A drug-gene network for understanding drug mechanism of action

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Chemogenomics experiments, where genetic and chemical perturbations are combined, provide data for discovering the relationships between genotype and phenotype. Traditionally, analysis of chemogenomic datasets has been done considering the sensitivity of the deletion strains to chemicals, and this has shed light on drug mechanism of action and detecting drug targets. Here, we computationally analyzed the largest chemogenomics dataset (Hillenmeyer *et al*. 2008), which combines more than 300 chemicals with virtually all gene deletion strains in the yeast *S. cerevisiae*. In addition to sensitivity relation between deletion strains and chemicals, we also considered the deletion strains which are resistant to chemicals, and proved that resistance interactions between genes and chemicals also have biological meaning.

We found a small set of genes whose deletion makes the yeast cell resistant to many chemicals. Curiously, these genes were enriched for functions related to RNA metabolism. Our approach allowed us to generate a network of drugs and genes that are connected with resistance or sensitivity relationships. As a quality assessment, we showed that the higher order motifs found in this network make biological sense. Moreover, by using this network, we constructed a biologically relevant network projection pertaining to drug similarities, and subsequently analyzed this network projection in detail. We propose the drug similarity network as a useful tool for understanding drug mechanism of action.

The proposed technique involves (i) finding multi-drug resistance (MDR) and multi-drug sensitivity (MDS) genes, (ii) constructing a deletion strain-drug network by using fitness defect scores of deletion strains in the presence of a particular drug and performing quality assessments to qualify the robustness of the network, (iii) generating a drug similarity network using sensitivity and resistance relationships between drugs and

deletion strains, again performing several quality assessments, and quantifying interrelationships between the similarities found in this network and orthogonal datasets, including chemical structural similarities and side effects similarities of drugs.

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1. Maureen E. Hillenmeyer *et al.* (2008) The Chemical Genomic Portrait of Yeast: Uncovering a Phenotype for All Genes, *Science*, **320**:362_365.