The Impact of Retroactivity on the Signal Processing of Transduction Networks

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***Short Abstract* — Retroactivity is an impedance-like effect found at the interconnection of biomolecular systems. Just like impedance in electrical circuits, it causes the behavior of a system to change upon interconnection. In this abstract, we describe theoretical and experimental work that characterizes the effects of retroactivity on the dynamic behavior of signal transduction modules. We further show how these modules can be re-engineered to attain insulation from retroactivity.**

***Keywords* — retroactivity, insulation, signal transduction, frequency response.**

I. Purpose

Biological signal transduction networks are commonly viewed as circuits that pass-along information -- in the process amplifying, enhancing sensitivity, or performing other signal-processing tasks – to downstream transcriptional and other components. In this classical view, the presence or absence of such components should not change the operating characteristics of the circuit. By contrast, recent theoretical work [1] has suggested that the behavior of discrete modules might dramatically change upon coupling to other components through retroactivity, an impedance-like effect similar to that found in electrical, hydraulic, or mechanical networks. However, to our knowledge, there has not been any experimental study of the dynamic effects of retroactivity, nor have there been theoretical studies quantifying how the basic signal-processing time scales (response time, bandwidth) are affected.

Employing a combination of theory and experiments on an *in vitro* covalent modification cycle (the PII/PII-UMP cycle of *E. coli* [3]), we found that the time-scales of signal communication are modulated, in a surprising way, by the concentrations of downstream targets. Specifically, we found non-intuitive time-scale changes: for a Goldbeter-Koshland [2] covalent modification cycle, the presence of targets speeds-up signaling; by contrast, for a zeroth-order cycle, targets slow-down signaling. The bandwidth, the range of frequency where the system can process information, decreases in the presence of targets. This way, targets participate in establishing trade-offs between noise-filtering capabilities and a circuit's ability to process high-frequency stimulation. Insulation from retroactivity could be attained by increasing the amounts of converting cycle enzymes, corresponding to engineering high-gain feedback. The present work complements studies of stoichiometric retroactivity [3], that is, the effect of sequestering by downstream targets on the steady states of an upstream system. Related *in vivo* work using intact larvae also suggested that target effects may play a significant role in the distributions of components of MAPK cascades [4].

We conclude that the view of signaling networks as independent relay devices, whose operating characteristics are not affected by their substrates, is fundamentally flawed. Our study highlights a fundamental and hereto unrecognized property of intracellular communication, bringing up issues that are generally relevant to biological signal transmission.

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