Surprising dynamic flexibility in bacterial two-component systems with transcriptional feedback

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Bacteria adapt to environmental changes with signal-induced transcriptional programs involving multiple layers of feedback control. Therefore, a mechanistic understanding of adaptation dynamics requires an integrated view of underlying networks. Most bacterial signaling occurs through two-component systems, comprised of a sensor histidine kinase (SHK) that responds to signals by affecting phosphorylation state of a transcriptional response regulator (RR). Commonly, RR and SHK are expressed from a single operon that is positively autoregulated by phosphorylated RR. The role of this feedback is not well understood, but it has been associated with overshoot kinetics in the Mg^{2+}-responsive *Salmonella* virulence regulation system PhoPQ and “learning” from previous signaling events during *E. coli* phosphate limitation in the PhoBR system. These distinct dynamical responses may indicate that feedback can be positive or negative depending on post-transcriptional events.

To test this hypothesis we built a generalized integrative mathematical model that includes mechanistic details from several bacterial two-component systems and employed a genetic algorithm to search for the simplest model with overshoot kinetics reminiscent of *Salmonella* PhoPQ. We found that a source of exogenous RR phosphorylation (e.g. crosstalk with other two-component systems) is necessary to attain such kinetics. Furthermore, we found that the effective sign of feedback can be tuned by signal strength and that overshoot kinetics require negative feedback. The model predicts that negative feedback accelerates responses, in large part due to overshoot kinetics. When the system is in the positive feedback regime, the response range increases and thereby allows “learning” behavior at the cost of response time. Decoupling transcriptional feedback shows that autoregulation of RR resembles positive feedback, contributing to wider response range while autoregulation of SHK resembles negative feedback, contributing to faster responses. Stoichiometric autoregulation of both genes in a single operon therefore resolves an evolutionary trade-off between fast responses and wide response range. Our results suggest that two-component signaling architecture has evolved for flexibility, showing context-appropriate response characteristics that are tuned by the strength and duration of signaling events.