Mechanisms for High Fidelity Cell Signaling

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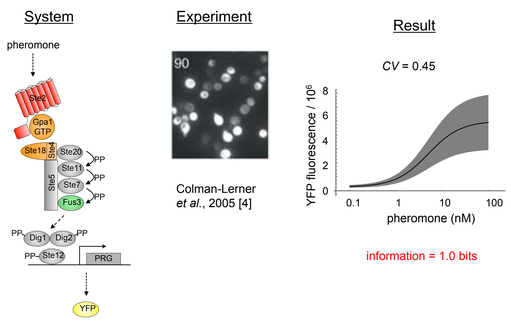
Introduction

Cells make decisions, including fate decisions, based upon information that they collect about their environment using signaling systems. This raises the questions of how accurately these systems can transmit signals and what mechanisms they use to improve transmission fidelity. Using modeling methods and analyses of published data, we show (*i*) signaling is relatively precise, with at least 2.3 bits of information per signal, (*ii*) information can be maintained in a signaling pathway through “dose-response alignment,” in which relative activity levels are maintained along a signaling pathway, and (*iii*) “push-pull” mechanisms, in which both active and inactive species transmit signals, can preserve dose-response alignment.

Signaling is precise

Recent publications have suggested that cell signaling is noisy, with only about 1 bit of information transmitted in each separate signal[1-3]. One bit is equivalent to 2 distinguishable states, so this suggests that cells can distinguish whether an external ligand is present or absent, but cannot detect ligand concentrations at finer levels of detail. We find a similar result when analyzing yeast data with the same approach:



Mathematics

define: d = dose, r = response

mean response: $r(d)$

standard deviation of response: $\sigma(d)$

conditional response: $p(r \mid d)$

dose distribution: $p(d)$ assume: $p(d) \sim \frac{r'(d)}{\sigma(d)}$

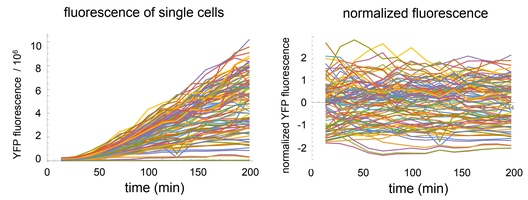
joint distribution: $p(r,d) = p(r \mid d)\,p(d)$

mutual information: $I(r;d) = \int_d \int_r p(r,d) \log \frac{p(r \mid d)}{p(r)}\, dr\, dd$

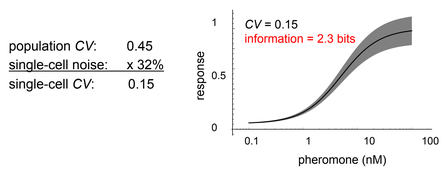
if Gaussian noise and $cv = \sigma(d)/r(d)$ is constant

then: $I(r;d) = \log_2 \frac{\ln r_{max} - \ln r_{min}}{cv\sqrt{2\pi e}}$

However, most response variability arose from temporally consistent cell-to-cell differences, not signaling noise:



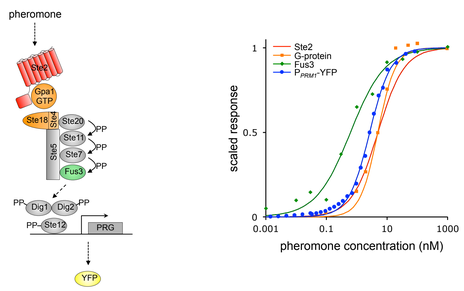
We recomputed dose-response-noise curves, now for the noise for single cells:



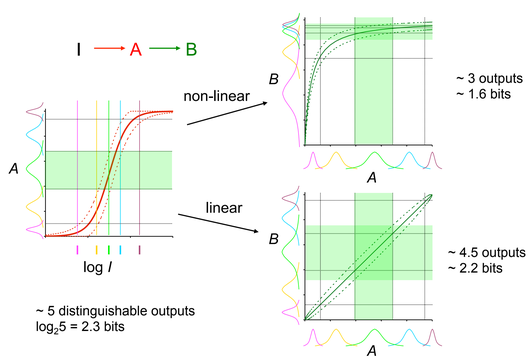
Thus, cell signaling is actually precise to *at least* 2.3 bits of information, or 5 distinguishable pheromone levels.

DoRA maximizes information

Yeast cells, and others, exhibit substantial dose-response alignment (DoRA): *i.e.* dose-response curves at multiple stages of the signaling pathway align with each other[5].

