensin receptor block, or calcium channel blocker.[19] Some combinations of drugs might be avoided in practice, such as the use of clonidine, verapamil, or diltiazem together with a beta-blocker.[19] How to select drug combinations for personal treatments is still a very challenging issue waiting for network or systems pharmacology modeling. What should also be noted is that "dirty drug" phenomenon[7–11] can

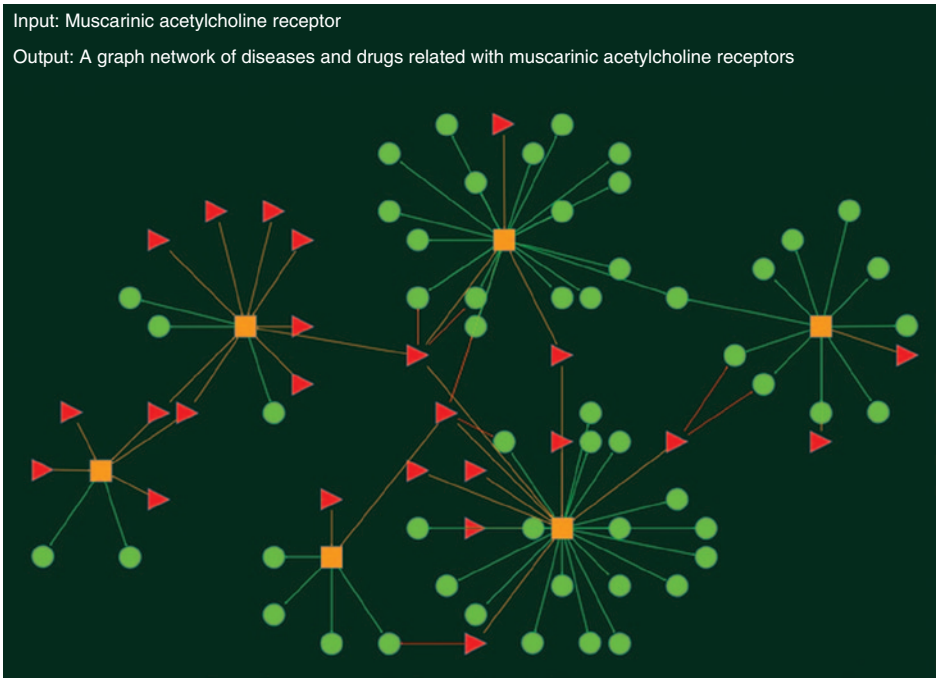

Figure 2 A target-centric view of visual network pharmacology obtained by the term "muscarinic acetylcholine receptor."

