

# Role of memory in the dynamics of Ras activation in chemotaxing cells

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*Eukaryotic chemotaxis involves a poorly understood interplay between directional sensing and persistence of movement. Here we study this coupling at the level of Ras activation, a signaling component that is downstream from the G protein-coupled chemoattractant receptors. Imaging protein localization in flattened cells, we find that when gradients are suddenly replaced with lower uniform concentrations, activated Ras patches disappear and then return at the front with a concentration-dependent delay. This is consistent with a model based on the local-excitation-global-inhibition mechanism coupled to a bistable memory module. This observed memory may help explain persistent motion and resolve the “back-of-the-wave” paradox.*

## I. INTRODUCTION

THE traditional view of the chemotaxis network involves upstream components creating an internal representation of the gradient that gets further amplified in establishing a well-defined cell front and back. One proposed mechanism for the initial step is the local-excitation-global-inhibition (LEGI) model, in which a membrane localized activator and a diffusible inhibitor opposingly regulate the response [1-4]. It is not clear, however, how this gradient sensing is coupled to persistence of movement [5] and how cells respond to changing gradients. To address these questions, we followed subcellular localization of activated Ras, a protein that is immediately downstream from the G protein-coupled chemoattractant receptors and activates a range of downstream effectors, in cells of the social amoeba *Dictyostelium discoideum* migrating in microfluidic devices designed to subject flattened cells to rapidly changing gradient conditions.

## II. RESULTS

### A. Experimental: Gradient to uniform

In a first set of experiments, we studied the response of chemotaxing cells when a gradient is suddenly replaced by a uniform stimulus. We found that patches of activated Ras at the front of the cell disappear immediately after the

replacement if the uniform concentration is lower than the average concentration in the gradient, but come back with a concentration-dependent delay. In contrast, if the new uniform concentration is higher than the previous concentration, patches remain at the front.

### B. Experimental: Gradient reversals

In a second set of experiments, we measured the response of activated Ras in cells when a strong gradient was suddenly replaced by a gradient in the opposite direction. We found that when the strength of the reversed gradient is smaller than some threshold, activated Ras is predominantly localized in the old gradient direction, suggesting that memory interferes with weak gradient detection at the level of activated Ras.

### C. Model

To understand the role of memory in the above experiments, we built a simple conceptual model of Ras dynamics by adding a bistable memory module to the LEGI model of Ref. [3]. The dynamics of this module is controlled by activated Ras and its output feeds back to Ras. A parameter search of this model revealed that the inclusion of the bistable module is able explain the experimental data. In particular, the model exhibits the experimentally observed concentration-dependent time delay in the first set of experiments while the response to gradient reversals is found to depend on the strength of the new gradient.

## III. DISCUSSION

This finding may shed light on the so-called back-of-the-wave paradox: if cell motion is solely determined by the sign of the gradient then symmetric chemoattractant waves should not lead to net cell motion, in sharp contrast to experimental observations. We propose that cells utilize the discovered memory such that they only respond to the front of wave while ignoring the back.

## REFERENCES

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