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Mantra 2.0: an online collaborative resource for drug mode of action and repurposing by network analysis

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ABSTRACT

Summary: Elucidation of molecular targets of a compound [mode of action (MoA)] and its off-targets is a crucial step in drug development. We developed an online collaborative resource (MANTRA 2.0) that supports this process by exploiting similarities between drug-induced transcriptional profiles. Drugs are organized in a network of nodes (drugs) and edges (similarities) highlighting 'communities' of drugs sharing a similar MoA. A user can upload gene expression profiles before and after drug treatment in one or multiple cell types. An automated processing pipeline transforms the gene expression profiles into a unique drug 'node' embedded in the drug-network. Visual inspection of the neighbouring drugs and communities helps in revealing its MoA and to suggest new applications of known drugs (drug repurposing). MANTRA 2.0 allows storing and sharing user-generated network nodes, thus making MANTRA 2.0 a collaborative ever-growing resource.

Availability and implementation: The web tool is freely available for academic use at http://mantra.tigem.it.

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1 INTRODUCTION

We developed a computational approach to predict drug mode of action (MoA) and drug repurposing from the analysis of the connectivity map (Lamb *et al.*, 2006), a compendium of gene expression profiles (GEPs) following drug treatment of human cell lines with 1309 bioactive small molecules (Iorio *et al.*, 2010). The approach was based on generating, for each drug, a single 'prototype' ranked list (PRL) of differentially expressed genes following drug treatment across multiple cell lines or at different dosages (Iorio *et al.*, 2010). We devised a drug similarity measure based on gene set enrichment analysis (GSEA; Subramanian *et al.*, 2005) to compute similarity between two PRLs. Transcriptional similarities were represented as a network. The position of a drug within the network was shown to provide insights about its MoA by exploiting previous knowledge on neighbouring drugs.

Here we introduce a collaborative online resource, named MANTRA 2.0, implementing our computational approach to drug discovery integrated with a relational database engineered to analyse and store user-provided GEPs and metadata following small-molecule treatments, single gene perturbations or disease states. An example of a workflow can be found in the help section of the MANTRA 2.0 website. MANTRA 2.0 guides the user beginning with GEP upload and annotation, which are then automatically transformed into a node in the network by connecting it to similar nodes, according to our similarity measure. The result is visualized as an interactive network (Fig. 1) that can be explored to reveal similarities among drugs, genes and diseases.

2 METHODS

2.1 GEP database

We used a relational database (PostgreSQL) for GEPs. The database contains three types of profiles: drug-induced, gene perturbation and disease. Each experiment is stored together with additional metadata.

2.2 Microarray analysis pipeline

MANTRA 2.0 integrates a microarray data analysis pipeline to upload experiments in the drug network. Raw file formats (CEL) for Affymetrix chips HG-U133A, HT_HG-U133A, HG-U133A_2 and HG-U133_Plus_2 are supported. The pipeline implements the MAS5 and Robust Multiarray Averaging (RMA) algorithms (Gautier *et al.*, 2004). Differential expression analysis between treated and untreated samples is performed with a Bayesian *t*-test (Baldi and Long, 2001) and Benjamini–Hochberg false discovery rate correction. MANTRA 2.0 also accepts preprocessed ranked lists of probes (HG-U133A) if raw data are not available or a custom data analysis pipeline is preferred.

2.3 Generation of PRL and evaluation of similarity

PRLs are generated by merging the ranked lists corresponding to the same drug by applying the Borda count method in a hierarchical manner (Iorio *et al.*, 2010). The resulting PRL represents a node in the network. To obtain pairwise distances between the new node and the nodes already

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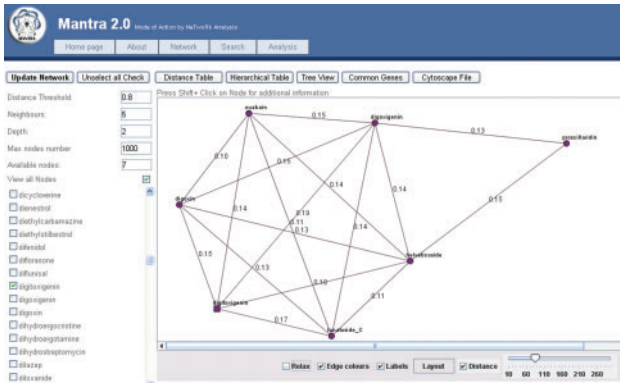

Fig. 1. MANTRA 2.0 web interface. Drugs are represented as nodes in a network. Edges are labelled with the distance between the two drugs

present in the network, we implemented a GSEA-based distance (Iorio *et al*., 2010). Both the merging procedure and the similarity computation algorithms have been implemented in C language and built as a dynamic-link library.

2.4 Visualization and interactive graphical user interface

The network can then be searched for neighbouring nodes or communities. The user interface has been implemented in ASP.NET and VB.NET frameworks. A customized version of the MEDUSA (Hooper and Bork, 2005) visualization system (v.1.03) has been used for the network view.

3 IMPLEMENTATION

MANTRA 2.0 has been designed with attention to usability and reliability. The tool consists of three main workspaces: Analysis, Network and Search.

3.1 The Analysis workspace

The 'Analysis' workspace allows the user (i) to add or remove nodes in the network. A node can be created by uploading microarray-based GEPs with metadata. The PRL is added to the internal database, similarity distances are computed and the new node becomes part of the network; and (ii) to identify which drugs in the network up- or downregulate a specific set of genes by applying GSEA against each PRL in the network.

3.2 The Network workspace

The 'Network' workspace, shown in Figure 1, provides an interactive visualization of the network. The network is made up of nodes representing PRLs and edges connecting significantly similar pairs of PRLs. Nodes corresponding to drug treatments are colour-coded if they belong to the same drug community (Iorio *et al*., 2010). The network can be navigated by means of a point and click interface. A number of options are available to limit the number of nodes and edges visualized according to both topological and similarity distance thresholds. The visualized subnetwork can be downloaded in the form of tabular data or exported to Cytoscape (Shannon *et al*., 2003). It is also possible to obtain a summary of common differentially expressed genes for the selected nodes.

3.3 The Search workspace

The 'Search' workspace allows searching the network for nodes of interest. Queries can be performed with drug/gene synonyms, by matching text in the node description or by proximity to a given node within a threshold.

4 CONCLUSION

MANTRA 2.0 is a collaborative resource for elucidating drug MoA and for drug repurposing. The network framework makes it easy to discover unexpected relationships among drugs, genes and diseases. The possibility of uploading and sharing user's data allows for the growth of the network, thus making MANTRA 2.0 an ever-growing collaborative resource for drug discovery.

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Conflict of Interest: none declared.

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