Directional Accuracy in a Model of Gradient Signaling during Yeast Mating

Rati Sharma[1] and Elijah Roberts[2]

I INTRODUCTION

The mating response of the yeast *Saccharomyces cerevisiae* is widely used as a model system for studying chemotropism. Haploid yeast sense nearby cells of the opposite mating type by detecting a pheromone gradient and then polarize and grow a mating projection in the direction of the gradient in an attempt to mate with a partner [1]. Experiments monitoring individual yeast cells in an artificial gradient show that they polarize with a broad distribution of directions centered on the gradient [2], but the probability distribution of the direction is not theoretically understood. Here, we present a hybrid model that uses both deterministic and probabilistic features to study the response of the circuit architecture to a gradient stimulus. In particular, we use a simplified model of the reactions that lead to the formation of the pheromone-receptor complex and activation of the mitogen-activated protein kinase (MAPK) cascade [3]. We simulate the model using a fully probabilistic method, the reaction-diffusion master equation (RDME), with novel gradient boundary conditions accounting for a point pheromone emitter a short distance away, the gradient for which has reached a steady state. We analyze the response to the gradient for different shapes of the simulation volume.

II METHODS

A point pheromone emitter a short distance away from the matα cell creates a gradient. This gradient is modeled deterministically via partial differential equations (PDE) using the diffusion equation with constant flux conditions at the source and constant gradient conditions at the boundaries. The concentrations of the pheromone at the desired distance from the source are then selected and fed into the simulation volume which contains all the other species, namely the kinases, phosphatases and the receptors. The kinases themselves can exist in two states, unphosphorylated or phosphorylated and in the region of parameter space where both are stable states, the system is considered bistable, while the space where only one stable state exists, the system is considered monostable [4]. We model the reactions between these species in the bistable as well as the monostable conditions and carry out RDME based stochastic simulations of these reactions.

III RESULTS

RDME simulations were carried out through *lattice microbes* [6] on the set of reactions after the inclusion of a pheromone gradient across the diagonal in a 3D cubic simulation volume and in a cell shape simulation volume. In a 3D cubic volume, the reactions occur randomly across the entire volume and hence are more distributed. This leads to decreased clustering of the kinases and therefore higher switching times between the two stable states. On the other hand, in the cell shape simulation volume, all the reactions occur on the membrane and hence there is more localized distribution of the species which leads to enhanced clustering and lower switching times between the two states. We also compared the direction of the pheromone gradient to that of the phosphorylated kinases in the theta-phi plane and notice that it is only at lower diffusion coefficients that the phosphorylated kinases follow the direction of the pheromone.

IV CONCLUSIONS

The rates of reactions, the switching times between the two states and clustering of molecules depend a lot on the simulation volume. The signaling cascade is more efficient in a smaller and more compact simulation volume and this is the strategy that most cells use to survive and grow. In addition, diffusion coefficients also play a very important role in the enhancement of the signal in the direction of the pheromone gradient and therefore it is important to understand diffusion related dynamics within the cell.

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[1] Dept. of Biophysics, Johns Hopkins University, Baltimore, Maryland, USA. E-mail: rsharm28@jhu.edu

[2] Dept. of Biophysics, Johns Hopkins University, Baltimore, Maryland, USA. E-mail: eroberts@jhu.edu