Single-cell dynamics reflect underlying signaling mechanisms

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***Short Abstract* — Individual cells show differences in their signaling dynamics that can lead to alternate cellular fates. We exploited this phenomenon by developing a computer algorithm that searches for a common signaling mechanism that can explain the individual responses of each cell in a population. With no prior knowledge of the pathway, the algorithm successfully identified network motifs that were consistent with known pathway architectures. Predictions became better as more cells were added to the analysis, while random pairing of single-cell measurements responses led to poorer network predictions. Out results show that averaged measurements obscure mechanistic information that is naturally embedded in single-cell dynamics.**

***Keywords* — cell signaling, single-cell dynamics, network inference.**

I. Background

Cells use molecular signaling networks to respond to complex and changing environmental cues [1,2]. The components of signaling networks are often organized into specialized structures, or motifs, that allow the network to carry out a specific signal-processing goal [3,4]. For example, a network may contain strong negative feedback that allows it to adapt to different levels of an input signal. Understanding the functional roles of different network motifs is a major goal of systems biology because it provides a mechanistic description of how cellular systems work.

A major advance in our understanding of cell signaling has come from the ability to visualize signaling events in single, living cells. A collective observation from single-cell studies is that individual cells show considerable heterogeneity in their dynamic responses—even when exposed to the same stimulus. This observation suggests an exciting but untested possibility: if differences between individual cells have predictable effects on downstream responses, then it is possible that all cells share a common signaling mechanism that consistently interprets each cell's unique signaling dynamics. We reasoned that it may be possible to infer this mechanism given enough examples of the signaling response among individual cells.

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II. Results

We first considered how a single decoding mechanism could convert a set of varying input signals, representing individual cells, to a corresponding set of output signals. We chose a simple input signal representing a step function corresponding to a 2-fold increase. We then simulated this input signal in individual cells by allows the step function to vary in its delay, amplitude, and noise. For simpler network architectures, instantaneous measurements of input signal correlated well with the output signal. However, for more complicated signaling mechanisms, slices through time showed no correlation between input and output signal.

We next asked whether a common decoding mechanism could be inferred from single-cell traces with no prior knowledge of the system. To do this, we developed an algorithm, Mechanism Inference from Single Cells (MISC), which analyzes pairs of input and output signals among individual cells to infer a common signaling mechanism that produced them. An implicit feature of MISC is the ability to exploit heterogeneous time-series data by detecting mechanistic relationships between input and output signals. When applied to single-cell data describing the yeast stress response, we identified a small subset of networks that explained, in mechanistic terms, how these upstream signals may be integrated to produce the downstream responses. Network predictions became better as more cells were added to the analysis, providing a benchmark for the number of single cells needed to describe the underlying network.

III. Conclusions

Here, we show that single-cell measurements contain information that constrains the prediction of signaling mechanisms. Our results also demonstrate that more than one network may achieve the same functional goal but that the correct network is robust to topological perturbations. Thus, single-cell dynamics contains information that reflects underlying signaling mechanisms.

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