Modular composition of gene transcription networks

Andras Gyorgy and Domitilla Del Vecchio

Predicting the dynamic behavior of a large network from that of the composing modules is a central problem in systems and synthetic biology. Yet, this predictive ability is still largely missing because modules display context-dependent behavior. One major cause of context-dependence is retroactivity, an effect similar to loading by which the dynamic performance of a module is affected by connection to other modules. In the presence of retroactivity, properties of simple motifs can dramatically change. For example, a stable module can display sustained oscillations after interconnection, or an oscillator can stop functioning as a result of being connected to a downstream system. Here, we establish an analysis framework for gene transcription networks, which explicitly accounts for retroactivity and accurately predicts the behavior of interconnected modules from their properties in isolation. Specifically, a module's key properties are encoded by four retroactivity matrices: internal, external, scaling, and mixing retroactivity. All of them have an intuitive physical interpretation and can be easily computed from the macroscopic parameters (dissociation constants and promoter concentration) of each node in the module and from the module's topology. The internal and external retroactivity quantify 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 behavior of an arbitrary interconnection of modules. This framework reveals how interconnection topology and measurable parameter values control context-dependence due to retroactivity. It further provides a quantitative metric to identify modules that are less affected by interconnections in natural networks, while establishing concrete design guidelines to minimize retroactivity between modules in synthetic systems.