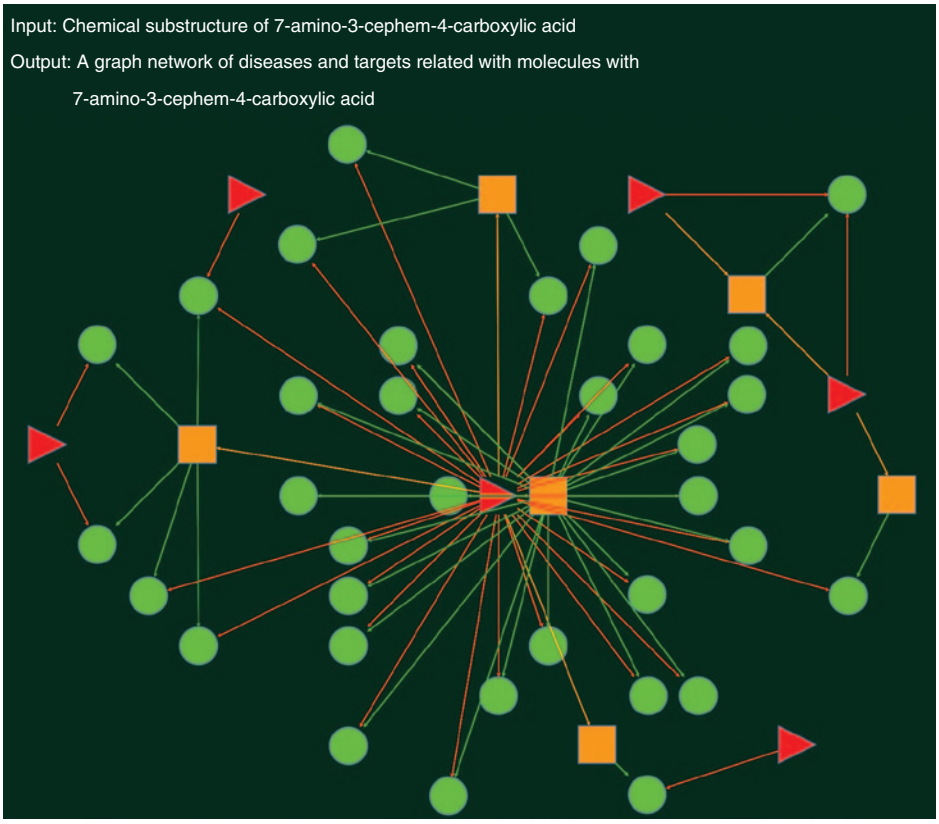

Figure 3 A drug-centric view of visual network pharmacology by chemical substructure (7-amino-3-cephem-4-carboxylic acid).

be found in this example, that is, the drug omapatrilat can bind to both neprilysin and angiotensin-converting enzyme.

Ropinirole has been originally used in the treatment of Parkinson's disease and has been further successfully repositioned in the treatment of restless legs syndrome. The drug target of ropinirole is mainly the dopamine receptor. Using VNP, several diseases are related with the dopamine receptor, which includes schizophrenia (**Supplementary Figure S2**).

Table 1 Comparisons with visualization tools

Name	Website	Data	Online server	Chemoinformatics and bioinformatics search tools
Arena3D	http://arena3d.org	Time-driven phenotypic differences of gene expression data	Desktop	Sequence similarity clustering claimed
		Users' network data	Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
ArrayXPath	http://www.snubi.org/software/ArrayXPath	Microarray gene expression data	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
AVIS	http://actin.pharm.mssm.edu/AVIS2	Biological networks	Server provided	Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools (e.g., sequence analysis) not yet found
BioLayout Express 3D	http://www.biolayout.org	General network graphs	Desktop Not yet based on server	Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools (e.g., sequence analysis) tools not yet found
Biological-Networks	http://biologicalnetworks.net	Biological networks	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
BioTapestry	http://www.biotapestry.org	Genetic regulatory networks	Desktop Web models provided	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
BisoGenet	http://bio.cigb.edu.cu/bisogenet-cytoscape	Molecular interactions information around a set of genes/proteins	Desktop as a Cytoscape plug-in	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
CellDesigner	http://www.celldesigner.org	Biochemical networks	Desktop Not yet based on server	Plug-ins needed to run chemoinformatics (e.g., chemical substructure searching) and
Cell Illustrator	http://www.cellillustrator.com	Biological processes and systems	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
CFinder	http://www.cfinder.org	General networks	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
Cytoscape	http://www.cytoscape.org	General networks	Desktop Not yet based on server	Plug-ins needed to run chemoinformatics (e.g., chemical substructure searching) and
GenePro	http://wodaklab.org/genepro	Protein and gene interaction networks	Desktop as a Cytoscape plug-in	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
GeneWays	http://anya.igsb.anl.gov/Geneways/GeneWays.html	Molecular pathway data from the research literature	Server provided	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
GEOMIi	http://sydney.edu.au/engineering/it/~visual/valacon/geomi/	Complex networks	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
Gephi	http://gephi.org	Networks and complex systems	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
Graphviz	http://www.graphviz.org	Graph visualization	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
Gridlayout	http://kurata21.bio.kyutech.ac.jp/grid/grid_layout.htm	Graph layout	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
Guess	http://graphexploration.cond.org/index.html	Graphs and networks	Desktop Web demo (plug-in needed)	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
Hive Plots	http://www.hiveplot.com	Drawing networks	Desktop Not yet based on server	Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools
Hybridlayout	http://www.cadlive.jp/hybridlayout/hybridlayout.html	Biochemical network maps	Desktop Not yet based on server	Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools not yet found
Hyperdraw	http://www.bioconductor.org/packages/release/bioc/html/hyperdraw.html	Visualizing hypergraphs	Desktop Not yet based on server	Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools (e.g., sequence analysis) not yet found
IM Browser	http://proteome.wayne.edu/PIMdb.html	Interaction data	Web server Java plug-in needed	Chemoinformatics (e.g., chemical substructure searching) tools not yet found
IPath	http://pathways.embl.de	Pathways maps	Server focusing on pathways	Chemical names mapped; no chemical structure searching functions found
JNets	http://www.manchester.ac.uk/bioinformatics/jnets	Protein interaction networks and general networks	Desktop Not yet based on server	Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools
KGML-ED	http://kgml-ed.ipk-gatersleben.de	KEGG Pathway diagrams	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found

