Modularity in Gene Transcription Networks

Engineered systems are modular. As a result, arbitrarily complex tasks can be executed by using a divide-and-conquer strategy: modules implementing subtasks can be integrated to produce the desired behavior. While evidence suggests that gene transcription networks evolved modularly, it was also demonstrated that signal propagation is bidirectional in these networks. This phenomenon is termed retroactivity, which allows downstream modules to change the behavior of upstream ones. Consequently, the input/output behavior of a module depends on its context, preventing the modular composition of large-scale systems. Here, we mathematically characterize this effect and restore the modular composition of gene transcription networks by appending the description of modules with retroactivities. Specifically, we introduce four retroactivity matrices (internal, external, scaling and mixing) with well-defined physical meaning. We also define the retroactivity of a node, which can be interpreted as the biological counterpart of impedance. We show that the four key retroactivity matrices can be calculated combining the retroactivity of each node, which is conceptually analog to how one determines the input impedance of interconnected electrical components. Furthermore, we provide a theorem similar to Thevenin's, connecting the behavior of isolated and connected modules. Based on this, we are able to quantify the effect of interconnection on the dynamics and trajectory of modules. Our work contributes equally to systems and synthetic biology with many applications. We show that while self-repression yields increased robustness to interconnection, it can slow down the response, contrary to previous results. In addition to this, we highlight a potential shortcoming of current network identification techniques. We define a robustness metric capturing how the behavior of modules change upon interconnection, so that modules in natural systems can be identified, illuminating how evolution applies the divide-and-conquer strategy to execute complex tasks. Finally, we present design principles to obtain robust modules so that large-scale synthetic circuits can be implemented in a modular fashion.