Symbolic Steady States and Dynamically Essential Subnetworks of Discrete Regulatory Networks

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Discrete modeling methods for biological regulatory networks have shown their worth in a variety of applications, in particular for systems where precise quantitative data is lacking. Utilizing a high level of abstraction, we can associate each network component, e.g. genes, proteins or receptors, with a finite number of activity levels representing e.g. strength of gene activity, intervals of substance concentrations or presence or absence of a signal. States of the network are then given by vectors of component activity. Information on interactions between components and the rules governing network dynamics in state space are captured in a discrete function f. There are different methods to derive the system's behavior from the function f. A deterministic representation of the dynamics is obtained by defining the successor of a given state as its image under f, which is called synchronous update. When we assume distinct time delays to be associated with different component update processes, we require that a state and its successor differ by one component value only. By considering all possible successors in agreement with f, we obtain a non-deterministic representation of the dynamics. Both approaches have been applied successfully, the synchronous method having advantages regarding complexity of analysis, the asynchronous update allowing for a more realistic representation of trajectories of the system (see e.g. [1], [2] and references therein).

One major difficulty for analyzing the dynamics of a discrete system is that the state space is exponentially larger than the number of network components. A well-known idea to approach this problem is to identify smaller building blocks of the system the study of which in isolation still renders information on the dynamics of the whole network. Clearly, the difficulty is that further components and interactions influence such a network building block once it is again embedded in the network. Conditions to identify suitable subnetworks that retain their behavior in the context of the complex network are needed to derive useful information on the network dynamics. Such *dynamically essential subnetworks* obviously play a crucial role for yielding certain dynamical properties. Relating their structural properties to their dynamical effects and associating them with definite biological functions then is a further step in the analysis and classification of the original network.

Methods to identify suitable subnetworks and results that allow us to derive dynamical properties of the network from the analysis of these subnetworks can be obtained by extending ideas developed for Boolean functions presented in [3] and [4]. The results hold for multi-valued discrete functions, considering both synchronous as well as asynchronous dynamics. We identify subsets of state space where some network components do not change their value on all trajectories in that part of state space by exploiting the properties of *symbolic steady states*. These are fixed points of an adapted function f^θ that coincides with f on state space, but also allows the consideration of symbolic values representing sets of component values for the network components. Thus a symbolic value is used when we do not have an exact value for a component but rather constraints concerning its value. The function f^θ allows us to propagate these constraints along trajectories, thus including all possible behaviors of the system that can arise from initial conditions in agreement with the constraints.

The fixed points of f^θ, i.e., the symbolic steady states, hold information about dynamically essential subnetworks. The *regular* components, i.e., those with a specified activity level, of a symbolic steady state act as a boundary between dynamically active subnetworks similar to the notion of *frozen core* introduced in the context of random Boolean networks (see [1]). We obtain a fine structural representation of the active subnetworks by considering the local interaction graph ([5,6]) associated with the symbolic steady state. Composition of attractors of the isolated subnetworks with respect to the symbolic steady state then yields attractors of the original network. With this fundamental property in mind, we are able to proof more general statements concerning the relation between structure and dynamics of the network, in particular inferring number and size of attractors from the existence of positive and negative circuits in the network.

Of course, not all networks lend themselves well for analysis using symbolic steady states. Criteria and methods for finding symbolic steady states can be formulated when looking at the SCC (strongly connected components) graph derived from the network structure. In [4] we considered the class of so-called networks with input layer, such as often used for modeling signal transduction processes, and obtained a complete description of the network dynamics from easily computable symbolic steady states. The results transfer to the multi-valued case.

Currently, main emphasis lies on applying the methods to established biological network models. This does not only allow for testing the suitability of the approach but also for a comparison of dynamically essential subnetworks derived from symbolic steady states with network modules of known biological importance.

References

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