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Modelling Systems Biology Wide and Deep*

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Abstract. Biological systems involve a wide amount of different molecular interactions. Each interaction can in turn present a deep level of mechanistic details. Most modelling methods can encompass only one of those two dimensions, that is the width or depth of biological systems. Rule-based modelling is a powerful method in that regard as it can model large systems with mechanistically detailed interactions. The advantage of including mechanistic details is that they allow a clear tracking of causal chains of events between biomolecules. This translates into a precise pinpointing of upstream regulators and a better understanding of complex biological systems.

Keywords: Systems biology · Rule-based modelling · Causality.

1 Introduction

Interaction networks [1] are one of the most popular objects of systems biology. They allow the representation of a very large amount of molecular interactions on a single graph. That is, interaction networks can encompass the width of biological systems. However, many functional relationships between biomolecules are more complicated than what can be represented in simple graphs [2]. Such networks can hence not depict in detail the depth of molecular interactions.

A consequence of this lack of detail is that wrong interpretations can occur when analyzing interaction networks. For example, consider the analysis of upstream regulators of a chosen molecule. In intricate graphs like signalling networks, it is not uncommon to have every output downstream of every input [3]. In these conditions, ignoring mechanistic and quantitative details usually leads to the perplexing result that the chosen molecule is regulated by all the other molecules in the network with indistinguishable intensities.

To include more details in the description of molecular interactions, reaction-based models like Petri nets [4] can be used. Such methods properly address the depth of molecular interaction mechanisms. However, this comes at the cost of

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a combinatorial explosion as the system to model grows. Very large models of biological organisms can hence not be built in a reaction-based setting.

Most organisms of interest to systems biology are large in terms of number and complexity of their constituent interactions. Methods are hence needed to deal with both the width and depth of biological systems simultaneously. Rule-based modelling [5, 6] can achieve such feat.

In this work, we present a large rule-based model example. Then, we show how causality analysis can be used to extract pathways to observables of interest. Unlike upstream analysis in interaction networks, those pathways leverage mechanistic details to provide a real causal explanation of molecular events.

2 Rule-Based Model

Rules distinguish themselves from reactions by focusing only on the parts of molecules that change during a transition, rather than fully defining the species involved. It allows the representation of mechanistic details while avoiding the vast majority of combinatorial issues. The Kappa [8] rule-based modelling language was used in this work.

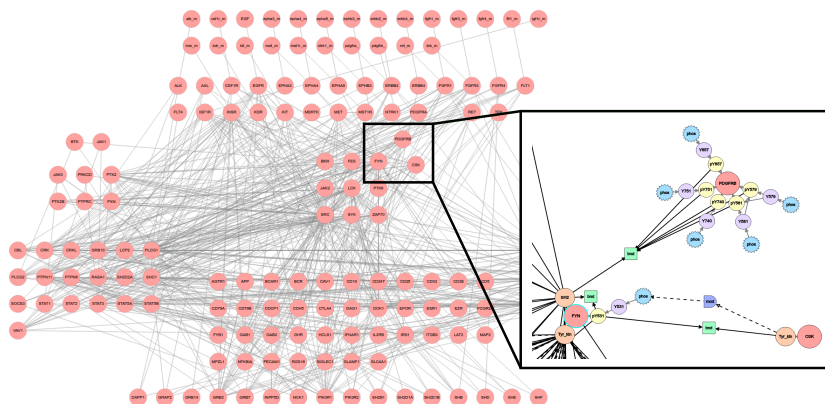


Fig. 1. Graph representation of the pYnet model built with Kami [7]. On the left is a contact map of the model, which bears resemblance to interaction networks. The inset on the right zooms in and highlights the structural details of selected proteins.

Fig. 1 shows a graph representation of a rule-based model which goes both wide and deep in its description of a biological system. Dubbed the pYnet, this model depicts tyrosine phosphorylation in human cell signalling. It contains 175 different proteins and about 1800 interactions taken from the literature and databases. For each interaction, the precise protein residues and domains involved are specified.

3 Causality Analysis

Causality analysis can be used to extract the upstream events which cause any observable of interest from a rule-based model, like the activation of a chosen protein. Since this analysis takes mechanistic details into account, it provides a clearer and more reliable picture than upstream analysis in interaction networks.

The first step of causality analysis is to extract stories to the observable of interest. A story consists in a graph that represents all the necessary events that lead to a single instance of the observable of interest during an execution of the model. Stories are extracted using either operational research techniques [9] or heuristic approaches [10].