Table 1 Continued on next page

Table 1 Continued

Name	Website	Data	Online server	Chemoinformatics and bioinformatics search tools
LEDA	http://www.algorithmic-solutions.com/leda/about/index.htm	Networks or graphs	C++ class library	Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools (e.g., sequence analysis) not yet found
MAVisto	http://mavisto.ipk-gatersleben.de	Motifs in network	Desktop Not yet based on server	Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools not
Medusa	http://coot.embl.de/medusa	Graph visualization	Desktop Not yet based on server	Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools (e.g., sequence analysis) not yet found
ModuLand	http://www.linkgroup.hu/modules.php	Complex networks	Desktop as a Cytoscape plug-in	Chemoinformatics (e.g., chemical substructure searching)and bioinformatics tools (e.g., sequence analysis) not yet found
Multilevel Layout	https://code.google.com/p/multilevellayout	Multilevel layout	Desktop as a Cytoscape plug-in	Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools (e.g., sequence analysis) not yet found
NAViGaTOR	http://ophid.utoronto.ca/navigator	Protein–protein interaction networks	Desktop Not yet based on server	Chemoinformatics (e.g., chemical substructure searching)and bioinformatics tools (e.g., sequence analysis) not yet found
NetMiner	http://www.netminer.com/index.php	Social network and general networks	Desktop Not yet based on server	Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools (e.g., sequence analysis) not yet found
Network Workbench	http://nwb.cns.iu.edu	General networks	Desktop Not yet based on server	Chemoinformatics (e.g., chemical substructure searching)and bioinformatics tools
Ondex	http://www.ondex.org	Networks or graphs	Desktop Not yet based on server	Chemoinformatics (e.g., chemical substructure searching) tools not yet found
Osprey	http://biodata.mshri.on.ca/osprey/servlet/Index	Complex interaction networks	Desktop Not yet based on server	Chemoinformatics (e.g. chemical substructure searching)and bioinformatics tools
Pajek	http://pajek.imfm.si/doku.php	Network analysis and visualization	Desktop Not yet based on server	Chemoinformatics (e.g., chemical substructure searching)and bioinformatics tools
PathDraw	http://rospath.ewha.ac.kr/toolbox/PathwayViewerFrm.jsp	Pathway visualization and manipulation	Desktop Not yet based on server	Chemoinformatics (e.g., chemical substructure searching)and bioinformatics tools (e.g., sequence analysis) not yet found
Pathway Tools	http://bioinformatics.ai.sri.com/ptools	Biological networks	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
PATIKA	http://www.patika.org	Pathway analysis	Server provided	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
PaVESy	http://pavesy.mpimp-golm.mpg.de/PaVESy.htm	Pathway visualization and editing	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
PhyloGrapher	http://www.atgc.org/PhyloGrapher	Eolutionary relationships within families of genes or proteins	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
PIMWalker	http://pimr.hybrigenics.com	Hybrigenics' public interaction data	Server provided	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
PIVOT	http://acgt.cs.tau.ac.il/pivot	Protein–protein interactions	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
PolarMapper	http://kdbio.inesc-id.pt/software/polarmapper	Protein interaction networks	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
ProteinNetVis	http://graphics.cs.brown.edu/research/sciviz/proteins/home.htm	Protein networks	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
ProteoLens	http://bio.informatics.iupui.edu/proteolens	Biological network	Desktop Not yet based on server	Chemoinformatics (e.g., chemical substructure searching) and sequence analysis
RedeR	http://bioconductor.org/packages/release/bioc/html/RedeR.html	Nested networks	Desktop Not yet based on server	Chemoinformatics and sequence analysis tools not yet found
RING	http://protein.bio.unipd.it/ring	Protein residue interaction networks	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
SoNIA	http://www.stanford.edu/group/sonia	Networks data	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found

