

Feedback-mediated dose response alignment reduces loss of information during signal transduction

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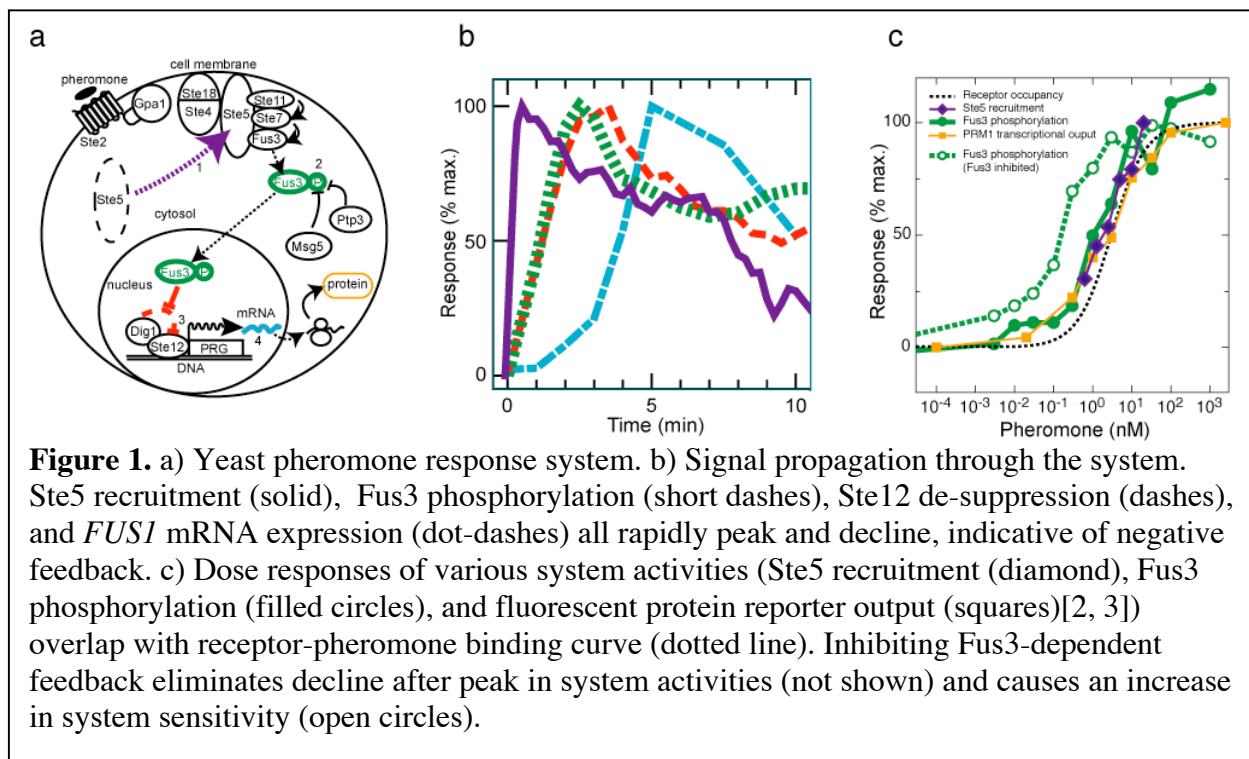
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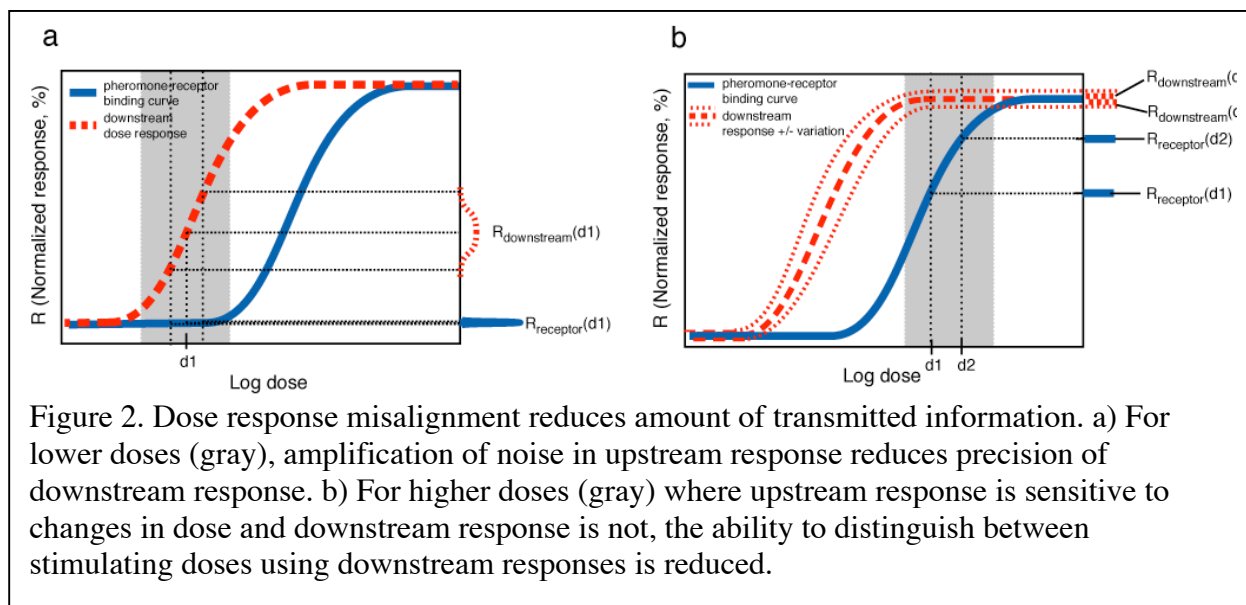
Extended abstract

