Fundamental limits to the precision of multicellular sensing

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***Short Abstract* — Recent experiments demonstrate that connected cells detect shallower chemical gradients together than alone, and that this enhanced sensitivity is lost when cell-cell communication is blocked. Here we derive the fundamental limits to the precision of gradient sensing by a chain of communicating cells. We show using linear response theory how precision is limited by finite molecule numbers, by exchange of messenger molecules between cells, and by the number of cells in the chain. Our results demonstrate that known fundamental sensing limits are sharpened when the need to communicate is respected. We compare our predictions with ongoing experiments.**

***Keywords* — cell sensing, gradient sensing, cell-cell communication, information theory**

I. Motivation

Recent experiments demonstrate that groups of hundreds of mammalian breast epithelial cells (collectives which we call 'organoids') respond to gradients of epidermal growth factor (EGF) that are too shallow for single cells to detect alone [1]. Moreover, this enhanced sensitivity is lost when organoids are treated with a drug that blocks gap junctions, the portals through with small molecules are exchanged between neighboring cells. These results demonstrate that enhanced gradient sensitivity in this system relies on cell-cell communication.

Fundamental limits to cell sensing have been studied for decades, beginning with the seminal work of Berg and Purcell [2]. More recently, their ideas have been extended to gradient sensing [3-5]. However, thus far no study has considered the need for spatially separated detectors to communicate with one another in order to integrate information. It therefore remains unknown what new limit the need to communicate places on sensory precision.

Here we develop a theoretical model of gradient sensing by communicating cells in an organoid. We demonstrate that the need to communicate sharpens known fundamental limits on gradient sensing, and we illustrate how the new limit depends on parameters of the system, which leads to specific predictions for the experiments.

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II. Methods

We model an organoid as a one-dimensional chain of communicating cells. Lacking knowledge of molecular details, we propose a minimal communication mechanism, in which each cell produces a 'global' and a 'local' chemical species in response to EGF. The global species is exchanged between neighboring cells, whereas the local species is not. The difference between local and global concentrations reports the strength and direction of the gradient, and thus serves as the readout. The relative error of the readout (variance over squared mean), calculated using linear response theory, quantifies the precision of gradient sensing.

III. Findings

The analytic expression for the relative error reveals a new limit to gradient sensing, imposed by the need to communicate. Indeed, we find a Berg-Purcell-like term, which comes from counting EGF molecules, and an additional term, which comes from noise intrinsic to the communication process. Importantly, the relative error saturates as a function of organoid size, whereas the Berg-Purcell limit does not. Saturation occurs because there is a length scale beyond which noise corrupts the communication: organoids longer than this length scale confer no further sensory benefit.

We also identify a mechanism by which the relative error can be reduced, if the local messenger is also exchanged. The exchange must be slow enough that the messenger remains more localized than the global messenger, yet fast enough to effectively count molecules over more than just one cell, which results in an optimal exchange rate.

We then compare our predictions to the experimental results. In particular, we present experimental evidence that sensory ability improves with organoid size, but then saturates beyond a particular size, in line with the theoretical prediction. Other comparisons of theory to experiment will also be discussed.

References

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