Table 1 Continued on next page

Table 1 Continued

Name	Website	Data	Online server	Chemoinformatics and bioinformatics search tools
Transcriptome-Browser	http://tagc.univ-mrs.fr/tbrowser	Transcriptional signatures	Server provided	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
UCSF structureViz	http://www.cgl.ucsf.edu/cytoscape/structureViz	Biological networks	Desktop as a Cytoscape plug-in	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
VANTED	http://vanted.ipk-gatersleben.de	Biological pathways	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
VisANT	http://visant.bu.edu	Biological networks and pathways	Server provided	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
VitaPad	http://sourceforge.net/projects/vitapad	Biological pathways and map experimental data to them	Desktop Not yet based on server	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
WebInterViewer	http://interviewer.inha.ac.kr	Networks	Server provided	Chemoinformatics tools (e.g., chemical substructure searching) not yet found
yFiles	http://www.yworks.com/en/index.html	Visualization of networks and diagrams	Server, APP, and packages provided	Chemoinformatics (e.g., chemical substructure searching) and sequence analysis tools not yet found
yWays	http://www.yworks.com/en/products_yfiles_extensionpackages_ep2.htm	Visualization of networks and diagrams	Server, APP, and packages provided	Chemoinformatics (e.g., chemical substructure searching) and sequence analysis tools not yet found
VNP	http://cadd.whu.edu.cn/ditad/vnpsearch	Diseases-Targets-Drugs network pharmacology relationships	Yes	Chemical substructure searching and sequence similarity calculation functions embedded

The tools compared are from Table 1 of ref. 4.

After searching literatures, ropinirole is found to be an effective adjunctive treatment for schizophrenia.[20] Through the drug target (via VNP searching) as a bridge, it is possible to find potential new indications of an old drug. However, ropinirole can also cause nausea, dizziness, hallucinations, orthostatic hypotension, sudden sleep attacks, hypersexuality, punding, and compulsive gambling.[21] How to distinguish side effects and drug repositioning is another challenge of network or systems pharmacology modeling techniques.

In drug discovery cases, fully understanding the complex network relationships among diseases, targets, and drugs still remains a big challenge, yet it is essential for understanding multiple mechanisms of diseases, selecting important therapeutic targets, reducing side effects, and discovering new therapeutic indications of old drugs.[22]

Method comparisons

A comprehensive comparison is carried out to compare network pharmacology visualization tools and disease-related data, as shown in **Tables 1** and **2** respectively. The software comparison table (**Table 1**) includes (i) data, (ii) online server; and (iii) chemoinformatics and bioinformatics search tools. The table on data comparisons (**Table 2**) is composed of (i) data different from that in VNP and (ii) the detail regarding whether there is a network pharmacology server visualizing the data. From the comparisons, the technical novelty of VNP is highlighted as the first network pharmacology server combined with bioinformatics and chemoinformatics tools for network analysis of multifactorial diseases, promiscuous target proteins, and "dirty" drugs.

METHODS

Substructure searching

Chemoinformatics is the application of computer and informational techniques to a range of problems in the field of chemistry, in which a key tool is to find a mapping for a query to a target molecule. Our group implemented chemoinformatics tools to search substructure in biochemical reaction database.[23]

Sequence similarity searching

In this work, we applied protein Smith–Waterman similarity methods[24–26] to compare a query biological sequence with different target protein sequences. The software package is downloaded from the FASTA (a protein sequence similarity software) team at Virginia University (http://fasta.bioch.virginia.edu/fasta_www2/fasta_list2.shtml).

Graph visualization

In this work, the diseases, targets, and drugs are treated as graph nodes, and the connections among them are regarded as graph edges. Our purpose is to position the nodes of a graph in two-dimensional space so that all the edges are of more or less equal length and there are as few crossing edges as possible, by assigning forces among the set of edges and the set of nodes, based on their relative positions, and then using these forces either to simulate the motion of the edges and nodes or to minimize their energy.[27] A Fruchterman–Reingold force-directed graph-drawing algorithm is implemented to assign forces among the sets of edges and nodes (diseases, targets, and drugs) of a graph drawing.

Web server

On the Web server side, Apache, Python, Django, C++, Javascript, and Ajax tools are used to integrate the related chemoinformatics, bioinformatics, graph layout, and visualization tools.

Acknowledgments. This study was supported by grants from the National Natural Science Foundation of China, the Ministry of Science and Technology of China (973 and 863 Programs), the program for New Century Excellent Talents in Universities, and the National Mega Project on Major Drug Development.

