Logic modeling in quantitative systems pharmacology

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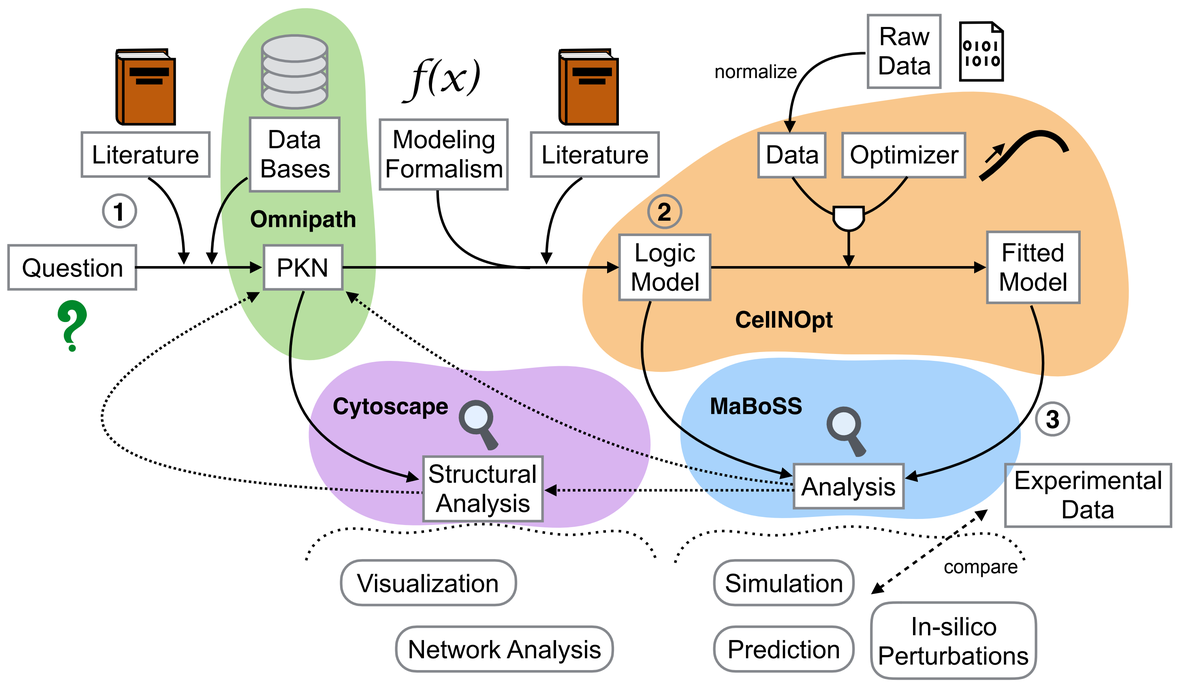
Motivation

The structure and functioning of signaling networks is complex, and they are differently deregulated in different contexts in non-trivial ways. To ensure efficiency of the drug treatments, a good knowledge of these complex interactions and how patient mutations affect the cellular fate is necessary. Among modeling techniques, logic modeling has proven to be very versatile and able to provide useful biological insights. Here, we show how to build a logic model from literature and experimental data and how to analyze the resulting model to obtain insights of relevance for systems pharmacology, using a prostate cancer example that involves some of the key phosphorylation pathways of this malignancy. We use data describing the phosphorylation response of key proteins in prostate cancer cell lines in response to the addition of several ligands and inhibitors (Lescarbeau & Kaplan 2014).

