149d Tuning Resistance in the Map Kinase Pathway: Lessons for Synthetic Biology from a Developmental Network in *C. Elegans*

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Diverse stimuli (e.g., stress, growth factors and cell adhesion) stimulate common intracellular signaling mechanisms en route to affecting cell responses. An example of such a core signaling mechanism is the MAP kinase cascade. Regardless of the upstream stimulus and the downstream cell response, the core MAP kinase signaling "protocol" is similar: it involves serial activation of three kinases, each one deactivated by phosphatases. Strategies to tune the quantitative performance of such common signaling protocols will provide broad access to re-engineer numerous stimulus-cell response relationships.

We have identified quantitative features of the MAP kinase module with greatest likely relevance for biological function. These features include signal amplification, module responsiveness to the amount of input, and the range of module output. Our computational analysis reveals that a metric of module resistance to signal activation quantitatively predicts the effect of manipulating the expression level of chief module components. The resistance quantitatively predicts both dynamical properties and design trade-offs, such as achieving higher range while lowering responsiveness to input. Taken together, these results demonstrate that altering MAP kinase signaling by tuning its resistance is a feasible engineering strategy for redesigning the quantitative performance of this common signaling protocol.

Further, we demonstrate that this strategy is exploited in natural systems. The resistance of the MAP kinase cascade is tuned by lateral signaling (involving Notch-Delta) among neighboring cells during *C. elegans* vulval development. In turn, the MAP kinase pathway affects the level of lateral signaling, completing an intercellular feedback loop. Our mathematical model of this intricate intercellular network highlights the quantitative advantages of this MAP kinase resistance-dependent control strategy, as compared to the classical Notch-Delta self-regulatory loop in which MAP kinase is not involved.