Using the automated building of computational models to understand cardiotoxic drug responses

Robert P. Sheehan[1], Huan Wang[1], Benjamin M. Gyori[1], John A. Bachman[1], and, Peter K. Sorger[1]

Sorafenib, a tyrosine kinase inhibitor used in the treatment of a number of cancers, has been shown to cause cardiotoxic side effects. "Omics" level profiling of cardiomyocytes showed significant changes in glycolysis and amino acid metabolism following treatment, however the mechanistic connection to Sorafenib is still unclear. We hope to better understand the mechanistic dynamics through a novel computational model, using the INDRA (Integrated Network and Dynamical Reasoning Assembler) software to automate the model building process. INDRA allows us to read published literature, extract mechanistic information, and build a rule-based model. With added functionality to improve rule context generation and constrain model scope for small driven models, we built a model that connects known Sorafenib targets to enzymes that participate in glycolysis and amino acid metabolism.

I. Background

TYROSINE kinase inhibitors, including Sorafenib, have been shown to induce of cardiac side effects including heart attack, high blood pressure, QT prolongation, and cardiomyopathy [1]. Using human induced pluripotent stem cells (hiPSC)-derived cardiomyocytes we found that Sorafenib treatment induces metabolic changes, including changes in oxygen consumption, glucose uptake, lactate production, and serine production, as well as causing differential expression of genes and proteins enriched for GO terms related to key metabolic pathways.

To explain how Sorafenib causes these effects, we aim to build a computational model that can connect canonical targets of Sorafenib to metabolic pathways. However, modeling such a broad hypothesis is a difficult task, since mechanistic models are typically less exploratory and building such a far-reaching model would be a slow and error-prone process. To address these issues we are using the INDRA [2] software to automate the process. INDRA allows us to read thousands of published papers, extracting any mechanistic statements. This results in a large corpus of detailed information which can be automatically assembled into many types of models, including an executable rule-based model [3]. However, these models are often so large and highly connected that they are difficult for a human to parse, and computationally difficult or impossible to simulate. Additionally, key context governing when a model rule fires is often missing or incomplete, leading to unexpected and incorrect dynamics. To use these models to answer highly specific questions about a system, we need additional tools to help us reduce and focus our model.

Acknowledgements: This work was funded by DOD|Defense Advanced Research Projects Agency (DARPA). Grant Numbers: W911NF-14-1-0397, W911NF-15-1-0544. FDA BAA-1300119

[1]Laboratory of Systems Pharmacology, Harvard Medical School, Boston, MA. E-mail: robert_sheehan@hms.harvard.edu

II. Results

A. By inferring rule context and identifying meaningful pathways from an assembled set of rules, we can build an accurate and simulatable model with minimal intervention.

To build use-case driven models, we need to improve automated model assembly by improving the context governing when a model rule fires, and by limiting the scope of the model. By enforcing appropriate activating and inhibitory conditions for each model rule, we improve model accuracy and reduce simulation time by reducing the number of possible model species. We are able to infer many of these conditions by assuming directionality in a signaling cascade, and enforcing that events happen in order, initiated downstream of a receptor or specified starting point. This results in a model that is better behaved and quicker to simulate. To improve model scope definition, we leverage graph analysis and path finding tools to identify short paths between elements of interest, such as drug targets and experimental outputs. This allowed us to automate the building of a model that is easier to visualize and simulate.

B. Automated model construction and simulation shows that Sorafenib perturbs regulation of PKM2 through phosphorylation and transcription

We used INDRA to build a model that connects targets of Sorafenib to enzymes that participate in glycolysis. This model, which focuses on events downstream of the FLT3, KDR, and PDGFRA tyrosine kinases, is able to recreate our data, notably showing that Sorafenib treatment leads to an increase in PKM2 activity, causing increased flux through glycolysis and reduced serine synthesis. Model calibration using high dimensional, single-cell immunofluorescence data [4] will allow us to make quantitative predictions on how Sorafenib causes changes in glycolysis that are absent following treatment with less toxic drugs.

III. Conclusion

Automated construction of models allows us to quickly and quantitatively explore new areas of biology. Using new model assembly tools allows the user to reduce a huge amount of mechanistic information mined from the literature to a smaller set of pathways of interest. This results in a model that can be simulated and calibrated to data.

References

[1] Force, T, et al. (2007). *Nat Rev Cancer* **7**(5), 332-44.
[2] Gyori, BM, et al. (2017). *Mol Syst Biol* **13**(11), 954.
[3] Blinov, ML, et al. (2004). *Bioinformatics* **20**(17), 3298-9.
[4] Lin, JR, et al. (2015). *Nat Commun* 6, 8390.