Logarithmic signaling regulate MAPK stress response and survival

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***Short Abstract* — Here, we present an integrated experimental and theoretical framework to build predictive mathematical models of cell signaling and report our discovery of logarithmic signaling in eukaryotic MAPK signal transduction. We perturb single cells with time-varying stimulations and monitor in real-time MAPK nuclear import. We use the measured responses to infer ODE models to capture and predict the dynamics of proteins in signal transductions. Through validating this framework, we discovered that, compared with standard step-like cell stimulations, distinct signaling responses upon diverse temporal stimulations better constrain model parameters and improve model predictions. We then predict and experimentally confirm that this eukaryotic MAPK pathway employs a logarithmic signal transduction mechanism, similar to *E. coli* chemotaxis.**

***Keywords* — signal transduction, single-cell experiments and analysis, predictive modeling, computational biology**

I. Introduction

SIGNALING mechanisms enable cells to sense, respond, and adapt to changing environments. Understanding signal transduction mechanisms at both molecular and network levels is critical to characterize key proteins and reaction rates in the cellular response. This insight is important to discover unknown regulatory mechanisms, to identify abnormal protein interactions in disease, and to computationally screen drug targets in disease states. However, it remains a challenge to precisely predict signaling response dynamics upon genetic, pharmacological, or environmental perturbations. In particular, it is unknown how cells sense and respond to dynamic signal inputs.

II. Methods and Results

We used the conserved High Osmolarity Glycerol (HOG) Mitogen-Activated Protein Kinase (MAPK) stress signaling pathway in the yeast *Saccharomyces cerevisiae* model system to address this knowledge gap.

A. Cell signaling upon time-varying stimulation

In experiments, we apply novel precisely-controlled time-varying cell stimulations that mimic physiological gradual changes and measure dynamic signal transduction in single cells using live time-lapse microscopy [1]. We exposed cells to different osmotic stimulations that change as step, pulse, linear and non-linear gradients over time. Under these conditions, we observe differential modulation of Hog1 intensity, duration, and rate of activation.

B. Predictive mathematical models of cell signaling

To quantitatively understand the HOG signal activation, we inferred mechanistic signaling models of the HOG pathway [2,3]. We discovered that, compared to using only step-like cell stimulations, utilizing distinct signaling responses collected under multiple diverse time-varying cell stimulations better constrains model parameters and substantially improves model predictions on time-dependent activities of signaling proteins. We employ genetic perturbations to express signaling proteins at varying concentration levels [4] to validate the models based on their predictions and use validated models to investigate further the impact of proteins and different signaling mechanisms on cellular response.

C. Eukaryotic logarithmic signaling

Next, we investigated signaling mechanisms to understand how different osmostress gradients lead to distinct signaling activation dynamics and cell growth phenotypes within the conserved MAPK HOG pathway. We uncovered that the relationship between each stimulus input and the cellular response output is recapitulated through a logarithmic signaling mechanism enabling cells to sense and respond continuously to the relative changes of extracellular stimuli concentration with respect to the prevailing background over time, rather than absolute concentration or absolute changes. This signaling mechanism has significant consequences for the cells at both signaling and survival. It induces persistent pathway activation upon gradual stimulations that maximizes cell survival in severe stress conditions. We combine our computational modeling framework with genetic approaches to determine the molecular mechanisms and network topologies of logarithmic signaling.

III. Conclusion

This approach is applicable to different pathways in different organisms to predict signaling responses upon genetic mutations, altered environmental exposure or drug treatments in the future to identify therapeutic targets.

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