Stochastic Spatial Dynamics Enable Robust Cell Polarization

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Polarization is an essential behavior of living cells, yet the dynamics of this symmetry-breaking process are not fully understood. We examine, via experiments and modeling, the pheromone-induced formation of the yeast polarisome and we elucidate the intricate role of spatial stochastic effects in its formation. Comparing the results of equivalent deterministic and stochastic models, we find that the stochastic model can more robustly reproduce a highly polarized phenotype and the ability to track a moving pheromone input. In addition, only the stochastic model can reproduce both these characteristics of the wild-type phenotype, and the multi-polarisome phenotype of the *Spa2-delta* mutant.

***Keywords* — spatial stochastic, polarisome, cell polarization, yeast mating, signal tracking.**

We have constructed a spatial stochastic model of polarisome formation in mating yeast, focusing on the tight localization of proteins on the membrane. To our knowledge this is the first such model. This new model is built on simple mechanistic components with parameters fit to wild-type data. It is able to achieve a highly polarized phenotype with a relatively shallow input gradient. Preliminary results highlight the need for spatial stochastic modeling and simulation to reproduce experimental observations.

One of the best-studied examples of cell polarization is the growth of the mating projection during yeast mating. Yeast cells localize specific proteins to the front of the cell in response to a spatial gradient of mating pheromone secreted by a partner [1]. The spatial sensing and response exhibit remarkable sensitivity, dynamic range, and robustness. A single molecular entity located at the front of the cell, termed the polarisome, helps to organize structural, transport, and signaling proteins [2]. The function of the polarisome is well-conserved in eukaryotes, and analogous scaffold complexes may be responsible for such diverse structures as focal adhesions and synapses [3].

Prior work has produced deterministic (PDE) mathematical models that described the spatial dynamics of yeast cell polarization in response to spatial gradients of mating pheromone [4], as well as addressing the trade-off between amplification and tracking [5]. Noise plays an increasingly acknowledged role in intra- and intercellular signal transduction, protein interaction networks, and gene regulation [6], and as such, increased focus has been placed on developing stochastic models of biological systems. Recently, models of self-recruitment [7] and actin nucleation and directed transport [8] have highlighted the important role of spatial stochastics in initializing and maintaining polarization in the absence of an external cue.

In this work, we present a model that combines gradient-sensing, directed transport and self-recruitment. We focus on three molecular species: Bni1 (a formin that nucleates actin [9]), Spa2 (a scaffold protein), and actin. The mechanisms and rate constants in this model are based on evidence from the literature [2,9-10] and experiments.

Stochastic simulation of our model more robustly reproduced the balance between sharp polarization and the dynamic tracking and searching behavior seen in experiments than deterministic simulation. In addition, only stochastic simulation was able to reproduce the *Spa2-delta* mutant phenotype. The prediction of data that the model was not fit to also serves to validate the accuracy of the model. We show that spatial stochastic models are necessary to reproduce these biological phenomena with mechanisms that are simple and biologically plausible.

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