Dynamics of Complex Gene Transcription Networks: From Single Modules to Multi-Module Systems

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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. Specifically, a module's key properties are encoded by three retroactivity matrices: internal, scaling, and mixing retroactivity. All of them have a physical interpretation and can be computed from macroscopic parameters (dissociation constants and promoter concentrations) and from the modules' topology. 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.

We illustrate how our framework predicts and explains surprising and counter-intuitive dynamic properties of naturally occurring network structures, which cannot be captured by existing models of the same dimension. For example, we show that negative autoregulation can slow down the response of a system instead of speeding it up. We demonstrate that a gene can respond to a perturbation applied to a different gene even in the absence of a regulatory path between the two genes. As a result, system identification techniques based on perturbation analysis could erroneously identify non-existent regulatory linkages if retroactivity is not accounted for in the corresponding models. An activator-repressor clock displays sustained oscillations when internal retroactivity is neglected, while oscillations are quenched once internal retroactivity is accounted for. However, by carefully adjusting the module's internal retroactivity through the addition of DNA load for the repressor, we can restore oscillations. A genetic toggle switch that can be flipped by a transient external stimulation requires a substantially longer stimulation to be flipped once it is connected to

just a few downstream targets. The interplay between scaling and internal retroactivity plays a role in performance/robustness trade-offs, which we illustrate considering the single-input motif. These facts are relevant, in particular, when designing synthetic circuits and multi-module systems.

Finally, based on measurable biochemical parameters and the interconnection topology, 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.