Accurate information transduction in dynamic biochemical signaling networks

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Randomness inherent to biochemical reactions in signal transduction (intrinsic noise) and fluctuation in cellular state that occurs prior to ligand binding (extrinsic noise) can degrade information transmitted through signaling networks. We analyzed the ability of temporal signal modulation, i.e. dynamics, to overcome noise induced information loss. Our work demonstrates that cells can utilize signaling dynamics to overcome the degrading effects of extrinsic noise and thereby substantially increase the information transmission capacity of biochemical signal transduction pathway.

Signaling dynamic, noise, information theory.

I. Purpose

THE role of biological signaling networks is to reliably transmit specific information about the extracellular environment to multiple intracellular downstream effectors, allowing the cell to adjust its physiological state to changing conditions. Biological noise can interfere with signal transduction and degrade the transmitted information. How well can signaling pathways perform their core function in the presence of noise is a fundamental question in signal transduction. Application of information theoretic approaches allows the estimation of upper bounds of the information transmission capacity of noisy biochemical signaling pathways (*1–3*). Previous estimation suggested that noise limits the ability of cells to distinguish between multiple input levels of ligand concentration. Analysis of single cell responses to multiple levels of ligands argued that due to noise cells lose most of the information about the concentration of ligands to the extent that they can only reliably distinguish between two levels of activating ligand (*4*, *5*). The suggestion that noise degrades most of the information on ligand concentration that is contained in the response of key signaling hubs such as NfkB, Calcium, and Erk, was especially surprising given the demonstrated ability of these signaling hubs to differentially respond to multiple classes of ligands (*6*, *7*). Furthermore, the recent development of an optogentic tool that enables single-cell dose-response measurements have shown high precisions in cellular response that persists for multiple hours (*8*). Therefore it is unclear to what extent does noise limit the information transmission capacity of a biochemical signaling pathways.

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II. Results

We show that the dynamic response of three central signaling pathways, Erk, Calcium, and NfkB has significantly more information transmission capacity compared to a static response of these pathways. A general theory for information loss due to intrinsic and extrinsic noise sources identified a key role for dynamics in overcoming extrinsic noise induced information loss. Simulation of a computational model of the Erk signaling networks confirms our analytical results and exemplify that signaling dynamics can completely eliminate the degrading effects of extrinsic noise. Analysis of information transmission as a function of response magnitude and variability shows that the observed benefit from Erk dynamics is indeed due its ability to mitigate extrinsic noise.

III. Conclusion

The robustness of biological systems is epitomized by their ability to function in the presence of large uncertainties. A fundamental question is to what extent biological noise limits biological systems ability to perform their key function. We showed that signaling dynamics allows biochemical signaling networks to mitigate a major source of noise and therefore perform their key function: reliable signal transduction.

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