Fold-change detection in a social amoeba and cell-cell signaling robust to variations in cell density

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***Short Abstract* — We show at the single cell level that cAMP signaling response in *Dictyostelium* cells demonstrates fold-change detection, i.e., an adaptive response dictated by the fold change in input stimulus. During *Dictyostelium* development, the response mediates cell-cell signaling and its resultant oscillation in the concentration of cAMP. The oscillation is known to be robust to variations in cell density. Through mathematical modeling, we show that FCD enables cell-cell signaling to be robust to cell density. The relation between FCD and the robustness is further supported from observation of cAMP oscillation at the population level.**

***Keywords* — adaptation, fold-change detection, cell-cell signaling, collective behavior, robustness.**

I. Background

MANY sensory systems show adaptation—an ability to respond to a change in input stimulus then recover their original output. Recent studies suggest prevalence of an adaptive response called fold-change detection (FCD), i.e., a response that depends on the fold change in input stimulus but not on its absolute level [1-3]. However, there has been no direct observation of such responsiveness in eukaryotic cells.

Here, we study adaptation in cAMP signaling response in the social amoeba *Dictyostelium discoideum* at the single-cell level. Binding of extracellular cAMP (input signal) to the membrane-bound receptors elicits transient synthesis and secretion of intracellular cAMP (output signal) through a series of complex signaling cascade [4-6]. To monitor the real-time change in cytosolic cAMP, we carried out time-lapse live-cell imaging of cells expressing Förster Resonance Energy Transfer (FRET)-based cAMP sensor [7]. Cells were isolated in a small perfusion chamber to prevent cell-cell interaction and well-defined time-varying input signal was delivered by employing a pair of syringe pumps.

II. Results

A. cAMP signaling response follows FCD

To characterize responses to relative changes in input stimuli, we exposed the cells to step increase in extracellular cAMP from nonzero basal level. We found that the main initial peaks in cytosolic cAMP observed immediately after the step increase follows FCD. Moreover, despite its marked cell-cell variability, the peak amplitude is reproducible in each individual cells when they are exposed to successive step inputs with identical fold-change but different absolute level. These results suggest that FCD is a robust property to cell-cell variation.

B. The FCD property enables cell-cell signaling to be robust to variations in cell density.

In *Dictyostelium* development, cell-cell signaling mediated by cAMP signaling response results in a collective oscillation in the concentration of cAMP. We therefore asked whether there are any advantages in FCD in cell-cell signaling. One of the characteristics of the collective oscillation in cAMP is its robustness to variations to cell density. An analysis of a mathematical model describing communicating cells capable of FCD revealed that FCD renders the output of the system, i.e., intracellular cAMP, independent of the parameter of cell density. To test the predictions of the model, we studied populations of cells interacting with each other in the perfusion chamber. It was shown that the dynamic properties of both intracellular and extracellular cAMP are consistent with those of the models. Thus, we conclude that cell-cell signaling in *Dictyostelium* development achieves robustness to variations in cell density by the FCD property of the constituent cells.

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