



Università degli Studi di Salerno

PhD thesis in
COMPUTER SCIENCE

**Automatic Discovery of
Drug Mode of Action
and
Drug Repositioning
from Gene Expression Data**

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Abstract

The identification of the molecular pathway that is targeted by a compound, combined with the dissection of the following reactions in the cellular environment, i.e. the drug mode of action, is a key challenge in biomedicine.

Elucidation of drug mode of action has been attempted, in the past, with different approaches. Methods based only on transcriptional responses are those requiring the least amount of information and can be quickly applied to new compounds. On the other hand, they have met with limited success and, at the present, a general, robust and efficient gene-expression based method to study drugs in mammalian systems is still missing.

We developed an efficient analysis framework to investigate the mode of action of drugs by using gene expression data only. Particularly, by using a large compendium of gene expression profiles following treatments with more than 1,000 compounds on different human cell lines, we were able to extract a synthetic consensual transcriptional response for each of the tested compounds. This was obtained by developing an original rank merging procedure. Then, we designed a novel similarity measure among the transcriptional responses to each drug, ending up with a “drug similarity network”, where each drug is a node and edges represent significant similarities between drugs.

By means of a novel hierarchical clustering algorithm, we then provided this network with a modular topology, containing groups of highly interconnected nodes (i.e. network communities) whose exemplars form second-level modules (i.e. network rich-clubs), and so on. We showed that these topological modules are enriched for a given mode of action and that the hierarchy of the resulting final network reflects the different levels of similarities among the composing compound mode of actions.

Most importantly, by integrating a novel drug X into this network (which

can be done very quickly) the unknown mode of action can be inferred by studying the topology of the subnetwork surrounding X . Moreover, novel potential therapeutic applications can be assigned to safe and approved drugs, that are already present in the network, by studying their neighborhood (i.e. drug repositioning), hence in a very cheap, easy and fast way, without the need of additional experiments.

By using this approach, we were able to correctly classify novel anti-cancer compounds; to predict and experimentally validate an unexpected similarity in the mode of action of CDK2 inhibitors and TopoIsomerase inhibitors and to predict that Fasudil, a known and FDA-approved cardiotoxic agent, could be repositioned as novel enhancer of cellular autophagy.

Due to the extremely safe profile of this drug and its potential ability to traverse the blood-brain barrier, this could have strong implications in the treatment of several human neurodegenerative disorders, such as Huntington and Parkinson diseases.