

Constraint-driven optimization approach to build a Petri Net defence response model in plants

Dragana Miljkovic^{1*}, Matjaž Depolli³, Marko Petek², Tjaša Stare², Marina Dermastia², Kristina Gruden², Igor Mozetič¹, Nada Lavrač¹

¹ Department of Knowledge Technologies, Jozef Stefan Institute, Ljubljana, Slovenia

² Department of Biotechnology and Systems Biology, National Institute of Biology, Ljubljana, Slovenia

³ Department of Communication Systems, Jozef Stefan Institute, Ljubljana, Slovenia

[*Dragana.Miljkovic@ijs.si](mailto:Dragana.Miljkovic@ijs.si)

Even though there is a huge interest in the biological community, the global defence response model in plants for simulation purposes has not been developed so far. One of the reasons is the mechanism complexity. Moreover, in this particular case, there is only one publicly available experimental dataset with time series longer than two time points per gene expression, which makes the model construction difficult.

For these reasons, having in mind that there is huge domain knowledge available, the only feasible approach to construct the model turned out to be manual development by biology experts. After thorough search for appropriate modelling formalism, we have selected Hybrid Functional Petri Net (HFPN) [1] since it combines the intuitive graphical representation and the Ordinary Differential Equations calculations.

Basically, the manually developed HFPN model contains 46 biological reactions, where each differential equation describes one reaction that contains one speed rate parameter. Moreover, there are 10 inhibition threshold parameters to estimate. The output of the model is 61 time series data with 1000 time points that represent dynamical behaviour of biological molecules when the virus attacks the plant. Having such a complex model with 61 differential equations that represent each biological molecule and 56 unknown parameters in total, the manual parameter estimation to satisfy the biological expectations was unattainable. Moreover, the set of solutions is infinite.

To overcome this problem, we have to compute the evolution of this system with different values of parameters. This enables us to locate the values of parameters that violate the minimal number of constraints. The constraints are provided by the experts and represent unary and binary biological molecules relations. More specifically, the constraints are limited only to the output, i.e. time series of 61 biological molecules. If the simulation results do not match expert expectations, the model and the constraint definitions are revised and the optimization parameter search is repeated.

Finally, the system yields both simulation results and optimized model parameters, which provide an insight into the biological system.

Our constraint-driven optimization approach allows for an efficient exploration of the dynamic behaviour of the biological models and also increases their reliability.

Acknowledgments

This work has been supported by the European Commission under the 7th Framework Programme FP7-ICT-2007-C FET-Open, contract no. BISON-211898, AD Futura scholarship and the Slovenian Research Agency grants P2-0103 and J4-2228.

[1] Matsuno H, Doi A, Drath R, Miyano S. *Genomic Object Net: Hybrid Petri net for describing biological systems*. Currents in Computational Molecular Biology. 2001; 233-4.