Automation of Model Design and Analysis for Big Mechanisms

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Short Abstract — **In this paper, we describe a framework for automated development of executable models using information extracted from literature. The framework also includes model analysis and correction methods. The final objective is to have a representation for models of complicated mechanisms that allow for easy model exchange and improvement, facilitating the discovery of interventions (e.g., treatments or drugs in case of cell mechanisms).**

Keywords — **automation, modeling, inference, interaction graphs, simulation, model checking, cell signaling pathways**

I. Purpose

Understanding complicated mechanisms usually requires collecting information from various sources such as published literature and integrating it all within a model. A large number of models in existing literature that were developed over the years for a particular biological system, for example, are rendered useless when they cannot be updated, validated or corroborated with each other. By designing a unified model knowledge database that can be exchanged, tested and improved, we can advance and accelerate knowledge exchange. Our aim is to automate reading and model building procedures, followed by model checking and improvement. With the assistance of experts in natural language processing, causal inference and cancer immunology, we hope to achieve the goal of developing a system that can learn, execute and manage models for large, complicated mechanisms, enabling informative simulations.

II. Proposed framework

Here we briefly discuss our framework for automation. Information extracted from literature using natural language processing algorithms is entered into a standardized format that can be further processed by causal inference algorithms. This yields an interaction graph with nodes and edges for the connections in the model. Models from databases such as [1], [2] and Biological Expression Language (BEL) can also be translated to generate the interaction graph.

This is followed by inference of an executable model that involves automated inference of element update functions by combining qualitative interaction graphs and any other available quantitative information. We perform simulations of such models using deterministic and stochastic approaches [3], [4]. The simulation results are further used for sensitivity and controllability analysis of the modeled system. Probabilistic and statistical model checking is performed using tools described in [5]. Perturbation analysis considers the effects of altered causal relationships in steady-state and transient behavior [6], [7]. We are currently developing automated hypotheses extraction that follows model analysis. This step will lead to refinements to the model, guide new literature search and help design new wet lab experiments to validate generated hypotheses.

III. Conclusion

The focus of our project is development of a completely automated model design and analysis procedure. We are applying this approach on models of cell signaling and metabolism networks, as well as to cell-cell communication scenarios in cancer.

References

[1] Demir E, Cary MP, Paley S, et al. "BioPAX – A community standard for pathway data sharing." *Nature biotechnology*. 2010;28(9):935-942. doi:10.1038/nbt.1666.

[2] Steven Eker, Merrill Knapp, Keith Laderoute, Patrick Lincoln, Carolyn Talcott, "Pathway Logic: Executable Models of Biological Networks", Electronic Notes in Theoretical Computer Science, Volume 71, April 2004, Pages 144-161, ISSN 1571-0661, http://dx.doi.org/10.1016/S1571-0661(05)82533-2

[3] N. Miskov-Zivanov, D. Marculescu, and J. R. Faeder, "Dynamic behavior of cell signaling networks: model design and analysis automation." in Proc. of Design Automation Conference (DAC), Article 8, 6 p., June 2013

[4] N. Miskov-Zivanov, P. Wei, C.S.C. Loh, "THiMED: Time in Hierarchical Model Extraction and Design," in Proc. Of Computational Methods in Systems Biology (CMSB), pp. 260-263, November 2014.

[5] N. Miskov-Zivanov, P. Zuliani, E. M. Clarke, and J. R.Faeder, "Studies of biological networks with statistical model checking: application to immune system cells," in Proc. Of ACM Conference on Bioinformatics, Computational Biology and Biomedicine (ACM-BCB), September 2013, pp. 728.

[6] A. Garg, K. Mohanram, A. Di Cara, G. De Micheli, and I.Xenarios, "Modeling stochasticity and robustness in gene regulatory networks," Bioinformatics, vol. 25, pp. i101-i109, 2009.Tavel, P. 2007. *Modeling and Simulation Design*. AK Peters Ltd., Natick, MA.

[7] N. Miskov-Zivanov, M. S. Turner, L. P. Kane, P. A. Morel, and J. R. Faeder, "The duration of T cell stimulation is a critical determinant of cell fate and plasticity," in Science Signaling, 6, ra97, November 2013.

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