# Modularity in Complex Gene Transcription Networks

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A promising approach to decipher the complexity of biomolecular networks is to predict their behavior from that of the composing modules. Unfortunately, the behavior of a module changes once connected in the network [1] due to retroactivity effects. Retroactivity arises whenever two molecules bind describing the effect that these molecules become unavailable for other reactions. Recent experimental evidence demonstrates that the effects of retroactivity can be severe in signaling pathways [2], changing both the dose-response curve of a module and its dynamic response to input stimuli. Despite playing an important role in system phenotype, retroactivity is not yet characterized in complex gene transcription networks.

Here, we mathematically characterize retroactivity. We first introduce the retroactivity to the input of a gene, similar to the impedance of an electrical component, as a function of measurable biochemical parameters. Second, we define the internal retroactivity of module M accounting for loading effects presented by the genes in M on its own dynamics. Then, we introduce the input retroactivity of module M to module N describing the load module M presents to N. Both retroactivities can be calculated by combining the retroactivity to the input of genes in M, just as we determine the equivalent impedance of an electrical circuit at any two terminals by combining the impedances of the individual components. Based on these retroactivities, we describe how interconnected modules affect each other's behavior. We therefore recover the advantage of a modular approach to understand the dynamics of complex systems by augmenting the description of a module with internal and input retroactivites.

We illustrate the implications first by demonstrating that neglecting retroactivity can lead to the conclusion that negative feedback speeds up the system response to input perturbations, while in fact, it can slow down the response. Second, we focus on an activator-repressor clock and investigate coupling effects and noise propagation due to combinatorial regulation.

[1] D. Del Vecchio, A. Ninfa, and E. Sontag (2008) Modular Cell Biology: Retroactivity and insulation. *MSB* **4**:161.

[2] P. Jiang, A. Ventura, E. Sontag, S. Merajver, A. Ninfa, and D. Del Vecchio (2011) Load-induced modulation of signal transduction networks. *Science Signaling* **4**(194):ra67.