CoRa –A general approach for quantifying biological feedback control

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***Abstract*— Feedback control is a fundamental underpinning of life, underlying homeostasis of biological processes at every scale of organization, from cells to ecosystems. The ability to evaluate the contribution and limitations of feedback control mechanisms operating in cells is a critical step for understanding and ultimately designing feedback control systems with biological molecules. CoRa –or *Control Ratio*– is a general framework that quantifies the contribution of a biological feedback control mechanism to adaptation using a mathematically controlled comparison to an identical system that lacks such feedback. CoRa provides a simple and intuitive metric with broad applicability to biological feedback systems.**

***Index Terms*— Feedback, Homeostasis, Control**

Feedback control is a mechanism by which a system can assess its own state and use this information to react accordingly [1]. In particular negative feedback is instrumental in the ability of biological systems to restore homeostasis after a perturbation [2], a property known in engineering as disturbance rejection and in the biological sciences as adaptation. Despite the importance of feedback, no systematic and generalizable approaches exist to quantify the contribution of a negative feedback loop to adaptation in biological networks. In order to tackle this problem, we have developed **CoRa** –or **Co**ntrol **Ra**tio.

CoRa follows the classical notion of Mathematically Controlled Comparisons [3] by assessing the performance of a biological system with feedback control to a locally analogous system without feedback. The *locally analogous* system without feedback has identical structure and parameters to those of the feedback system, except for the feedback link, and both systems rest at the same steady-state value before the perturbation. As a result, the divergence in their behavior after they are challenged with a perturbation isolates and quantifies the contribution of the feedback control. CoRa

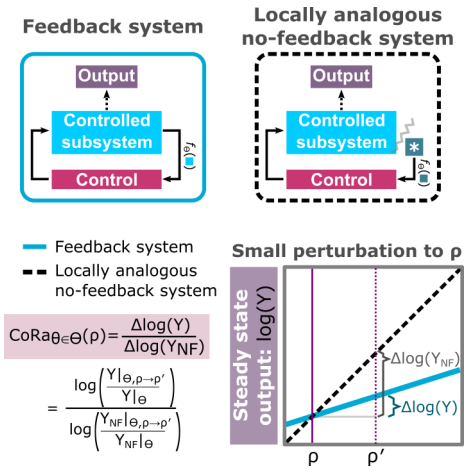

Fig. 1. **Explaining the CoRa approach.** (Top) Diagram of a system with feedback and its locally analogous system without feedback, and (bottom) mathematical definition of CoRa.

can be defined and computed for any biological system described by a solvable set of ordinary differential equations, irrespective of its complexity. CoRa can also be efficiently computed across different parameter values of a system, allowing a global view of the performance of its feedback under different conditions.

Then, CoRa provides a framework for the systematic evaluation and comparison of biochemical feedback control systems, which is essential for understanding the general principles of biological homeostasis. Additionally, we have shown how CoRa can be used to better characterize a specific feedback control system –taking advantage of CoRa being agnostic to the complexity of the system–, to compare different feedback control mechanisms –extracting the underlying general principles–, as well as efficiently design and optimize a feedback control circuit for a particular function of interest.

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