

di Bernardo D, Thompson MJ, Gardner TS, Chobot SE, Eastwood EL, Wojtovich AP, Elliott SJ, Schaus SE, and Collins JJ. Chemogenomic profiling on a genome-wide scale using reverse-engineered gene networks. *Nature Biotechnology* in press, 2005.

Lay summary:

Background: To design the “best” drugs we need to know exact modes of action, i.e., the molecular targets that mediate therapeutic as well as side effects. To date there have been few ways to predict optimal drug design. For many drug candidates, the targets are unknown and difficult to identify among the thousands of gene products in a typical organism, resulting in hit-or-miss pharmacologic development.

Findings: The authors designed a mathematical algorithm to compute the likelihood that cellular responses occurring and/or cell products being produced as a result of administration of a chemical compound are in fact targets of the compound. The authors start by using expression profiles to infer a quantitative network model of the regulatory influences operating among genes in a given organism. They use their model as a sort of filter to check that after administration of a variety of treatments, gene expression levels in the cell, relative to the levels of all other genes, are consistent with the inferred model. Those that are inconsistent are ranked, with the most inconsistent being considered as due to the compound. The authors applied the method to a set of 515 whole-genome expression profiles resulting from a variety of treatments of baker’s yeast, and found that for most of the treatments, they could correctly predict the target and the pathway. Then they tested the approach on PTSB, a compound that inhibits growth in baker’s yeast and in human lung carcinoma cells, but whose mode of action is unknown. They predicted and validated that thioredoxin (a protein capable of protecting protein thiols from being oxidized in the cell) and thioredoxin reductase are its target.

Importance for public health: This paper provides a new tool for drug design. As data sets appropriate for analysis using the algorithm described become increasingly available, and as more information is generated from use of the method over an ever-expanding range of disease processes, the authors look forward to great leaps in the predictive power of network models and consequent improvements in drug target identification. The day is coming when drugs are designed that act with maximum effect upon diseased cells only, having no side effects attributable to undesirable actions on other cells.

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Abstract:

A major challenge in drug discovery is to distinguish the molecular targets of a bioactive compound from the hundreds to thousands of additional gene products that respond indirectly to changes in the activity of the targets¹⁻⁸. Here, we present an integrated computational-experimental approach for computing the likelihood that gene products and associated pathways are targets of a compound. This is achieved by filtering the mRNA expression profile of compound-exposed cells using a reverse-engineered model of the cell’s gene regulatory network.

We apply the method to a set of 515 whole-genome yeast expression profiles resulting from a variety of treatments (compounds, knockouts and induced expression), and correctly enrich for the known targets and associated pathways in the majority of compounds examined. We demonstrate our approach on PTSB, a novel growth inhibitory compound with a previously unknown mode of action, by predicting and validating thioredoxin and thioredoxin reductase as its target.