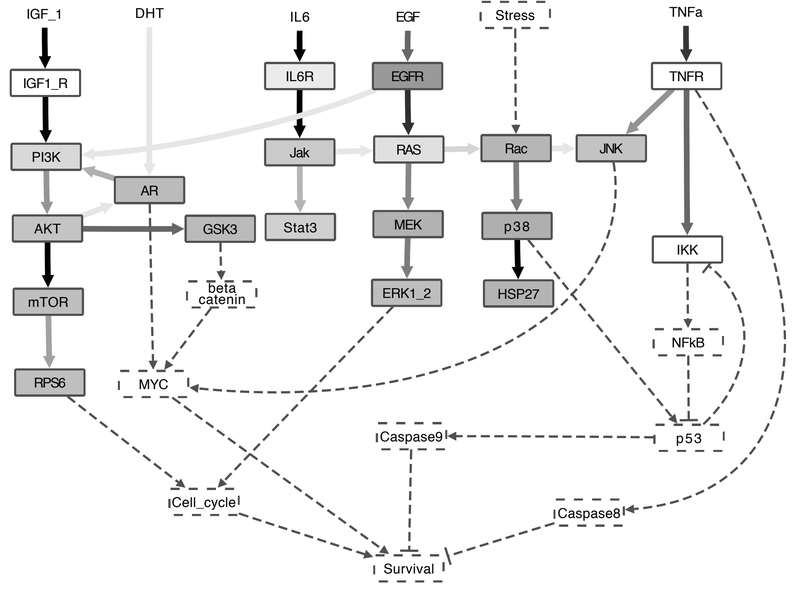
Different steps of the pipeline include:
1. selecting a system and a question of interest and building a first version of the network
2. choosing a modeling formalism and improving the model with data
3. analyzing the model, making predictions and comparing them to experimental data

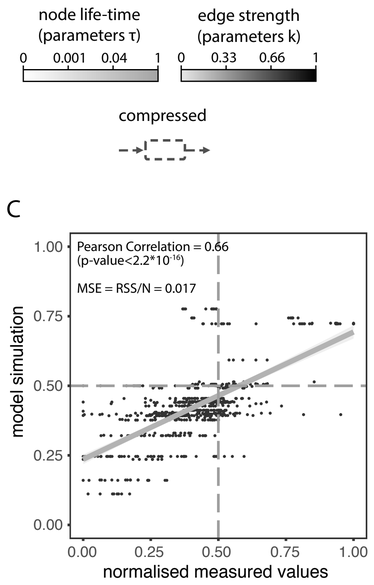
Tools

Our workflow uses the following free tools (but others could also be used):
- Omnipath (Türei et al. 2016) for building the signaling network from literature
- CellNOpt (Terfve et al. 2012) to fit the model to experimental data
- MaBoSS (Stoll et al. 2012) to simulate and predict treatment response
- Cytoscape (Shannon et al. 2003) for visualization

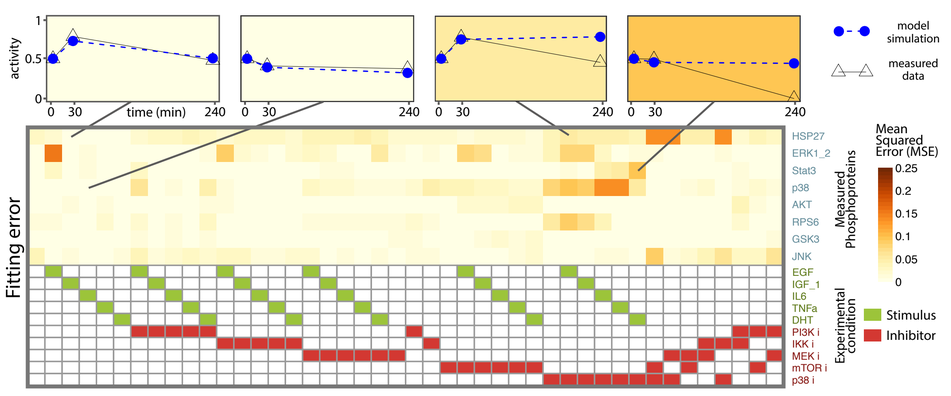


Prior knowledge network (PKN) related to prostate cancer derived from public resources. The network includes components from the apoptotic pathway (p53, Caspase 8, and Caspase 9) and Myc for the cell cycle activation and their regulation of Survival.

