Advantages and limitations of network-based information processing in biological signaling systems

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***Short Abstract* — Biochemical noise limits a cell's ability to resolve and appropriately respond to different inputs based on the output of a single signaling pathway, however, signaling through networks comprised of multiple pathways might overcome this limitation. We developed an integrative framework for measuring the amount of information transduced by signaling processes and applied it to tumor necrosis factor (TNF) signaling, revealing that multiple pathways yield only moderate benefits due to an upstream noisy bottleneck. Negative feedback to this bottleneck can enhance its limiting effect despite decreasing the noise magnitude. Information bottlenecks can likewise limit networks comprised of multiple genes or cells.**

***Keywords* — Information theory, signaling networks, biochemical noise, signal discrimination, tumor necrosis factor (TNF), NF-κB, JNK**

I. Introduction

SIGNALING networks are biochemical systems dedicated to communication and information processing. Just as stochasticity can lead to potentially undesirable variations in regulated gene expression among isogenic cells [1], noise in biochemical signaling can lead to inaccurate information processing and inappropriate decision making by a cell.

We developed a general integrative theoretical-experimental framework to quantitatively predict and measure the maximum information about the signaling input received and acted upon by living cells. We illustrate the utility of this framework by extensively analyzing signaling initiated by the inflammatory cytokine tumor necrosis factor (TNF). TNF signaling is an excellent model system because cells are sensitive to TNF doses spanning ~4 orders of magnitude, and noise in TNF signaling is a subject of intense study [2,3] but its impact on the ability to transmit information about TNF dose have not been addressed. We experimentally investigated the signaling properties of the molecular network triggered by TNF, obtaining an extensive 4-dimensional compendium of experimental data reporting on a single cell level (in nearly 40,000 cells), in individual wildtype or genetically perturbed cells, the simultaneous activation at early and late time points of the NF-κB and JNK pathways, the two canonical pathways activated by TNF.

II. Results & Conclusion

We find that the amount of information transduced about signal dose through a single biochemical communication channel to the concentration of a responding transcription factor can be highly restricted by noise, and that the information gained by signaling through multiple channels can likewise be severely limited by information bottlenecks. For signaling networks consisting of multiple pathways, the bottleneck can come in the form of noise at the level of receptor complex activation, common to all of the pathways.

Negative feedback to this receptor-level bottleneck can suppress the noise, but the information gain is limited or even negated by the simultaneous suppression of the dynamic range of the response. We also analyzed the benefit of time integration by using a signaling network consisting of many genes. Here, the relevant bottleneck limiting the information gain is the extent to which rapid fluctuations (as compared to the integration time scale) contribute to overall variability.

The limitations imposed by the bottlenecks we identified each tend to constrain the capacity of the TNF signaling network in a single cell to ~1 bit, information that is only sufficient, e.g., to resolve the presence or absence of TNF. However, a network consisting of multiple cells working together can circumvent the ~1 bit limitation and achieve substantial gains in information about the signal dose. Even so, such networks can be limited by the number of available cells that can function collectively, or by a bottleneck formed by the information present in the initiating signal itself.

The benefits and tradeoffs of any particular strategy or mix of strategies for generating informative responses can be analyzed using the approaches outlined in this study, allowing one to quantitatively determine what a specific signaling system can do reliably in the presence of noise.

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