Network controllability: theory and applications

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Abstract

The intrinsic robustness of living systems against perturbations is a key factor that explains why many single-target drugs have been found to provide poor efficacy or to lead to significant side effects. Rather than trying to design selective ligands that target individual receptors only, network polypharmacology aims to modify multiple cellular targets to tackle the compensatory mechanisms and robustness of disease-associated cellular systems, as well as to control unwanted off-target side effects that often limit the clinical utility of many conventional drug treatments. However, the exponentially increasing number of potential drug target combinations makes the pure experimental approach quickly unfeasible, and translates into a need for algorithmic design principles to determine the most promising target combinations to effectively control complex disease systems, without causing drastic toxicity or other side-effects. Building on the increased availability of disease-specific essential genes, we concentrate on the target structural controllability problem, where the aim is to select a minimal set of driver/driven nodes which can control a given target within a network. That is, for every initial configuration of the system and any desired final configuration of the target nodes, there exists a finite sequence of input functions for the driver nodes such that the target nodes can be driven to the desired final configuration. We investigated this approach in some pilot studies linking FDA-approved drugs with cancer cell-line-specific essential genes, with some very promising results.

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