VisualGNA : Une Interface Graphique pour la Simulation Qualitative de Réseaux de Régulation Génique

VisualGNA : A Graphical User Interface for the Qualitative Simulation of Genetic Regulatory Networks

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Résumé

Les méthodes développées pour la simulation qualitative de systèmes dynamiques se sont révélées être des outils puissants pour l'étude des réseaux de régulation génique. Nous avons développé une méthode pour la simulation qualitative de réseaux de régulation génique grands et complexes, implémentée dans un outil appelé GNA (Genetic Network Analyzer). Nous présentons ici VisualGNA, l'interface graphique de GNA, et ses diverses fonctionnalités.

Mots clés : *réseaux de régulation génique, interface utilisateur, simulation qualitative.*

Abstract

Methods developed for the qualitative simulation of dynamical systems have turned out to be powerful tools for studying genetic regulatory networks. We have developed a method for the qualitative simulation of large and complex genetic regulatory networks, implemented in a simulation tool called GNA (Genetic Network Analyzer). We present here VisualGNA, the graphical user interface component of GNA, and its different functionalities.

Keywords: *genetic regulatory networks, graphical user interface, qualitative simulation.*

It is now commonly accepted in biology that most of the properties of an organism emerge from the interactions among its genes, proteins, metabolites, and other molecules. This implies that, in order to understand the functioning of an organism, the networks of interactions involved in gene regulation, metabolism, signal transduction, and other cellular and intercellular processes need to be elucidated. As the size and complexity of most networks of interest prohibits an intuitive understanding on the molecular level of their behavior, formal methods supported by efficient and user-friendly computer tools need to be developed.

We have developed a method for the qualitative simulation of large and complex genetic regulatory networks [2]. Within the framework of our method, genetic regulatory networks are modeled by a class of piecewise-linear differential equations that have been well-studied in mathematical biology [3]. Most of the time, precise numerical values for the kinetic parameters in the equations are not available. Therefore, we specify qualitative constraints on the parameter values that can usually be inferred from biological data. Given the differential equations and parameter constraints, having the form of algebraic inequalities, the possible qualitative behaviors of the system can be determined through qualitative simulation. More specifically, qualitative simulation results in a graph of qualitative states and transitions between them.

The qualitative simulation method has been implemented in a computer tool called Genetic Network Analyzer (GNA) which is available for non-profit academic research purposes (http ://www-helix.inrialpes.fr/gna). It has been developed in Java 1.3, and can be used on different platforms (Windows NT, Linux and Unix). Moreover, GNA has been used to analyze several genetic regulatory networks of biological interest, such as the complex network of genes controlling the initiation of sporulation in *B. subtilis* [1]. The current version of this network includes about 20 genes.

Basically, GNA consists of two modules interacting with each other. On one hand, we find the GNA kernel which performs the actual simulation process, and on the other hand, a graphical user interface (GUI) called VisualGNA, which allows a user-friendly access to the simulation functionalities. VisualGNA facilitates the use of the simulator

by assisting the biologist in the specification of the model of a genetic regulatory network as well as the interpretation of the simulation results. A special effort has been made to separate the mathematical and the visualization aspects, thus allowing the simulation kernel and the graphical user interface to evolve independently.

The input of the qualitative simulator consists of a set of differential equations supplemented by parameter inequalities. The user has to prepare a text file with this information using a structured modeling language. The computer tool analyses the model description contained in the file and VisualGNA displays the genes and their mutual interactions in an interaction graph.

VisualGNA also helps the user in interpreting the output of a simulation. A GNA simulation results in a graph of qualitative states and transitions between qualitative states, where each state gives a measure of the level of expression of all the genes in the network. A simulation report summarizes important information, in particular the occurrence of qualitative states without successors and cycles of qualitative states (which give an indication of functional states of the biological system) as well as their basin of attraction. In order to facilitate the interpretation of large transition graphs, the user can focus on interesting parts of the graph by selecting, extracting, and expanding subgraphs.

A path of qualitative states in the transition graph gives an indication of the qualitative evolution of gene products over time. Two different ways of exploring these predictions are provided by VisualGNA. First of all, the user can visualize a qualitative state sequence as a set of gene expression profiles, one for each gene product. A second way to visualize this information is to project the gene expression levels associated with a state on the interaction graph, where the level of expression of each gene is represented by a color intensity. A sequence of qualitative states is then visualized as a sequence of projections on the interaction graph, resulting in an intuitive picture of the global change of gene expression over time.

Given the importance of graphs in VisualGNA, and more precisely of graphs display in the input and output parts of the tool, two algorithms have been implemented to display graphs in a pleasant and intuitive way, the hierarchical algorithm of Sugiyama and a force-directed placement algorithm. This makes the interaction graph and the state transition graph easier to interpret for the user.

Future versions of VisualGNA, currently under development, will especially improve the support provided in specifying the input of the simulator. Instead of providing the model in the format of a text file, mathematical modeling of a genetic regulatory network will be integrated in the user interface. As a first step, the user will be able to draw an interaction graph summarizing the regulatory influences between the genes in the network on an abstract level. This graph might be extracted from an interaction database. Then, the user can add, step by step, information about these influences and thus turn the graph into a mathematical model. The model edition process is supported by automatic verification of the global correctness and consistency of the entered model elements.

GNA provides predictions of the possible qualitative behaviors of a genetic regulatory networks which can be directly compared with gene expression profiles obtained by means of quantitative RT-PCR or DNA microarrays. We are currently working on extensions of the method to validate and identify models of genetic regulatory networks using gene expression data. This will allow the simulation method and its computer tool to evolve into a more general approach towards the computer-supported analysis of genetic regulatory networks.

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