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SIGNAL FIDELITY AND ROBUSTNESS IN *ESCHERICHIA COLI* PHOSPHATE RESPONSE WITH SYNTHETIC PROMOTERS

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Escherichia coli regulates inorganic phosphate (P_i) uptake in order to survive under varying environmental conditions. The sensory machinery consists of a two-component system (TCS), an histidine kinase and a response regulator that relays the signal to the genetic components. Achieving a quantitative understanding of the biochemical mechanism in TCS has implications in biotechnology applications. This way, targeted genetic modification on organisms can be applied in order to enhance their natural capacity for certain tasks and to fine-tune their behaviour.

Building on previous work, here we give a detailed mathematical analysis of various models of *E. coli* response mechanism for P_i intake. Our analysis is done in relation to signal fidelity in response to external P_i concentration with two contributions.

As the first contribution, we propose a spectrum of models with varying levels of detail. Choosing a more refined model over a simpler one provides advantages in terms of a higher detail in biochemical resolution. In contrast, a simpler model can be instrumental by abstracting away from many system parameters, and this way can guide an analysis with a focus on the dominant model trends. Starting from the most detailed model proposed in [1], we present a spectrum of reduced models that agree with the biological notions in the literature. These models contain a smaller number of reactions and parameters in their chemical reaction network representations. Moreover, they are in qualitative agreement with the more detailed model in terms of their steady state dynamics.

As the second contribution, we analyse the input-output robustness to variations in the concentrations of the system components. We study the system's equilibria and their relation to protein total concentrations. Input-output robustness is a favourable feature for the systems that provide a response signal to an incoming stimulus. The output level of a TCS response to an input signal is generally sensitive to changes in the protein concentrations, which often vary from cell to cell. Therefore, robustness of the input-output relation enables to finely tune the systems response to the external stimulus.

Starting from the two-component system proposed in [2], we modify its chemical reactions network until we get one of the reduced models we propose. Each step of this process is identified by a model, which is analysed in terms of its input-output relation (see Figure 1). Moreover, by bifurcation analysis, we

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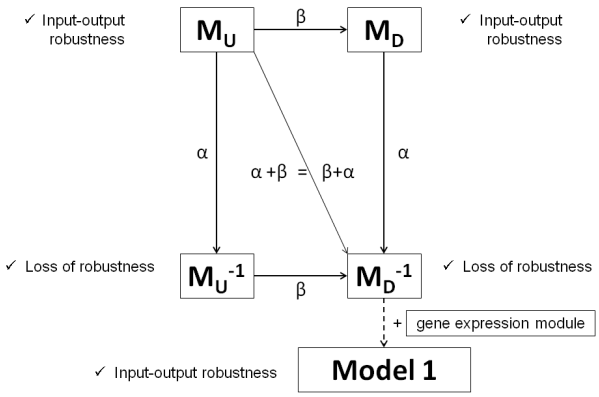

Figure 1: The construction scheme of the analyzed models. The solid arrows indicate going from one model to another through the addition of one reaction. The symbol -1 represents the addition of phosphorylated histidine kinase dephosphorylation (α), whereas the letter D identifies the addition of phosphorylated response regulator dimerization and the reverse reaction (β). The dashed arrow represents the transition from model M_D^{-1} to a larger one, Model 1, by adding the gene expression module.

study the steady state behaviour, which can vary in response to changes in the parameter values. Finally, we analyse the noise in the biochemical machinery in the phosphate economy of *E. coli*. The biochemical process of gene expression is a source of significant intrinsic noise that can imply a loss of coherence in the output signal. We quantify the effect of different synthetic promoter designs on signal robustness in conditions of different external P_i concentration regimes. The results with our reduced model confirm the observations in [3]. That is, an increased promoter binding rate is associated to a moderate decrease in the output fluctuation, while increased promoter unbinding rate comes with an appreciable increase in output fluctuations.

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