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Control of cancer-related signal transduction networks

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Intra-cellular signaling networks are crucial to the maintenance of cellular homeostasis and for cell behavior (growth, survival, apoptosis, movement). Mutations or alterations in the expression of elements of cellular signaling networks can lead to incorrect behavioral decisions that could result in tumor development and/or the promotion of cell migration and metastasis. Thus, mitigation of the cascading effects of such dysregulations is an important control objective. My group at Penn State is collaborating with wet-bench biologists to develop and validate predictive models of various biological systems. Over the years we found that discrete dynamic modeling is very useful in molding qualitative interaction information into a predictive model. We recently demonstrated the effectiveness of network-based targeted manipulations on mitigating the disease T cell large granular lymphocyte (T-LGL) leukemia. The root of this disease is the abnormal survival of T cells which, after successfully fighting an infection, should undergo programmed cell death. We synthesized the relevant network of within-T-cell interactions from the literature, integrated it with qualitative knowledge of the dysregulated (abnormal) states of several network components, and formulated a Boolean dynamic model. The model indicated that the system possesses a steady state corresponding to the normal cell death state and a T-LGL steady state corresponding to the abnormal survival state. For each node, we evaluated the restorative manipulation consisting of maintaining the node in the state that is the opposite of its T-LGL state, e.g. knocking it out if it is overexpressed in the T-LGL state. We found that such control of any of 15 nodes led to the disappearance of the T-LGL steady state, leaving cell death as the only potential outcome from any initial condition. In four additional cases the probability of reaching the T-LGL state decreased dramatically, thus these nodes are also possible control targets. Our collaborators validated two of these predicted control mechanisms experimentally. Our work suggests that external control of a single node can be a fruitful therapeutic strategy.