Crosstalk and competition in signaling networks

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***Short Abstract* — Signaling networks form highly interconnected and interdependent systems within cells, a result of "network crosstalk". It is currently unclear what types of effects these interconnections can have on the response of networks to incoming signals. In this work, we build off of the atomistic motif of a kinase/phosphatase pair acting on a single substrate, employing mathematical models to characterize the influence that multiple substrates have on one another. Our findings have strong implications for how we understand and classify crosstalk, as well as for the development and activity of specific kinase inhibitors.**

***Keywords* — signaling crosstalk, systems biology, ultrasensitivity, phosphatases**

I. Introduction

SIGNAL propagation through a network of interacting proteins is central to a cell's ability to process and respond to stimuli. Intracellular signaling networks are extremely complex in metazoans, a fact that makes reasoning about their behavior difficult [1,2]. A major source of this complexity is network crosstalk [3-7], and while it is clear that crosstalk is incredibly widespread in mammalian signaling networks, we currently do not have a clear conceptual picture of how this highly interconnected architecture might influence the response of a network to incoming signals.

In this work we seek to understand how the competition and promiscuity induced by crosstalk ultimately determine network behavior. In "classic" crosstalk, an enzyme is shared between two pathways and can transfer signals from one pathway to another [3-7]. We use computational models to expand this classic motif and reveal the influence of substrate saturation and phosphatase architecture on crosstalk.

II. Results

The fundamental observation we have made is that shared signaling enzymes can couple the responses of different substrates, at times in a non-intuitive fashion. For instance, if the targets in question share the same kinase/phosphatase pair, we find all of the targets in this case will respond in a switch-like manner to incoming signal.

In the case in which only the kinase is shared between substrates, the saturating substrate acts as a "gatekeeper" for the other substrates in the loop. While the gatekeeper remains in its unphosphorylated state, other substrates are unable to respond to incoming signals.

Nearly all experimental characterizations of crosstalk have focused on kinases; the potential for phosphatases to couple signaling response on their own has, to our knowledge, not been previously considered. We demonstrate that when substrates share a phosphatase, this phosphatase can elicit an ultrasensitive response of a target to signals from kinases that do not directly act on the target in question.

Our work highlights the inherent difficulty of predicting *a priori* the effects that kinase inhibitors will have on cells. These effects will ultimately depend not only on the kinase connectivity of the network, but also on the degree of saturation in the targets and the phosphatase architecture.

III. Conclusion

Ultimately, our work indicates that studies on signaling and regulatory networks need to be increasingly mindful of the highly interconnected and interdependent structure of the network themselves. This is especially true of phosphatases – in order to understand the real consequences of rampant kinase crosstalk, we clearly must obtain more reliable information regarding which phosphatases act on which targets, what adaptor domains they employ, etc. Our findings also highlight the fact that individual elements of signaling networks can exhibit responses that are sensitive to the context in which the element is found. Care must be taken to ensure that this dependence on network architecture informs our interpretation and understanding of how networks function and interact with each other.

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