

From Single Modules to Multi-Module Systems in Gene Transcription Networks

Andras Gyorgy¹ and Domitilla Del Vecchio²

¹Department of Electrical Engineering and Computer Science, MIT, 77 Massachusetts Avenue, Cambridge, MA 02139

²Department of Mechanical Engineering, MIT, 77 Massachusetts Avenue, Cambridge, MA 02139

Predicting the dynamic behavior of a complex network from that of the composing modules is a central problem in systems and synthetic biology. Unfortunately, modules display context-dependent behavior. As a result, our current ability of predicting the emergent behavior of a network from that of the composing modules remains limited. One cause of context-dependence is retroactivity. This phenomenon is similar to loading in electrical networks and influences the dynamic performance of a module upon connection to other modules. Here, we establish an analysis framework for gene transcription networks that explicitly accounts for retroactivity to reliably predict how a module's behavior will change once it is connected to other systems. This framework carries substantial conceptual analogy with the electrical circuit theory based on equivalent impedances established by Thevenin. Specifically, relying on model reduction techniques for nonlinear systems, we demonstrate that a module's key interconnection properties are encoded by three retroactivity matrices: internal, scaling, and mixing retroactivity. All of them have a physical interpretation and can be computed from measurable biochemical parameters and from the modules' topology, similar to how one would compute the equivalent impedance of a network of interconnected electrical components. The internal retroactivity quantifies the effect of intramodular connections on an isolated module's dynamics. The scaling and mixing retroactivity establish how intermodular connections change the dynamics of connected modules. Based on these matrices and on the dynamics of modules in isolation, we can accurately predict the dynamic behavior of an arbitrary interconnection of modules. Further, using contraction theory we provide a quantitative metric that determines how robust the dynamic behavior of a module is to interconnection with other modules. Our metric can be employed both to evaluate the extent of modularity in natural networks and to establish concrete design guidelines to minimize retroactivity between modules in synthetic systems. Finally, we illustrate how our framework predicts and explains surprising and counter-intuitive dynamic properties of naturally occurring network structures, which could not be captured by existing models of the same dimension.