Fine tuning a logical model of cancer cells to predict drug synergies: combining manual curation and automated parameterization

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Therapies composed of combinations of drugs carry great promise for personalized therapy for a variety of diseases. We here demonstrate how automated adjustments of model topology and logic equations both can greatly reduce the workload traditionally associated with logical model optimization. Our methodology allows the exploration of larger model ensembles that all obey a set of observations, while being less restrained for parts of the model where parameterization is not guided by biological data. We benchmark the synergy prediction performance of our logical models in a dataset of 153 targeted drug combinations. We show that well-performing manual models faithfully represent measured biomarker data and that their performance can be outmatched by automated parameterization using a genetic algorithm. Whereas the predictive performance of a curated model is strongly affected by simulated curation errors, data-guided deletion of a small subset of regulatory model edges can significantly improve prediction quality. With correct topology we find evidence of some tolerance to simulated errors in the biomarker calibration data, yet performance decreases with reduced data quality.

References and useful liks….
https://www.biorxiv.org/content/10.1101/2021.06.28.450165v1
https://github.com/druglogics