Simulating Yeast Polarization in the Cloud

Michael Trogdon¹, Brian Drawert², Michael Lawson³, Salman Toor⁴, Ben Bales⁵, Debjani Banerjee², Andreas Hellander⁴, Tau-Mu Yi⁵ and Linda Petzold¹,²

Short Abstract — We have developed a discrete spatial stochastic model of cellular polarization during mating of Saccharomyces cerevisiae. Specifically we investigate the ability of yeast cells to sense a spatial gradient of mating pheromone and respond by forming a projection in the direction of the mating partner. Our results demonstrate that higher levels of stochastic noise result in increased robustness, giving support to a cellular model where noise and spatial heterogeneity combine to achieve robust biological function. This also highlights the importance of spatial stochastic modeling to reproduce experimental observations.

Keywords — Spatial stochastic modeling, yeast polarization, cloud-computing, yeast mating.

I. BACKGROUND

The importance of randomness (or stochasticity) in biological systems is well documented [1-2]. Within a cell, proteins critical to cell signaling pathways often exist in low copy numbers. Under these conditions, methods such as the stochastic simulation algorithm (SSA) [3] are a more accurate mathematical representation of the system compared to deterministic models, which rely on ordinary differential equations. Another important consideration is the spatial nature of many biological systems, which is not captured in a “well-mixed” description. Here we look specifically at the spatial polarization of proteins during the mating of yeast.

The yeast Saccharomyces cerevisiae exists in both a haploid and a diploid form. The haploid cells (of type a or α) can sense a spatial gradient of mating pheromone and respond by forming a projection in the direction of the mating partner. In [4] a combination of computational modeling and biological experiments showed that, in comparison to a deterministic model, a discrete spatial stochastic model can more robustly reproduce two key features of polarization observed in wild-type cells: a highly polarized phenotype via spatial stochastic amplification and the ability of the polarisome to track a moving pheromone input. This work demonstrated that stochasticity plays a critical role in yeast polarization and provided the foundation for more detailed mechanistic models.

II. CURRENT MODELING EFFORTS

Although the model presented in [4] did provide novel insight into key features of the polarization system, there is still much to be understood. We are currently working to extend this model by adding additional pathways known to be involved in the polarization cascade. In particular, our current mechanistic model integrates three components of the polarization process: the heterotrimeric G-protein cycle activated by pheromone bound receptors, the focusing of a Cdc42 polarization cap, and the formation of the tight localization of proteins on the membrane known as the polarisome. Open questions to be addressed by this model, in combination with biological experiments, include the role of stochastically diffusing extracellular ligand, the effect of stochasticity on the yeast cell’s ability to form a localized Cdc42 cap, and what feedback mechanisms exist between the components of the polarization process.

III. CONCLUSION

We have developed a discrete spatial stochastic model of cellular polarization during yeast mating. Past work has demonstrated the necessity of spatial stochastic modeling to reproduce experimentally observed features of the polarization process. Our current model includes three components of the polarization process: the G-protein cycle, the focusing of Cdc42, and the formation of the polarisome. Due to the complexity of modeling these systems and the need for massive computational resources to simulate them, we have developed StochSS, an integrated development environment (IDE) for discrete stochastic simulations of biochemical networks with cloud-computing capabilities that easily allows for large-scale computational experiments. StochSS provides access to state-of-the-art algorithms, and supports a wide range of hardware from desktop workstations to high-performance clusters in the cloud.

REFERENCES


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¹Department of Mechanical Engineering, University of California – Santa Barbara.
²Department of Computer Science, University of California – Santa Barbara.
³Department of Cell, Molecular, Computational, and Systems Biology, Uppsala University.
⁴Department of Information Technology, Uppsala University.
⁵Department of Molecular, Cellular, and Developmental Biology, University of California – Santa Barbara.