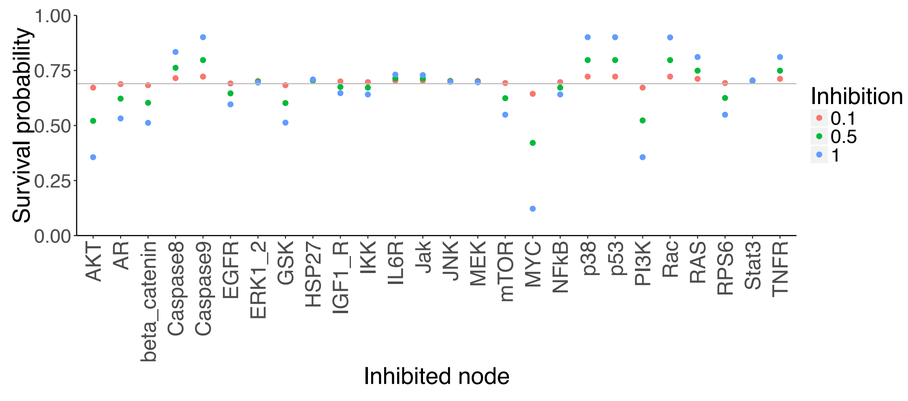


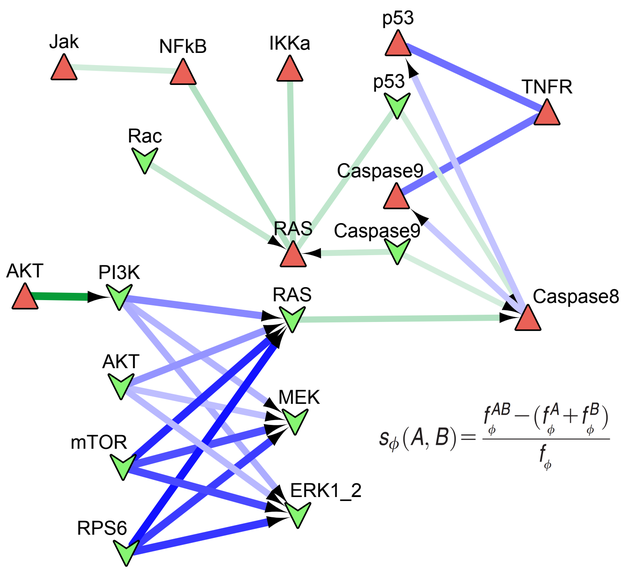


Prior Knowledge Network (PKN) transformed into a logic-based ODE model and fitted to the experimental data.



Stochastic simulations are used to predict prostate cancer cell survival against different node inhibitors. (baseline survival given by the gray line)





Network of synergistic and antagonistic interactions, with *Survival* as quantitative phenotype. Red triangles represent gain of function alterations and green glyphs represent loss of function alterations. Edges between two alterations show that a combined alteration has a drastic decreasing (in blue) or increasing (in green) effect on the Survival probability when compared to single alterations. Non symmetric interactions are represented by an arrow, where the source node is responsible for the predominant effect.

Conclusions

Logic modeling, as implemented in this pipeline, can be a useful approach to understand deregulation of signal transduction in disease and to characterize a drug's mode of action.
Beyond the validation of mechanistic hypotheses, the model can be used to predict the effect of new inhibitions, which can suggest new drug treatments or combinations of drugs.

References

Traynard, P. et al. (2017) CPT Pharmacometrics Syst. Pharmacol. Accepted Author Manuscript.
Türei, D., Korcsmáros, T. & Saez-Rodriguez, J. (2016) Nature methods, 13(12), pp.966– 967.
Lescarbeau, R.M. & Kaplan, D.L. (2014) BMC cancer, 14, p.325.
Terfve, C. et al. (2012) BMC systems biology, 6, p.133.
Stoll, G. et al. (2012) BMC systems biology, 6, p.116.
Shannon, P. et al. (2003) Genome research, 13(11), pp.2498–2504.

PrECISE (Personalized Engine for Cancer Integrative Study and Evaluation) is a European H2020 project focused on prostate cancer, an international collaboration that aims to translate into clinical advances many of the technical and methodological developments achieved during the last years.

Funding

The PrECISE project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 668858.

PrECISE is supported (in part) by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 15.0324-2. The opinions expressed and arguments employed therein do not necessarily reflect the official views of the Swiss Government.