Signaling mechanisms that can yield Dose-Response Alignment

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Introduction

The yeast pheromone response signaling system transmits information about the extracellular pheromone (e.g., α-factor) concentration to the cell nucleus. Experiments, from Brent’s laboratory and elsewhere, investigated the system response to pheromone at various “measurement points” in the signaling pathway (colored circles in cartoon). They found:

• The signaling system does not adapt over time, but functions at an essentially constant pace for >4 hours.
• Dose-response behaviors of the different measurement points are graded, meaning that the responses increase smoothly with increasing pheromone dose.
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DoRA is widely observed in other systems too, likely because it improves information transmission.

What mechanisms enable signaling systems to exhibit DoRA? - This is the topic of this poster

Methods

1. Rescale dose-response data so the y-axis gives the absolute fraction of protein that is activated, or fraction of maximal possible expression rate. These are best guesses, not hard numbers. Hill functions fit to these data become the inputs for further analysis.

2. In the modeling scheme, nodes (e.g. A, below) are in equilibrium between inactive and active states (e.g. A and A). Arrows connect the nodes, the source of each arrow enzymatically activates or deactivates the destination node. The following model performs negative feedback.

3. Computationally optimize model parameters to get the best fit between model and experimental dose-responses. Fit errors are quantified with a new “slope-weighted RMS difference” metric.

4. See what models can or cannot fit experimental data. The modeling scheme is not mechanically accurate. Its results are meaningful if the model has the same capabilities and constraints as real signaling systems. Both model and reality can exhibit any Hill function, and are essentially limited to Hill functions, which suggests the model is valid.

Results

1. A linear network architecture fits the data poorly.

2. Negative feedback never improved fits, whether alone or in combination. Upon optimization, negative feedback arrow rates were always set to zero.

3. A survey of all possible two-node networks showed two mechanisms that can enable DoRA.

• A low true negative feedback (or low true negative feedback that is similar), called “push-pull”.

• Enzymatic cooperativity, in which the rate equation exponents could be >1. Shown with blue bars.

4. Push-pull mechanisms enable a substantially better fit. Here, the normal arrow activates the downstream node while the low true arrow deactivates it.

Discussion

Push-pull mechanisms may arise in the yeast system from (i) parallel and complementary Fus3 and Ste5 pathways, (ii) a newly discovered G-protein activation mechanism.

Cooperativity may arise from (i) multiple phosphorylation in the kinase cascade, (ii) allosteric interactions in the Ste5 scaffold and other protein complexes.

Conclusions

The observed Dose-Response Alignment (DoRA) in the yeast pheromone response signaling system likely does not arise from negative feedback. Instead, it likely arises from novel push-pull mechanisms, and/or cooperativity. These are biologically plausible.

References


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