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Design methods and constraints for biological integral control

Synthetic biology includes an effort to use design-based approaches to create novel "controllers," biological systems aimed at regulating the output of other biological processes. The design of such controllers can be guided by results from control theory, including the strategy of integral feedback control, which is central to regulation, sensory adaptation, and long-term robustness. Realization of integral control in a synthetic network is an attractive prospect, but the nature of biochemical networks can make the implementation of even basic control structures challenging. Here we present a study of the general challenges and important constraints that will arise in efforts to engineer biological integral feedback controllers, or to analyze existing natural systems. Constraints arise from the need to identify target output values that the combined process plus controller system can reach; and to ensure that the controller implements a good approximation of integral feedback control. These constraints depend on mild assumptions about the shape of input-output relationships in the biological components, and thus will apply to a variety of biochemical systems. We summarize our results as a set of variable constraints intended to provide guidance for the design or analysis of a working biological integral feedback controller.