Logical Modeling of Developmental Genetic Regulatory Networks with NetBuilder

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ABSTRACT

Eukaryotic gene expression is controlled by the interactions of transcription factors (TFs) with the *cis*-regulatory domains of genes and the basal transcription apparatus. TFs themselves are the products of the transcription and translation processes, and together with genes and the machinery for transcription, translation, transport, and signaling, they form the genetic regulatory networks (GRNs) that control development.

GRNs can be modeled on different levels, from simple Boolean state machines to detailed series of coupled differential equations (see [1] for a review). The simplest models often lack sufficient predictive power, whereas the most complex ones usually have a great number of parameters whose values have not been, or cannot be, determined experimentally. Therefore, many modeling approaches focus on simplifying the details of the biochemical steps (thereby reducing parameteric degeneracy), whilst maintaining the essential features of the interactions (thereby retaining predictive power).

In attempts to reconstruct GRNs from experimental data, "box-and-arrow" diagrams are often used to outline the network structure. These diagrams help modelers in formulating hypotheses. However, accurate predictions of the behavior of the modeled system require appropriate mathematical models, not just drawings and intuition. Maybe because intuition has played a role in their conception, 'good' box-and-arrow diagrams do depict the (often non-linear) 'interesting' control structures and leave out 'uninteresting' detail. Such box-and-arrow diagrams form an ideal basis for setting up, and simulating the behavior of adequate, but sufficiently reduced, mathematical models. NetBuilder comprises software that allows modelers to build graphical representation of GRNs by placing predefined components on a canvas, and drawing connections between components to represent interactions. Components include genes and their products, 'switches' (elements that need some kind of activation), and inter-cellular signal receptors. A number of predefined basic operators are available to specify the type of interaction. In later versions, users will also be given the option to define new operators, if required.

When a graphical model has been built, NetBuilder can generate a mathematical description of the graph, and simulate the behavior of the model. Alternatively, the model description can be exported, and third party software may be used to perform the simulations.

The following basic assumptions are made when translating the graphs into a biologically justifiable mathematical model. 1) TF binding and RNA polymerase activation are instantaneous with respect to mRNA elongation and translation. 2) Slow processes, such as mRNA and protein production and breakdown, transport and signaling, determine the network dynamics. These processes are modeled using time delays, or differential equations of the form $d\boldsymbol{x}/dt = k_+ - k_-\boldsymbol{x}$ (where k_+ is the production rate of component $\boldsymbol{x}$, and k_- its breakdown rate). 3) Where component $\boldsymbol{x}$ is a mRNA, the value of k_+ is calculated from current TF concentration to equilibrium dissociation constant ratios, and a set of constants (weights) that quantify the effect of particular bound TF configurations on the assembly of the basal transcription apparatus and hence on the overall mRNA production rate. In their simplest form, the weights can be set to specify Boolean operations ('and', 'or', 'not') and their continuous counterparts, but more intricate input-output relations can also be effectively modeled in this way.

Evaluation of the graphs is currently done within the logical framework outlined by Yuh et al. [2, 3]. However, we plan to provide the user with a choice between various modeling formalisms and resolutions, from Boolean networks to sets of coupled differential equations. Furthermore, we are preparing NetBuilder to plug into the Systems Biology Workbench [4], and we are also developing a parser that will enable NetBuilder to read and write the SBML format (see [4]).

REFERENCES

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