Stochastic Modeling and Simulation of Cell Polarization During Mating in Budding Yeast

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We have developed a spatial stochastic model of cell polarization in yeast, along with a computational framework for the accurate and efficient simulation of this model. The new computational method is based on a hybrid of the SSA and the Finite State Projection algorithm for reaction-diffusion systems.

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 the 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 the synapse [3]. Fig. 1 gives a schematic description of the polarisome.

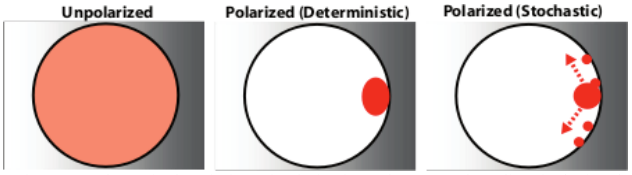

Figure 1: Schematic description of polarization. The external gradient is depicted by the background shading outside of the cell. The internal component is initially uniformly distributed in the cell (unpolarized) but becomes localized to the front.

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]. A limitation of these methods is their inability to determine the role of noise in symmetry breakdown and the failure to match mutant phenotypes (e.g. transient "secondary polarisomes").

Noise plays an increasingly acknowledged role in intra- and inter-cellular signal transduction, protein interaction networks and gene regulation [6]. A goal of our spatial stochastic model is to explore the possibility that noise in the system allows non-leading edge sites to temporarily cross the activation threshold (the concentration that activates a nonlinear bi-stable switch) and thus form multiple transient polarisome sites. Exploration of this possibility required further model development. Experiments underway in Yi's group provide validation, using fluorescent microscopy techniques to attain *in vivo* time-lapse data of protein localization and concentration [7].

Efficient and accurate computational techniques are required for stochastic simulation of biochemical reaction networks. For well-mixed systems, Gillespie's stochastic simulation algorithm (SSA) [8] is commonly used. The Finite State Projection (FSP) method [9] offers an alternative means of simulation, via direct solution of the Chemical Master Equation. When the well-mixed assumption does not apply (e.g. polarization), algorithms have been proposed for spatial stochastic simulation ([11] and others), but current methods are still extremely expensive and typically involve substantial restrictions on the time step.

We have developed a computational method to efficiently simulate the large number of diffusion transfer events that occur in the stochastic simulation of spatially inhomogeneous systems. The new hybrid algorithm uses the FSP to calculate a large number of diffusive events at once, allowing large simulation time steps and providing a bound on the error. We show how the special structure of the diffusion operator can be exploited to improve the efficiency of the FSP method. The FSP method is combined with SSA simulation of the reaction channels to create an efficient and accurate method for simulation of reaction-diffusion systems.

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