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## **(G\*) (POS-51) Achieving robust perfect adaptation while suppressing stochastic fluctuations in biochemical reaction networks**

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Chemical reaction networks allow cells to sense and adapt to sustained environmental perturbations. Due to inherent stochasticity and low copy numbers, biochemical regulatory modules must achieve adaptation despite significant fluctuations, limiting the applicability of classical control theory to understand and rationally design such modules. Recent theoretical work has established the class of molecular control modules capable of achieving robust perfect adaptation (RPA) for average abundances in stochastic reaction networks. RPA ensures the controlled signal perfectly adapts to disturbances, despite parameter variations and unknown details in the controlled network. All molecular control modules exhibiting this property are an extension of the antithetic integral feedback (AIF) motif, whose adaptation property has been demonstrated experimentally. It has been suggested that increased fluctuations about the average controlled species abundance is the price to pay for RPA in these systems. We present evidence that this apparent noise penalty may indeed be unavoidable in generalized AIF topologies studied in the literature. However, we show different couplings between the controller and the controlled system avoid this penalty and even permit reduced fluctuations relative to an open-loop control strategy. Additionally, we quantify trade-offs amongst sensitivity, settling time, energetic cost, and fluctuations in several generalized AIF topologies in the presence of inevitable intracellular dilution effects, which results in imperfect adaptation. These results clarify our understanding of noise in biochemical adaptation and suggest design considerations for achieving RPA while suppressing stochastic fluctuations in biochemical networks.

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