The Noise is the Signal: Information Flow in Single Cells and Cellular Populations

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***Short Abstract* — Intracellular signaling networks controlling critical cell-fate decisions (*e.g.* apoptosis) have been shown to exhibit exceedingly high levels of noise, preventing the reliable transmission of information. Our results reveal that this poor information transfer in individual cells is required to increase the information available to cellular populations, so that a single extracellular stimulus can induce graded behavior among an isogenic population of cells. We also show that responses relevant to individual cells (*e.g.* chemotaxis) exhibit more reliable information transfer. Thus, noisy signaling is not necessarily a consequence of some inherent physical limitation. Our work provides an explanation for the observed high levels of noise prevalent in certain metazoan signaling networks, and how noise might be exploited by evolution.**

***Keywords* — Information Theory, Cellular Heterogeneity**

I. Introduction

SIGNALING networks allow cells to make fate-altering decisions based on changing environmental factors. Apoptosis and commitment to cell division are typical binary responses to a signal, whereas chemotaxis and gene expression are examples of continuously variable responses. Traditionally, increasing the information available to the cell via these signaling networks has been viewed as beneficial, spurring investigation of the reliability of dose-response behavior given certain network motifs (*1*). However, the observed heterogeneity among certain isogenic cellular populations confounds this perspective and has become an object of considerable interest in recent years (*2*). Recently, the application of information theory to intracellular signaling has provided a means to quantify the impact of variability (*3*).

Levchenko and coworkers employed this strategy to characterize maximum information transduction (*i.e.* the channel capacity) in the TNF-α signaling network and found that the network transferred less than 1 bit of information from the extracellular stimulus to the transcription factor, NF-κB (*4*). Due to stochasticity in gene expression, the channel capacity between stimulus and phenotypic response is likely even lower.

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II. Results

To explore information transfer in the context of a system with a clear phenotypic output (i.e. cell death), we examined the channel capacity of extrinsic apoptosis signaling (*5*). Measuring individual cells' intracellular response to signal resulted in low channel capacities (<0.4 bits), however, if population-level response (fraction dead) is considered, the channel capacity increases dramatically (>3 bits, dependent on population size). Using a simple theoretical model, we showed that an increase in population-level channel capacity generally involves a corresponding decrease in channel capacity in single cells.

One possible explanation of these findings is that noise in individual cells arises from some kind of biophysical limit on information transfer, and organisms might simply take advantage of that limit to control cellular populations. To test this possibility, we considered two cases where the response of individual cells is paramount: eukaryotic chemotaxis and mating in yeast cells. In each case, we found single-cell channel capacities much higher than those previously observed (>2 bits). This implies that signaling networks are *capable* of transmitting relatively high levels of information despite the inherently stochastic nature of biochemical signaling.

III. Conclusion

Our findings strongly suggest that the low channel capacities previously observed at a single cell level does not reflect an inherent physical limit, but rather a natural trade off between information transfer at the single cell vs. population levels. This implies that the level of noise in individual signaling networks and cells can be regulated to produce reliable information at the level of individuals or populations, depending on the phenotypic requirements of the organism. Ultimately, our work provides a framework for understanding the high levels of noise observed in a wide variety of growth factor signaling networks in metazoan cells (*2, 5*).

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