# Efficient method for generating minimal intervention sets in Gene Regulatory Networks

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In the last few decades, technological and experimental advancements in molecular biology have allowed the study of the effect of drugs on human cell signaling pathways. These advancements have enabled a more precise understanding of the mode of action of drugs and positively influenced the design of new drug compounds. The flipside, however, has been the dawning realization of the complexity of signaling events involved in the mode of action of a drug. Whereas the design of compounds has become increasingly target-specific, the overall effects of a drug on adjacent cellular signaling pathways remain difficult to predict because of the complexity of the interactions involved. Off-target effects of drugs are known to influence their efficacy and safety, whereas highly target-specific drugs might be too limited and ineffective in the context of cellular signaling. Finally, even when the signaling pathways targeted by a drug are known, the presence of point mutations in some of the components of the pathways can render a therapy ineffective in a considerable target subpopulation.

Some of these issues can be addressed by predicting the influence that one or more drug moieties have on a complex system of signaling pathways. Conversely, these issues can also be addressed by predicting which elements of the signaling pathways have to be targeted in order to attain a pre-defined phenotype. Our work describes a set of algorithms that aim to perform these predictions computationally. We believe that these algorithms will help in the identification of drug targets and the design of combination therapies.

Major contributions of this work:

a) It describes novel algorithms for enumerating *minimal intervention sets* (MIS) in signaling pathways. The algorithms have potential application in screening a library of drug compounds against an underlying pathway of gene-proteins and protein-protein interactions in a disease pathway.

b) Our algorithms report a list of compatible off-targets along with every MIS. This is in contrast to the algorithms in [1, 2], which do not report compatible off-target effects when enumerating the MIS of genes/proteins in a given pathway. Therefore, a library of drug compounds screened with respect to the MIS reported by the algorithms in [1, 2] may potentially result in many false-positives.

c) Our algorithms also demonstrate how miRNAs, which are known to notoriously target the expression of many genes at the same time, can be studied effectively within the framework of pathway dynamics by accounting for the MIS of nodes in the pathway.

d) Finally, we demonstrate, with an application on T-helper cell signaling pathway, how enumeration of the MIS can be combined with known experimental data and observations from literature to infer missing edges in a signaling pathway.

[1] **Regina Samaga et al., Journal of Computational Biology**, Jan. 2010, 17(1): 39-53.

[2] **Guy Karlebach and Ron Shamir**, **BMC Systems Biology**, Feb. 2010.