SOFTWARE

GenNet: A Tool for Qualitative and Quantitative Modeling of Gene Regulatory Networks

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Abstract

Background: Gene regulatory networks have an important role to study the behaviour of genes. By analysing these Gene Regulatory Networks we can get the detailed information i.e. the occerance of deseases by changing behaviour of GRNs. Many different approaches are used (i.e. qualitative modeling and hybrid modeling) and various tools (i.e. GenoTech, GINsim) have been developed to model and simulate gene regulatory networks. GenoTech allows the user to specify a GRN on Graphical User Interface (GUI) according to the asynchronous multivalued logical functions of René Thomas, and to simulate and/or analyse its qualitative dynamical behaviour. ReneTh́omas discrete modeling of gene regulatory network (GRN) [?] is a well known approach to study the dynamics of genes. It deals with some parameters which reflect the possible targets of trajectories. Those parameters are priory unknown. These un-known parameters are fetched using another model checking tool SMBioNet[?]. SMBioNet produces all the possible parameters satisfying the given Computational Logic Tree (CTL) formula as input. This approach involving logical parameters and conditions also known as qualitative modeling of GRN. However, this approach neglects the time delays for a gene to pass from one level of expression to another one i.e. inhibition to activation and vice versa. To find out these time delays, another modeling tool HyTech[?] is used to perform hybrid modeling of GRN.

Results: We have developed a Java based tool called GenNet http://www.genotech.org to facilitate the model checking user by providing a unique GUI layout for both qualitative and quantitative modeling of GRNs. As we discussed, three separate modeling tools are used for complete modeling and analysis of a GRN. This process is much lengthy and takes too much time. GenNet assists the modeling users by providing some extra features i.e. CTL editor, parameters filtering and input/output files management.

Conclusion: GenNet takes a GRN network as input and does all the rest of computations i.e. CTL verification, K-parameters generation, parameter implication to GRN, state graph, hybrid modeling and parameter filteration autometicaly. GenNet serves the user by computing the results within seconds that were taking hours and days of mannual computation.

Keywords: Qualitative modeling; Quantitative modeling; GRN Modeling and analysis; K-parameters; Time delays; CTL verificaton

Background

In any given cell, thousands of genes are expressed and work in concert to ensure the cell's function, fitness, and survival. Each gene, in turn, must be expressed at the proper time and in the proper amounts to ensure the appropriate functional outcome. The regulation and expression of some genes are highly robust; their expression is controlled by invariable expression programs. For instance, developmental gene expression is extremely similar in a given cell type from one individual to another. The expression of other genes is more variable: Their levels are noisy and are different from cell to cell and from individual to individual. This can be highly beneficial in physiological responses to outside cues and stresses. Recent advances have enabled the analysis of differential gene expression at a systems level. Gene regulatory networks (GRNs) involving interactions between large numbers of genes and their regulators have been mapped onto graphic diagrams that are used to visualize the regulatory relationships.Gene regulatory networks have an important role to study the behaviour of genes. By

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analysing these Gene Regulatory Networks we can get the detailed information i.e. the occerance of deseases by changing behaviour of GRNs. Many different approaches are used (i.e. qualitative modeling and hybrid modeling) and various tools (i.e. GenoTech, GINsim) have been developed to model and simulate gene regulatory networks. GenoTech allows the user to specify a GRN on Graphical User Interface (GUI) according to the asynchronous multivalued logical functions of René Thomas, and to simulate and/or analyse its qualitative dynamical behaviour. ReneTh́omas discrete modeling of gene regulatory network (GRN) [**?**] is a well known approach to study the dynamics of genes. It deals with some parameters which reflect the possible targets of trajectories. Those parameters are priory unknown. These un-known parameters are fetched using another model checking tool SMBioNet[**?**]. SMBioNet produces all the possible parameters satisfying the given Computational Logic Tree (CTL) formula as input. This approach involving logical parameters and conditions also known as qualitative modeling of GRN. However, this approach neglects the time delays for a gene to pass from one level of expression to another one i.e. inhibition to activation and vice versa. To find out these time delays, another modeling tool HyTech[**?**] is used to perform hybrid modeling of GRN.
As we discussed, three separate modeling tools are used for complete modeling and analysis of a GRN. This process is much lengthy and takes too much time. In this research we propose GenNet, a tool to perform both qualitative and quantitative modeling of GRN under a single GUI interface. Moreover, GenNet facilitates the modeling users by providing some extra features i.e. CTL editor, parameters filtering and input/output files management.

Implimentation

Figure 1 elucidates the layered architecture, upon which our implimentation is based. We use existing coed of SMBioNet and HyTech for parameter estimation and hybrid modeling of GRN respectively. These are shown in figure 1 as layer 2. In order to compute logical parameters, SMBioNet uses a model checker NuSMv (shown as layer 3). On top of layer 2, we develope a Graphical User Interface (GUI) to access features of both SMBioNet and HyTech tools. For this purpose, we use the existing interface of GenoTech which uses a drag and drop model for construction of biological networks asa labelled directed graphs. We extend the existing interface of GenoTech by adding new features, which enable the user to build the SMBioNet model, directly from GenoTech graph. This alliviates the requirement to code SMNioNet input model separately. Moreover,, it facilitates by generating default logical parameters which can be modified by the user.