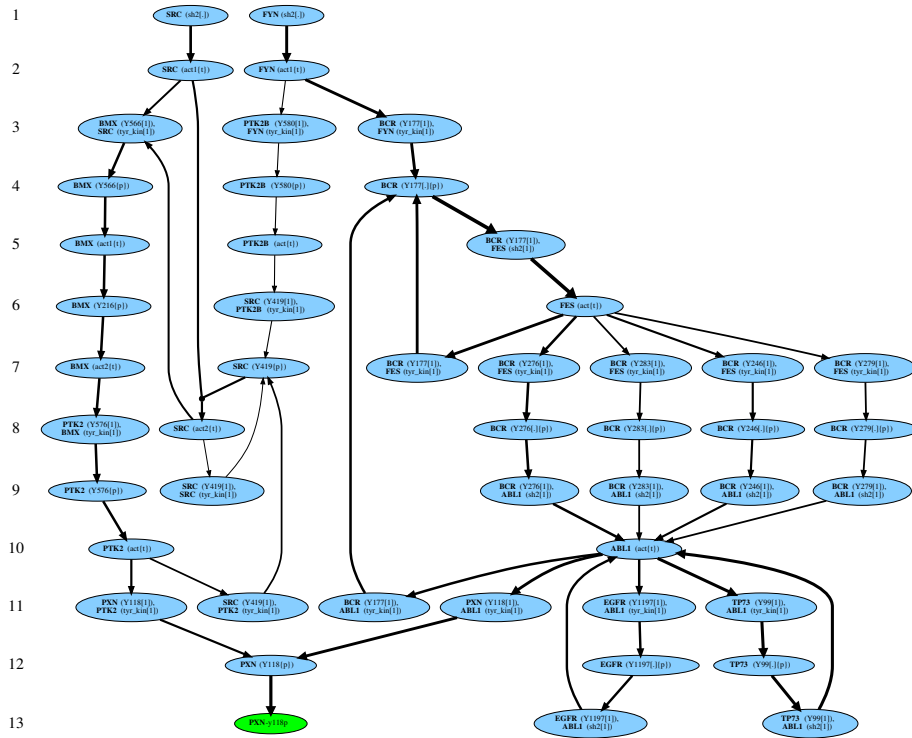


Fig. 2. Example of a pathway obtained from causality analysis of the pYnet model. Node labels contain protein names in bold. Sites modified at each step are written following the Kappa syntax [8] in normal font. The width of edges represents their quantitative contribution.

Then, all the stories to the observable of interest are folded into a single quotient graph. Proper folding requires finding the correct trade-off in the amount of

context to consider from story events [11]. Too much contextualization leads to unnecessarily large pathways while too few loses information. The contextualization and folding steps are carried by the Python package KappaPathways [12]. The resulting graph shares a lot of similarities with biological pathways.

Fig. 2 presents an example of a pathway obtained from causality analysis on the pYnet model. It allows a clear understanding of the steps which lead to the phosphorylation of tyrosine 118 from protein Paxillin (PXN). In comparison, going upstream from the node representing PXN in an interaction network would not have allowed a distinction between the structural features involved at each backward step. It would hence have most likely resulted in a much larger graph.

4 Conclusion

Rule-based modelling allows the construction of wide and deep models of biological systems. Causality analysis of those models provides detailed explanations for the occurrence of molecular events. Combining rule-based modelling with causality analysis could be the best method to truly understand complex biological systems.

References

1. Barabási, A.-L. et al.: Network medicine: a network-based approach to human disease. *Nature Reviews Genetics* **12**, 56–68 (2011)
2. Klamt, S. et al.: Hypergraphs and Cellular Networks. *PLOS Computational Biology* **5**(5), 1–6 (2009)
3. Rowland, M. et al.: Crosstalk and the evolvability of intracellular communication. *Nature Communications* **8**, 16009 (2017)
4. Heiner, M. et al.: Petri Nets for Systems and Synthetic Biology. In: *Formal Methods for Computational Systems Biology*, pp. 215–264. Springer (2008)
5. Danos, V. et al.: Rule-Based Modelling of Cellular Signalling. In: *CONCUR*, pp. 17–41. Springer (2007)
6. Blinov, M.L. et al.: Graph Theory for Rule-Based Modeling of Biochemical Networks. In: *Transactions on Computational Systems Biology VII*, pp. 89–106. Springer (2006)
7. Harmer, R. et al.: Bio-curation for cellular signalling: the KAMI project. *IEEE/ACM transactions on computational biology and bioinformatics* **16**, 1562–1573 (2019)
8. Boutillier, P. et al.: The Kappa platform for rule-based modeling. *Bioinformatics* **34**(13), i583–i592 (2018)
9. Danos, V. et al.: Graphs, Rewriting and Pathway Reconstruction for Rule-Based Models. In: *FSTTCS*, pp. 276–288 (2012)
10. Laurent, J.: KaFlow, <https://github.com/jonathan-laurent/KaFlow>. Last accessed 10 Jun 2021
11. Légaré, S. et al.: Distinguishing Context Dependent Events in Quotients of Causal Stories. Accepted In: *Jobim proceedings* (2021)
12. Légaré, S.: KappaPathways, <https://github.com/slegare2/KappaPathways>. Last accessed 10 Jun 2021