Eukaryotic cells use signal transduction pathways to sense and transmit information about external conditions. Studies of these systems generally focus on time scales that overlook rapid system behaviors potentially important for information encoding and transmission. By measuring multiple system activities at much shorter timescales, we identified a new, rapid feedback mechanism that helps maximize the amount of information transmitted through a prototypic multi-step GPCR and MAPK signal transduction pathway, the yeast pheromone response system [1]. This negative feedback aligns the dose response of downstream system points with the receptor-pheromone binding response. By doing so, the feedback minimizes degradation of information about external pheromone dose transmitted through the cell into the nucleus.

We genetically labeled endogenous system proteins with fluorescent proteins. After system stimulation, using image-based cytometry [4] we measured MAPK scaffold Ste5 membrane recruitment by fluorescence translocation and release of transcription factor Ste12 activity from Dig1 repression by changes in FRET. Additionally, we measured levels of active MAP kinase Fus3 and of Fus1 mRNA (Fig. 1a). Upon system induction, all measured activities peaked and declined to a lower level, suggesting the action of negative feedback(s) (Fig. 1b). Both decline of Ste5 recruitment, which occurred within 60 seconds, and decline in active Fus3 required Fus3 kinase activity. This Fus3-dependent feedback acted downstream and independently of a known Sst2-dependent feedback that reduces G-protein activity. These observations established active control of scaffold recruitment as a mechanism for regulating signal amplitude, in addition to known mechanisms that regulate G-proteins. The Fus3-dependent feedback also regulated the sensitivity of system response, as inhibiting the feedback shifted the response curve to make Fus3 activation 20-fold more sensitive (Fig. 1c). Breaking the feedback also caused dose responses of system points downstream of the receptor to be misaligned with the curve for pheromone-receptor binding.



This misalignment causes loss of dose information transmitted between the receptor and a downstream system point at two dose regimes. At low doses, where receptor occupancy is changing little while the downstream response is changing significantly, any noise in the upstream response will be amplified in the downstream response, thus decreasing its precision (Fig 2a) [5]. At high doses, where receptor occupancy is changing significantly while the downstream response is nearly saturated, two easily distinguishable upstream responses will result in two less distinguishable, saturated downstream responses (Fig 2b).



These results show that the pheromone response system actively regulates signal to transmit information about measured pheromone concentration with minimal loss. Our results underscore the importance of measuring overall system dynamics at appropriate timescales, to uncover new regulatory mechanisms in signaling systems, and to relate biological mechanism to the fundamental physics of information sensing and transmission.

References

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