LA Grid Summit 2011
November 3rd & 4th 2011
Florida Atlantic University

Partnership for International Research and Education
A Global Living Laboratory for Cyberinfrastructure Application Enablement
Model-checking for Gene Regulatory Networks
Student: Marie Lluberes, PhD student, University of Puerto Rico at Mayagüez (UPRM)
Research Advisor: Jaime Seguel, PhD, UPRM
PIRE International Partner Advisor: David Sherman, PhD, INRIA Bordeaux, France

National Science Foundation

I. Research Overview and Outcome

ABSTRACT

The main purpose of this research is to develop an algorithm for the automated study of the dynamics of gene networks modeled as probabilistic Boolean networks (PBN) through the use of model-checking techniques. MAGNOME team at INRIA, Bordeaux, has developed a tool for simulation of biological models that allows a hierarchical and hybrid systems. This tool is known as BioRica. BioRica is easy to use and accurate. AltaRica, in turn, is the formalism used in BioRica for model-checking systems. As BioRica, AltaRica is easy to use and accurate, but its components don't provide for probabilistic transitions. This research explored to what extent AltaRica could serve as an intermediate step for the model checking of big systems whose transitions are better described in probabilistic terms.

PROBABILISTIC BOOLEAN NETWORKS (PBN)

A PBN is a $G(V, F)$ where $F = (F_1, ..., F_n)$, and each one of the sets $F_i = \{f_1^{(i)}, ..., f_{l(i)}^{(i)}\}$ is a set of Boolean functions representing the "top" predictors for that target gene. At each point in time or step of the network, the function $f_j^{(i)}$ is chosen with probability $c_j^{(i)}$ to predict gene x_i.

$$f_1^{(1)}: x_1(t+1) = \bar{x}_2(t) \qquad c_1^{(1)} = 1$$
$$f_1^{(2)}: x_2(t+1) = \bar{x}_1(t) \qquad c_1^{(2)} = 0.3$$
$$f_2^{(2)}: x_2(t+1) = x_1(t) \wedge x_3(t) \qquad c_2^{(2)} = 0.7$$
$$f_1^{(3)}: x_3(t+1) = x_1(t) \qquad c_1^{(3)} = 0.6$$
$$f_2^{(3)}: x_3(t+1) = \bar{x}_1(t) \wedge x_2(t) \qquad c_2^{(3)} = 0.4$$

PBN NETWORK WITH THREE NODES AND PREDICTORS FUNCTIONS

PBN STATE TRANSITION DIAGRAM

PBN of 3 genes

BioRica

BioRica is a platform to describe and simulate multi-models systems in biology. It addresses the need to compose existing models hierarchically and to simulate them efficiently.[3]

Multi-models systems are represented by a hierarchy of nodes.

IMPLEMENTING PBNs ON BioRica

- Each variable constitutes a *subnode* .
- The variable under consideration is a *state* variable and the variables on the predictor functions are *flow* variables.
- Consistency of variables among subnodes is granted by the use of *assertions*.
- Each predictor function is defined as a transition with an associated *event*. Here, the rule describing the transition (Boolean function) is given.
- The selection of a transition is made by giving a weight to each *event* and randomly choosing one of them with the "*choice*" external directive.
- All transitions are synchronized by setting the same time increase on the *events* with the "*law*" *external directive*.

```
node GeneX2
        state    x2:[0,1];

        flow     X1, X3:[0,1]:in
                 X2:[0,1]:out;

        event    ev1, ev2;

        trans    true|-ev1 -> x2 := not X1;
                 true|-ev1 -> x2 := X1 and X3;

        extern   choice<ev1>: 3;
                 choice<ev2>: 7;
                 law<ev1>:1;
                 law<ev2>:1;

        assert   X2 = x2;

        init     x2 := 0;
edon
```

Code for one node of PBN

RESULTS

Output of PBN simulation

Limitations:
- The tool doesn't provide for passing parameters as input.
- The "choice" directive works by adding al the parameters on all the directives and select based on the proportion that each rule represents of the addition. Different rules or set of rules corresponding to different variables can't be declared together under the same external directive, as it wouldn't represent the variable's cumulative distribution function.
- Neither formulas nor variables can be passed as parameters to compute probabilities or set synchronization steps. Only integers are accepted as parameters.

AltaRica: A MODEL-CHECKER FOR PBNs?

- AltaRica is a formalism designed for describing complex systems of interacting components.[4]
- BioRica is an adaptation for biological systems of AltaRica.
- ARC is an AltaRica toolbox for model-checking of systems described with AltaRica.

AltaRica graphical simulator

- In spite its straightforward use and effectiveness, AltaRica model checker cannot be used on PBN. The reason is that it doesn't provide for probabilistic transitions to be included as part of the system.

CONCLUSIONS

- BioRica is an excellent tool for simulation of small PBNs. Big PBNs would require a lot of coding. Its simplicity of use and accuracy makes it valuable.

- Although AltaRica can't be used on PBN as a model-checker, it can be used as a reduction tool. AltaRica main use will be to determine unreachable states and isolated states and use this result as a new problem to check with its respective probabilities.

FUTURE WORK

- Streamline the use of AltaRica as a reduction tool
- Include probabilistic directives on BioRica

REFERENCES

1. Shmulevich, I., Dougherty, E.R. and Zhang, W. 2002. From Boolean to Probabilistic Boolean Networks as Models of Genetic Regulatory Networks. IEEE. 2002; 90(10).
2. Shmulevich, I., Dougherty, E.R., Kim, S. and Zhang, W. 2002. Probabilistic Boolean Networks: a rule-based uncertainty model for gene regulatory networks. Bioinformatics (Oxford, England). 2002; 18(2):261-74
3. H. Soueidan, M. Nikolski, and D.J. Sherman. BioRica: A multi model description and simulation system. In Proceedings of Foundations of Systems Biology in Engineering (FOSBE), Stuttgart, Germany, September 2007.
4. A. Arnold, A. Griffault, G. Point and A. Rauzy. The AltaRica formalism for describing concurrent systems. Fundamenta Informaticae Vol. 40, issue 2-3, IOS Press, 2000.

II. International Experience

Bordeaux
- Declared *World Heritage* by UNESCO. Breathtaking architecture.
- Rue Sainte-Catherine is the longest pedestrian street in Europe. Excellent place to walk, eat and shop.

INRIA
- Commitment to build and spread scientific knowledge.
- In spite all the serious hard work, there is always time for harmonious sharing among coworkers.

MAGNOME
- Outstanding collaborative spirit.
- Great leadership and guidance.
- Best team of all INRIA!

PIRE
- Provided the opportunity of working on an environment highly enriched by the diversity on the background and nationality of employees and students. Working at INRIA may had been hard to get otherwise.
- The impressive breath of research topics, and the differences on approaching them, made step higher on my academic life.
- Met people which have become additional and significant nodes on my professional network, and with whom I still work.
- Broadened my cultural horizons, which in turn broadens my capacity of approaching and focusing on problems.

III. Acknowledgement