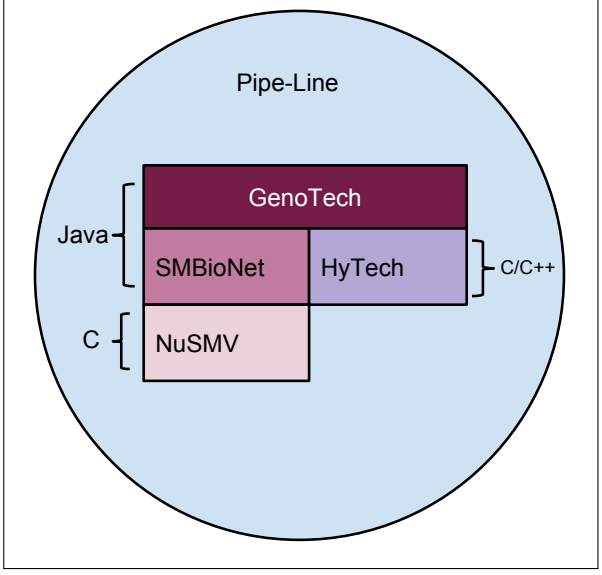

Figure 1 Implementation. GenNet implementation shows the layered architecture of the software.

The entity relationship diagram (ERD) of our developed pipe-lined tool GenNet is shown as figure 2. In ERD, main interaction of tools with each other is shown where GenoTech deals with GRN, State graph and Hybrid Model generation. Pipe-Line Module forward the GRN file along with CTL (produced by GenoTech) to SMBioNet which further interacts with NuSMv model checker to verify the model. SMBioNet returns the output to Pipe-Line Module, where parser refines each parameter and sends back to GenoTech. Further, parameters are applied to GRN to generate the state graph and hybrid model as HyTech input.

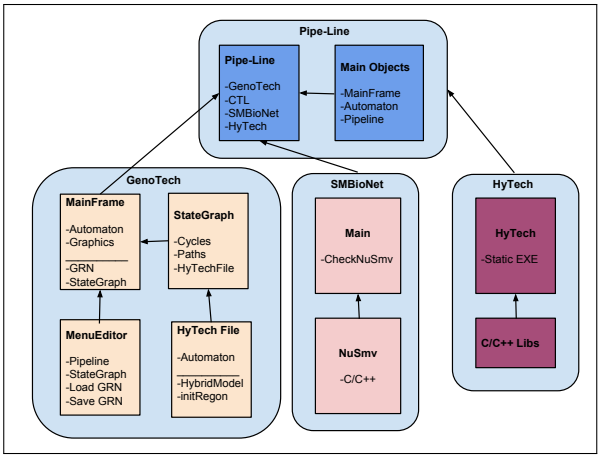

Figure 2 ERD. Entity relationship diagram shows the interaction between tools and their classes used.

The GenoTech models are by default stored as *XML* objects. We used Java Document Object Model (DOM) to parse and extract requred information to generate its SMBioNet model.The CTL formula is provided by the user which is appended to SMBioNet input model using Java string library.
The output of SMBioNet contains these set of logical parameters that satisfies the given CTL formula. This output is stored as a text file. We developed a parser that reads output produced by SMBioNet, and for eache parameter, it is possible to visualize its state graph along with important biological properties such as cycles, deadlock and importanct tragectories.
We also develope a parser to parse all states to hybrid model, morover, we have implemented the technique to parse custome hybrid model in which user have options to select whether to generate hybrid model of specific cycle or complete state graph. This hybrid model is saved as text file which is available to user for further modifications. HyTech is used to verify the hybrid model and the output is shown on the same GUI fo GenoTech.
Figure 3 shows the important features and capabilities of GenNet. Single GUI layout for GENOTECH, SMBioNet and HyTech provides very easy and fast modeling and analysis of biological regulatory networks (GRNs).GRN loaded or created by user parsed to SMBioNet input format and CTL formula editor is used to specify CTL logic which is further appended to SMBioNet iput file. Qualitative modeling and parameter estimation is performed using SMBioNet and selected models against specified CTL are shown as a list of parameter sets to user. User can select specific set of parameters which are directly applied to GRN model and the state graph is generated. User can view the Cycles, Deadlocks and nieghber states. Hybrid model can be generated from state graph, user have options to generate either hybrid model of complete state graph or a specific cycle. Also, user is facilitated to edit (can specify init-REG, initial loc etc) the generated hybrid model befor performing hybrid analysis using HyTech. HyTech output is also shown on Pip-Line GUI and user can find time delays, path constraints and inveriant kernal. The input and output files i.e. GRN, SMBioNet i/o files, Hybrid Model and result files are stored on disk so that user can reuse them.

Discussion and Results

Conclusion

Availability and requirements

Project name: GenNet
Project home page: http://genotech.org
Operating system(s): Linux
Programming language: Java

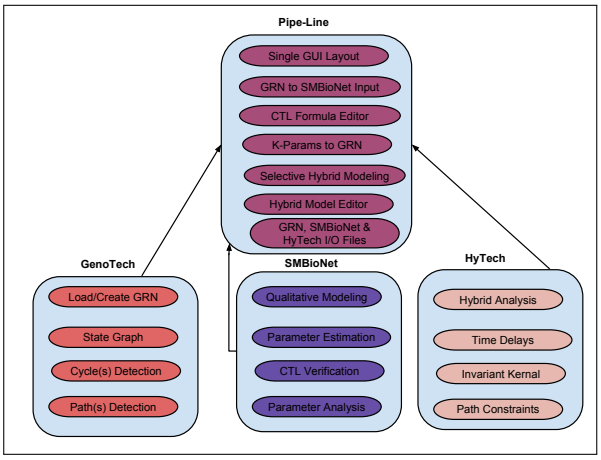

Figure 3 Features. Illustrates the main features of GenNet software tool.

Other requirements: OpenJdk-7-jre
License: GPL
Any restrictions to use by non-academics: For commercial use please contact the corresponding author.

Competing interests
The authors declare that they have no competing interests.

Author's contributions
Gilani developed, designed, performed testing and analyses using different case studies. Ahmad provided advice and commented on the manuscript; Gilani also wrote the paper. All authors read and approved the final manuscript.

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