

Design Principles for Regulator Gene Expression in a Repressible Gene Circuit**Wall, Michael E.^{1,2}, Hlavacek, William S.³, Savageau, Michael A.⁴****¹Computer and Computational Sciences Division, ²Bioscience Division, Los Alamos National Laboratory, Los Alamos, NM, USA; ³Theoretical Biology and Biophysics Group, Theoretical Division, Los Alamos National Laboratory, Los Alamos, NM, USA; ⁴Department of Biomedical Engineering, University of California, Davis, CA, USA**

We consider the natural design of a type of repressible gene circuit that controls biosynthetic activity in bacteria. In this type of circuit, a transcription factor (TF) acts to decrease the expression of an effector transcriptional unit (TU) when a signal molecule with which it interacts is present. The effector TU encodes one or more enzymes, or other proteins with effector functions (e.g. membrane transport). The TF can also independently influence the expression of its own gene, such that regulator gene expression is repressible (like effector genes), constitutive, or inducible. Thus, a signal-directed change in the activity of the TF can result in one of three patterns of coupled regulator and effector gene expression: direct coupling, in which regulator and effector expression change in the same direction; uncoupling, in which regulator expression remains constant while effector expression changes; or inverse coupling, in which regulator and effector expression change in opposite directions. We have investigated the functional consequences of each form of coupling using a mathematical model to compare alternative circuits on the basis of performance criteria for biosynthetic gene circuits; the criteria include stability, robustness and temporal responsiveness. Because these performance criteria may be more broadly applicable, the comparison may apply to gene circuits that regulate cellular functions other than biosynthesis. The results of the comparison depend on whether the TF acts as with a repressor or activator mode of control on the promoter of the effector TU. In the case of repressor control, direct coupling is optimal among the three forms of coupling, whereas in the case of activator control, inverse coupling is optimal. Results also depend on the sensitivity of effector expression to changes in the level of a signal molecule; the optimal form of coupling can be physically realized only for circuits with sufficiently small sensitivity. The theoretical results provide a rationale for autoregulation of regulator genes in repressible gene circuits and lead to testable predictions, which we have compared with data available in the literature and electronic databases.

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