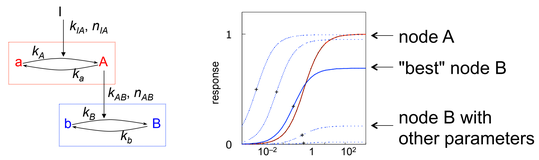


DoRA implies a linear transfer fuction. This reduces signal overlap, which improves information transmission:



Push-pull preserves DoRA

What mechanisms enable cells to exhibit dose-response alignment (DoRA)? We explored this using models of enzyme cascades, in which each enzyme or "node" has "active" and "inactive" states[7]. A system with a linear topology, in which each node activates the subsequent node, cannot produce DoRA[6]:



Mathematics

conservation: $[a]+[A]=1$ $[b]+[B]=1$

rates: $\frac{d[A]}{dt} = [a]\left(k_A + k_{IA}[I]^{n_{IA}}\right) - [A](k_a)$ $\frac{d[B]}{dt} = [b]\left(k_B + k_{AB}[A]^{n_{AB}}\right) - [B](k_b)$

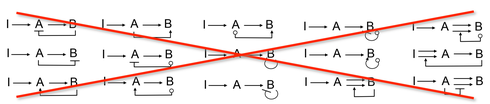
steady-states: $[A]_{s.s.} = \frac{k_A + k_{IA}[I]^{n_{IA}}}{k_A + k_{IA}[I]^{n_{IA}} + k_a}$ $[B]_{s.s.} = \frac{k_B + k_{AB}[A]^{n_{AB}}}{k_B + k_{AB}[A]^{n_{AB}} + k_b}$

slope-weighted root mean square (SWRMS) goodness-of-fit metric between model response, $y_m(I)$ and target response, $y_t(I)$:

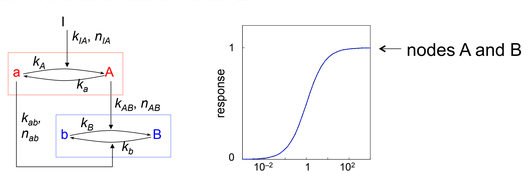
$$d = 100\sqrt{\int_0^\infty \left[y_m(I) - y_t(I)\right]^2 \left[c_t\left|\frac{dy_t(I)}{dI}\right| + c_m\left|\frac{dy_m(I)}{dI}\right|\right] dI}$$

where: $c_t = \frac{1}{2\left|y_t(\infty) - y_t(0)\right|}$ $c_m = \frac{1}{2\left|y_m(\infty) - y_m(0)\right|}$

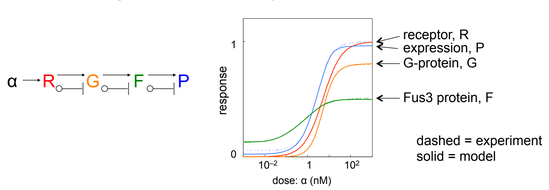
Most other network topologies also failed to exhibit DoRA. This was also true for combinations of arrows.



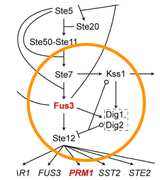
However, push-pull mechanisms enabled perfect dose-response alignment. Here, the "active" form of node A activates node B and the nominally "inactive" form of node A deactivates node B.

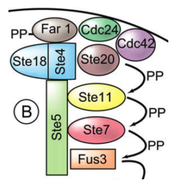


Varying enzyme cooperativity, meaning that reaction rates became non-linearly dependent on reactant concentrations (e.g. the n_{AB} parameter) also improved DoRA. Combining push-pull with cooperativity enabled excellent agreement with yeast experimental data:



Push-pull mechanisms may arise in the yeast system from (*i*) parallel and complementary Fus3 and Kss1 pathways, (*ii*) a newly discovered G-protein activation mechanism.

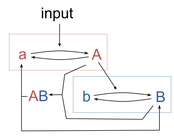




Cooperativity may arise from (*i*) multiple phosphorylation in the kinase cascade, (*ii*) allosteric interactions in the Ste5 scaffold and other protein complexes.

Negative feedback

Dose-response alignment can also arise from negative feedback, *if* the negative feedback operates through a Michaelis-Menten mechanism and the enzyme (B in the "active" form) is highly saturated, i.e. K_M << [A].



Conclusions

- Yeast cell signaling is relatively precise, with at least 2.3 bits of information per signal
- This information can be maintained through “dose-response alignment,” in which relative activity levels are maintained along a signaling pathway.
- Dose-response alignment is hard to achieve. However, it can arise from (*i*) “push-pull” mechanisms, in which both active and inactive species transmit signals, (*ii*) enzyme cooperativity, and/or (*iii*) negative feedback that involves enzyme saturation.

References

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