The Truth About A's and Alpha's: How Yeast Cells Find Each Other in a Noisy World

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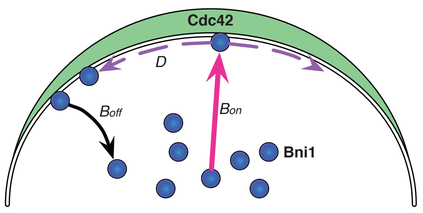
Introduction

Eukaryotic cells manage to perform precise tasks in the face of noise within the cell. Tight localization (or polarization) of proteins on the cell membrane in budding yeast during mating is an example of a precise spatial task. While the role players are known, the underlying mechanisms are not. How does the cell achieve such tight polarization in response to a broad directional cue? How does the cell balance this tight and stable polarization with the ability to track a change in input direction? How does it manage all this in a noisy environment? We have combined experimental and computational work to answer these questions.

Model Description:

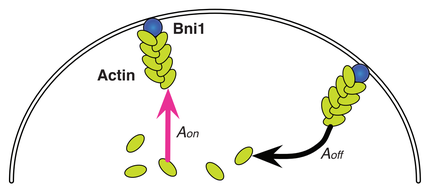
Spontaneous Recrtuitment

- Cdc42 recruits Bni1 to the membrane
- Bni1 diffuses laterally
- Bni1 can spontaneously dissociate from the membrane



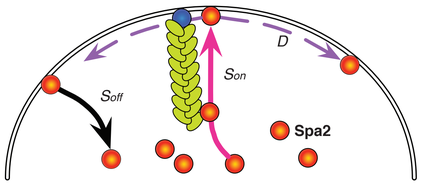
Actin Cable Nucleation

- Bni1 nucleates actin cables
- Actin cables stabilize the polarisome
- Cables may disassociate from the membrane



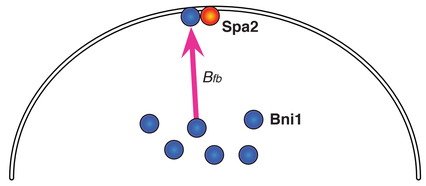
Directed Transport

- Spa2 is transported to the membrane
- Actin cables facilitate directed transport via Myosin
- Spa2 diffuses laterally



Positive Feedback

- Spa2 recruits Bni1 to the membrane
- Completers positive feedback (B-C-D)
- Strong feedback creates punctate polarisome

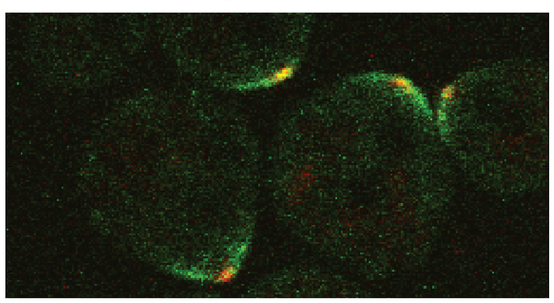


Results: Tight Polarization

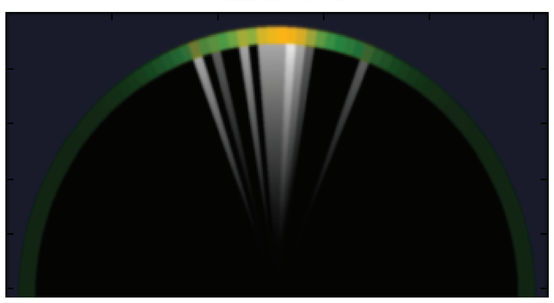
Stochastic model matches experimental observation

(Green: input (Cdc42). Red: output (Spa2))

