Modeling Gene Network Motifs Using Statecharts

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Motivation

Mechanisms regulating the expression of genes in an organism are often represented by using a gene regulatory network (GRN), which describes the interactions among genes, proteins and other components at the intra-cellular level. There have been several attempts to define formal mathematical and computational frameworks for modeling GRNs. They can be classified into quantitative approaches, using differential equations or stochastic models, and qualitative approaches, mostly based on boolean networks and Petri nets. Recently, Shin et Al. [1] have used Statecharts (SC) [2], a computational framework with a visual language and well-defined semantics, for modeling some gene network motifs [3]. Statecharts (SC) extend state transition diagrams by adding concurrency and hierarchy. These additional features, if correctly exploited, provide a solution to the scalability problems of boolean networks and Petri nets. SC have been extensively studied in software and systems engineering, and have demonstrated to be particularly well-suited for modeling and designing reactive systems, that is, systems which evolve reacting to internal or external events, or changed conditions. In the case of GRNs these events can be, for example, the introduction or removal of a protein or of another component. We have found that the modeling approach of Shin et Al. has some shortcomings, which we discuss below. First, their model of simple regulation may lead to misinterpretations, because they map two different simple regulation motifs on the same SC. This merging creates problems when the mapping is inverted, from the SC to network motifs, because it is not clear whether the SC should be mapped on both the original motifs (thus, possibly leading to an over-specification) or it should be mapped on only one of them. In the latter case, there is ambiguity on which of the two source network motifs the SC should be mapped on. Second, their model is incomplete, because the set of states of the elements in a GRN is only partially represented. In particular, if we consider the simple case where a gene X regulates a gene Y, we observe that they only model the scenario where the regulating gene X is expressed, ignoring the situation where it is not expressed, which could be significant if the same gene is part of a different network. Third, their model does not fully exploit the concurrency features of SC. This determines sub-optimality, because it does not allow to reduce the size of the system. This also makes their method not scalable: that is, the complexity of models grows faster than their size. Moreover, since the states of the regulated gene are modeled as substates of the regulating gene, they cannot

model networks containing genes which reciprocally regulate each other.

Methods

We present a method for translating a gene network motif to a SC and we show how it overcomes the limitations of the method proposed by Shin et Al., by applying it to a number of network motifs. Our method can be used for modeling GRN in an easy and intuitive way by taking advantage of the visual features of SC, and for interactively simulating the execution of the model even in the presence of perturbation by external events.

Results

We present an improved method for modeling network motifs by using SC, and we show its application on a number of recurrent patterns in GRNs, called network motifs. In our method, each element (gene, protein, signal) can be in one of two states: on (which means that the gene is expressed or that the protein is present) or off (which means that the gene is not expressed or that the protein is not present). Moreover, activating interactions in GRNs are translated to transitions from the off state to the on state for the gene being activated. Similarly, inhibiting interactions correspond to transitions from the on state to the off state. We also study the temporal evolution of gene networks in a discrete scenario. The considered model, although rough due to its discrete nature, allows us to simulate some interesting temporal properties of GRNs. For example, we are able to model the delay in the activation and the deactivation of the output gene in the coherent type-1 feedforward loop network (C1-FFL), and the pulse in the incoherent type-1 feedforward loop network (I1-FFL). We are not able to model more sophisticated temporal mechanisms which require the use of quantitative aspects, like acceleration.

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