

A Signaling Pathway Rationale for the Design of Combination Therapies for Cancer

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Cellular functions and activities are governed by complex signaling and regulatory networks. Diseases arise from abnormal behavior in these networks. Thus the design of targeted therapies from a systems biology approach, aims to identify which molecules to intervene in these networks, to repress a pathological behavior while minimizing side-effects. Accumulated empirical experience has shown that combination or multicomponent interventions are necessary to cope with the redundancy and multi-functionality that characterize biological networks [1]. Redundancy requires for several pathways to be targeted as alternate routes can compensate the disrupted pathways' function. Multi-functionality implies that intervening at molecules playing a central role in the cell may cause side-effects, requiring alternative points of intervention [2].

Hence systemic and efficient methods for the identification and ranking of optimal combinations of interventions can be very useful particularly, when addressing large networks.

We have developed OCSANA (Optimal Combinations of Interventions from Network Analysis), a free-available software for the identification and prioritization of optimal combinations of interventions to disrupt the paths in the network, from source nodes to target nodes. Additionally, it identifies effects with respect to non-targeted paths (side-effects) to further optimize the combinations of interventions. Our method is based on the network's structure (signed directed graph structure). The underlying algorithm is based on a classical mathematical problem, the so-called Minimal Hitting Set problem. We implemented OCSANA within the Cytoscape's plugin BiNoM-Biological Network Manager [3], to facilitate the assembling, usage and analysis of signaling networks in standard systems biology formats (such as SBML and BioPAX).

We have applied OCSANA to identify combination therapies from our cohort of human epidermal growth factor receptor over-expressing (Her2+) breast cancer tissues. First, we used transcriptome microarrays to compare Her2+ data with that obtained from normal breast tissue samples. We identified and assembled a signal transduction network of more than 2,500 nodes and 3,800 interactions that includes master regulators of the ERBB family pathways together with less expected molecular mechanisms, potentially involved in the molecular pathology of HER2+ breast cancer. With the assembled signal transduction network and with the aid of OCSANA, we tested *in silico* scenarios like those of the blocking effects of existent targeted therapies such as trastuzumab and lapatinib. We identified additional complementary therapeutic combinations of interventions and validated our theoretical predictions with recently published literature.

1. Fitzgerald et al. (2006) Systems biology and combination therapy in the quest for clinical efficacy, *Nat. Chem. Biol.*, **2**:458-466.
2. Samaga et al. (2010) Computing Combinatorial Intervention Strategies and Failure Modes in Signaling Networks, *J. Comp. Biol.*, **17**(1): 39-53.
3. Zinovyev *et al.* (2008) BiNoM: a Cytoscape plugin for manipulating and analyzing biological networks. 2008. *Bioinformatics* 24(6):876-877.