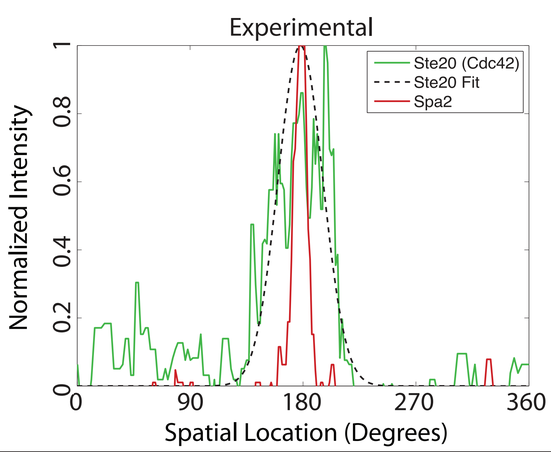
Experimental

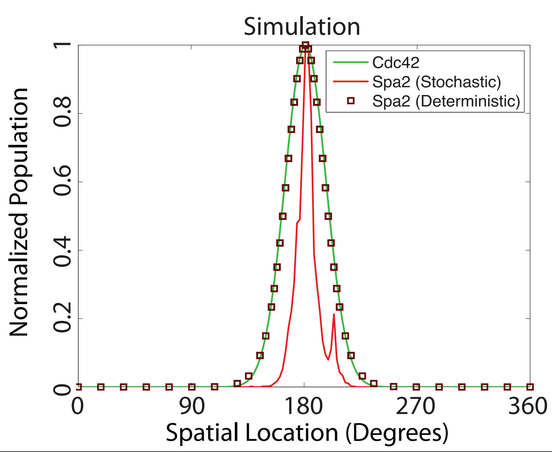


Simulation



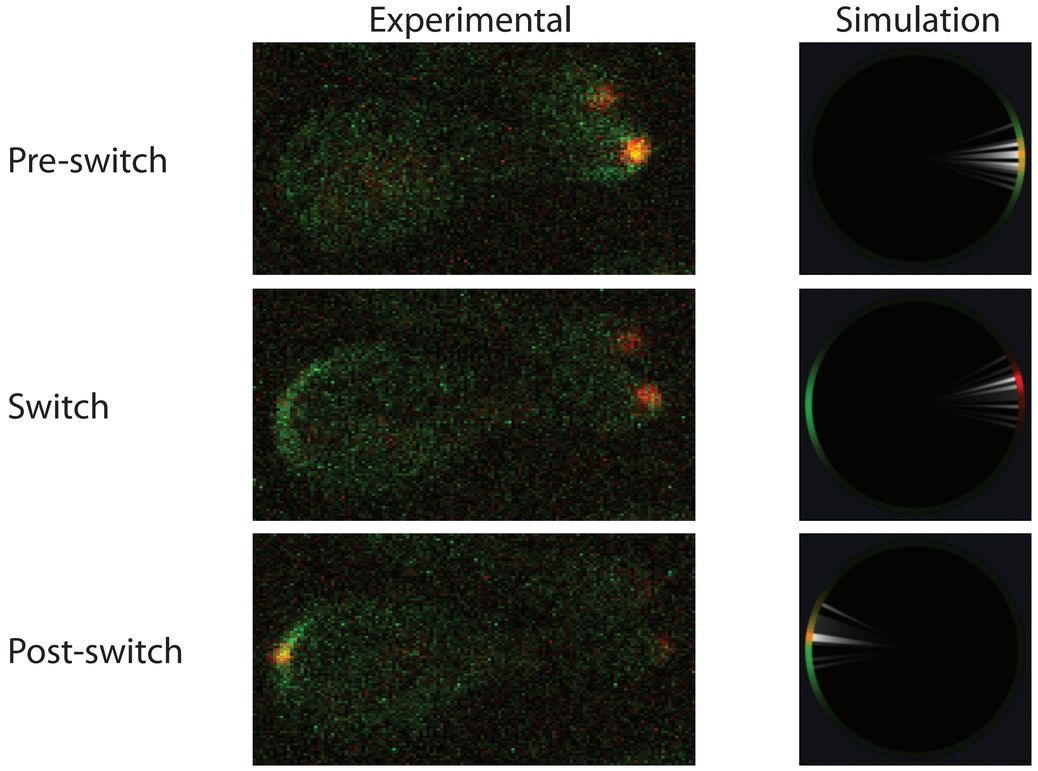
Deterministic model matches input, fails to produce tight polarization



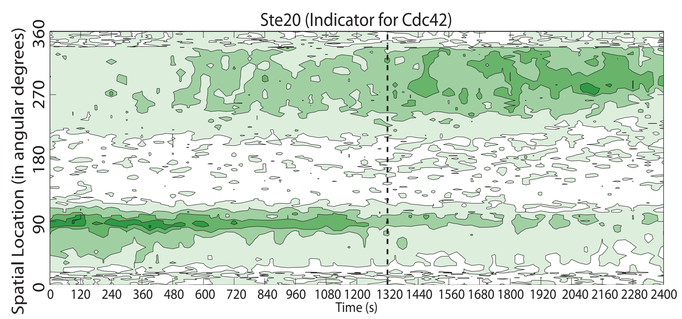


Results: Tracking

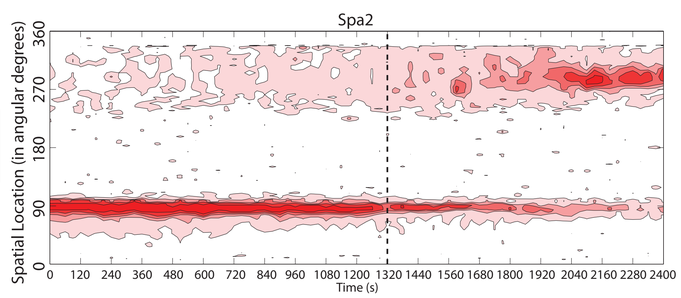
In experiments, the input Cdc42 (green below) switches direction from right to left. This is followed by Spa2 (red below). Stochastic simulation reproduces experimental observations.



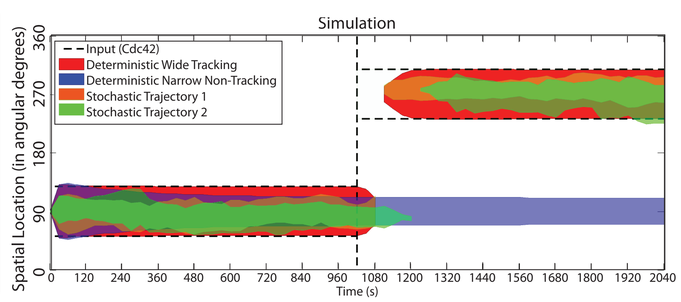
Experimental Data:
- Cdc42 (green) switches directions at t = 1320s



Experimental Data:
- Spa2 (red) switches directions at t = 1800s



At t = 1020s the input (Cdc42a) direction is switched (dashed black line).
- **Deterministic model produces tight polarization and fails to track (blue) OR**
- **Deterministic model tracks but provides only input gradient matching(red).**
- **Stochastic model produces tight polarization while tracking the input (orange and green are two sample trajectories).**



Conclusion:

We constructed a model based on protein interactions documented in the literature and our own experimental work. Our interdisciplinary work of combining experimentation and computation has led us to the counterintuitive conclusion that to achieve two high precision behaviors (tight polarization and tracking change in input direction) noise is not an impediment. In fact, our work indicates that the cells are utilizing the noise to drive these behaviors, a concept we term *spatial stochastic amplification*.