379d Optimization-Based Strategies for the Systematic Analysis and Therapeutic Disruption of Signal Transduction Networks

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Interest in the study of cell signaling cascades has exploded in recent years as the critical role of these networks in various cellular events is becoming better understood. Signal transduction involves the reception of an extracellular signal which then sparks a highly complex chain of intracellular events resulting in a particular cellular response. It is now known that biological responses to external stimuli are highly complicated and the result of multiple interacting pathways containing many common molecules. Furthermore, various biotechnological advances have revealed that cell signaling cascades are in fact an elaborate network of biological reactions, most involving the cycling of a particular chemical compound between its active and inactive states. In this work, we present an optimization based framework for extracting the maximum amount of information from cellular signaling networks based solely on their topological and structural features which describe the links between extracellular signals and intracellular responses. Knowledge of these input/output relationships has implications in drug target discovery by pinpointing which extracellular signals are required to stimulate particular cellular responses and by guiding efforts to prevent different responses through the disruption of key reactions in a signaling cascade. The proposed computational framework is applied to an integrated reaction framework consisting of nine human signal transduction networks obtained from the PANTHER ^{TM} database. Our results indicate that the developed framework is able to accurately identify the input/output relationships and precisely pinpoint the key disruptions to preclude different responses. Subsequently, computational studies conducted to validate the action of various chemotherapeutic and chemopreventive agents indicate that the proposed framework is able to reproduce the hypothesized drug action. Overall, our results show that the in addition to exhaustively identifying the minimal set of inputs required to elicit a particular cellular response and pinpointing key disruptions to eliminate an undesirable outcome the developed optimization framework can act as an efficient tool for validating current and hypothesizing novel drug targets.