

Quantitative model refinement with rule-based models, Petri net models, PRISM GCL models

Sepinoud Azimi¹, Diana-Elena Gratie¹, Bogdan Iancu¹ and Ion Petre¹

Short Abstract — Modeling biological phenomena resumes to building an abstract model that fits the available experimental data. The abstractization can be subsequently refined so as to include more details, while preserving the numerical fit, process called quantitative model refinement. Here, we consider a quantitative refinement of the heat shock response regulatory network model introduced in [5], using three frameworks: rule-based modeling, Petri nets and probabilistic model checking, and discuss the particularities of each platform.

Keywords — Quantitative model refinement, heat shock response, regulatory network, rule-based modeling, Petri nets, probabilistic model checking.

I. INTRODUCTION AND BIOLOGICAL BACKGROUND

QUANTITATIVE model refinement is the process of iteratively adding details to a reaction-based model, in such a way that the quantitative fit of the model is preserved. The method has been discussed in [1,2] for rule-based models, and in [3,4] for ODE-based models. We consider here three methodologies for refining the heat shock response model proposed in [5].

The cellular heat shock response is a highly-conserved defense mechanism among eukaryotes, meant to prevent cell apoptosis. Proteins misfold at high temperatures, and bind together forming aggregates that induce cell death. The gene regulatory network in charge with the heat shock response includes special chaperones, the heat shock proteins (HSPs), whose role is to assist misfolded proteins to refold correctly. The transcription of the HSP-encoding gene is promoted by heat shock factors (HSFs), which also play an important role in downregulating the response, see[5].

II. METHODS

Starting with the basic heat shock response model in [5], we considered as refinement the acetylation of HSFs. This small change propagates to all compounds containing HSFs, and all reactions they take part in, as in [3].

A. Rule-based modeling with Bionetgen and RuleBender

Within the rule-based modeling framework, the species in a model are described by their components, and the states of

each component. This makes the representation very compact and well-suited for data refinement. Implementing the refinement of our model resumed to adding an additional component for one of the species and adjusting some kinetic constants.

B. Modeling with Petri nets in Snoopy

Using simple Petri nets we could not restrict the explosion of the refined model. We implemented the refinement using colored Petri nets, an extension that allows data types. We identified multiple ways of modeling the refinement, and implemented two of them: one kept the representation of the basic model intact (plus the colors), and the other one used the minimum number of colors possible. A more compact representation was possible in both cases.

C. Modeling with PRISM guarded command language

We implemented the basic model as a CTMC within one PRISM module. Refining the model required to replace each guard that involved refined species with several guards, considering all possible reactions. This led to an increase in the model size similar to the ODE-based approach in [3]. We performed probabilistic model checking and found the implementation to be consistent with the behavior in [3].

III. CONCLUSIONS

Refining a model can be done within all three considered frameworks. Rule-based modeling is very suitable for a compact representation of the refined model. Colored Petri nets offer multiple modeling choices. Model checking can only be done on a fully-expanded model (i.e. no compact representation). We offer a detailed discussion in [6].

REFERENCES

- [1] Danos V, et al. (2009) Rule-based modeling and model perturbation. In *Transactions on Computational Systems Biology XI* Springer Berlin Heidelberg, pp. 116-137.
- [2] Murphy E, et al. (2010) Rule based modeling and model refinement. In *Elements of Computational Systems Biology* (Lodhi HM, Muggleton SH) John Wiley & Sons, Inc., Hoboken, NJ, pp. 83-114.
- [3] Iancu B, et al. (in press) Quantitative refinement of reaction models. *Int J Unconv Comput*.
- [4] Mizera A, Czeizler E, Petre I (2011) Self-assembly models of variable resolution. In *Transactions on Computational Systems Biology XIV* Springer, pp. 181-203.
- [5] Petre I, et al. (2011) A simple mass-action model for the eukaryotic heat shock response and its mathematical validation. *Nat Comp* **10**, 595-612.
- [6] Azimi S, et al. "Three approaches to quantitative model refinement with applications to the heat shock response", in preparation.

¹Computational Biomodeling Laboratory, Turku Centre for Computer Science, and Department of Information Technologies, Åbo Akademi University, 20520 Turku, Finland. E-mail: sazimi@abo.fi (Sepinoud Azimi), dgratie@abo.fi (Diana-Elena Gratie), biancu@abo.fi (Bogdan Iancu), ipetre@abo.fi (Ion Petre)