Discovery of synergistic key regulators for combination therapy

With the support by the National Natural Science Foundation of China，the research team led by Prof. Gao Lin（高 琳）at the Institute of Computational Bioinformatics，School of Computer Science and Technology，Xidian University，developed a network controllability-based algorithm for *de novo* identification of synergistic regulators as candidates for combination therapy，which was published in *Nature Communications*（2019，10：2180. DOI：https://doi.org/10.1038/s41467-019-10215-y）.

Complex diseases，such as cancer，arise from multiple deregulated pathways. Combination therapy，by exerting effects on more than one pathogenic pathway，is an effective strategy to combat drug resistance and disease heterogeneity. Existing methods for discovering combination therapeutic targets focused on identifying synergistic combinations of existing drugs. However，targets of existing drugs are limited to a small group of proteins. Thus，a large number of genes and their combinations remain unexplored as potential combinatorial therapeutic targets.

Motivated by this challenge，Gao's group developed the Optimal Control Node（OptiCon）algorithm for identifying synergistic key regulators in a disease-perturbed gene regulatory network. By using gene expression as a constraint in the standard network controllability framework，OptiCon first identifies a set of optimal control nodes（OCNs）as key regulators. The identified OCNs exert maximal control over deregulated pathways but minimal control over the pathways that are not perturbed by the disease. Next， using a synergy score that combines both genetic mutation and gene functional interaction information， OptiCon identifies a set of synergistic OCNs，which can serve as candidate targets for combination therapy. The predicted synergy was validated by CRISPR/Cas9-based double knockout growth assay. More interestingly，they found that a significant portion of genes regulated by synergistic OCNs participate in dense interactions between co-regulated subnetworks and contribute to therapy resistance. In a broader sense，the OptiCon algorithm proposed in the *Nature Communications* paper represents a general framework for systemic identification of synergistic regulators underlying a cellular state transition.
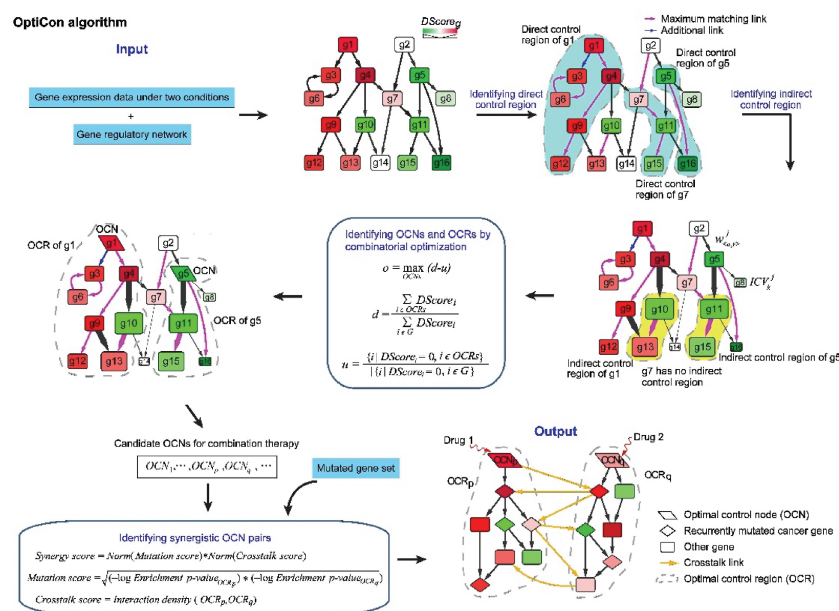

Figure Overview of the OptiCon algorithm.