Table 2 Comparisons with disease-related networks

Type of related data (types of network nodes)	Name and additional description, website	Reference	Data different from VNP	Network pharmacology server
• Disease • Disease-related genes	Human disease network (Cytoscape plug-in DisGeNET: http://ibi.imim.es/DisGeNET/DisGeNETweb.html)	Goh *et al.*, 2007, Feldman *et al.*, 2008, Bauer-Mehren *et al.*, 2010, and Stegmaier *et al.*, 2010	Drug and drug-related information missing	No online server
• Disease • Disease-related genes • Interactome • Publication	Gene-based, interactome-enriched, and scientific publication–based human disease networks	Zhang *et al.*, 2011a	The Orphan Disease Networks Drug and drug-related information missing	No online server
• Disease	Disease-responsive interactome module-based human disease network (disease correlations based on disease-induced changes in mRNA expression of interactome modules)	Suthram *et al.*, 2010	Elucidating relationships between diseases using preexisting knowledge of disease genes; and further found some disease correlations also sharing common drugs	No online server
• Interactome module • mRNA changes			The drug-related networks missing or not used	
• Disease	A Bayesian network-based disease-responsive transcriptome analysis to construct a human disease network	Huang *et al.*, 2010a	Transform public gene expression repositories into an automated disease diagnosis database.	No online server
• mRNA changes at the transcriptome level			Disease diagnosis system can be used to characterize complex phenotypes and to construct a disease–drug connectivity map.	
• Drugs			Target-related information missing.	
• Disease • Disease-related genes • Interactome • Protein/DNA interaction • Tissue • Drug	iCTNet: a Cytoscape plug-in to construct an integrative network of diseases, associated genes, drugs, and tissues (http://www.cs.queensu.ca/ictnet)	Wang *et al.*, 2011b	A large-scale network, assembling human disease–gene association, tissue–gene association, disease–tissue associations, protein–DNA interactions, protein–protein interactions, and drug target information	Running as desktop software acting as a Cytoscape plug-in. Use it locally. Without Web services functions. Users cannot search by using chemical structures or protein sequences.
• Disease • Disease-related genes • Interactome • Gene ontology terms	Biomine: an integrated bioentity network with >1 million entities and 8 million edges (http://biomine.cs.helsinki.fi)	Eronen & Toivonen, 2012	Protein interactions, gene–disease associations, and gene ontology annotations Focus on human genetics Drug-related information missing	Online server Users cannot search by using chemical structures.
• Disease • Expression patterns • MicroRNA targets • Network modules of interactome, transcriptome	PAGED: an integrated bioentity network with >1 million entities from 20 organisms (http://bio.informatics.iupui.edu/PAGED)	Huang *et al.*, 2012b	From multiple levels: the genome, transcriptome, posttranscriptome, and proteome The most comprehensive public compilation of gene sets The drug-related networks missing	Online server Users cannot search by using chemical structures.
• Disease • Disease-related genes • Interactome • Protein–gene regulation pathways • Gene ontology terms • Small molecule (drug) • Species	An integrated bioentity network	Bell *et al.*, 2011	Drug–disease information missing	No online server
• Disease • Adjacent members of metabolic pathways	Metabolic pathway–corrected human disease network	Lee *et al.*, 2008a	Relationships among genetic/epigenetic defects, the metabolic networks, and the disease phenotypes	No online server
• Disease • MicroRNA	MicroRNA/disease association-based disease network obtained from publication data	Lu *et al.*, 2008	MicroRNA–disease associations	No online server

Table 2 Continued on next page

Table 2 Continued

Type of related data (types of network nodes)	Name and additional description, website	Reference	Data different from VNP	Network pharmacology server
• Patient • Disease	Disease comorbidity network	Rzhetsky *et al.*, 2007 and Hidalgo *et al.*, 2009	Disease–genetic variation relationships	No online server
• Disease • Environmental factor • Disease-related genes	Etiome: a database + clustering analysis of environmental + genetic (= etiological) factors of human diseases	Liu *et al.*, 2009	Associations between disease and environmental factors	No online server
VNP	http://cadd.whu.edu.cn/ditad/vnpsearch/		Diseases-Targets-Drugs network pharmacology relationships	Network pharmacology server provided. Chemical substructure searching and sequence similarity calculation functions embedded.

The databases compared and the related references are from Table 2 of ref. 4.

Conflict of Interest. The authors declared no conflict of interest.

Author contributions. Q-N.H. wrote the manuscript. Q-N.H., Z-X.D., and J.L. designed the research. Q-N.H., Z.D., W.T., X.Y., and Z-B.M. performed the research and analyzed data.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ The complex relationships among "dirty" drugs, promiscuous proteins, and multifactorial diseases are not well visualized and explored using online Web servers.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ This study addressed applications of interactive visual network pharmacology tools to network diseases, targets, and drugs in a dynamics Web-based network graph.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ This study provides a Web-based benchmark network pharmacology tool to explore complex relationships among diseases, targets, and drugs.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✓ This article will accelerate applications of systems approaches in clinical pharmacology for target selection, drug repositioning, side effect investigations, and so on.

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