Instantiation of Patient-Specific Logical Models With Multi-Omics Data Allows Clinical Stratification of Patients

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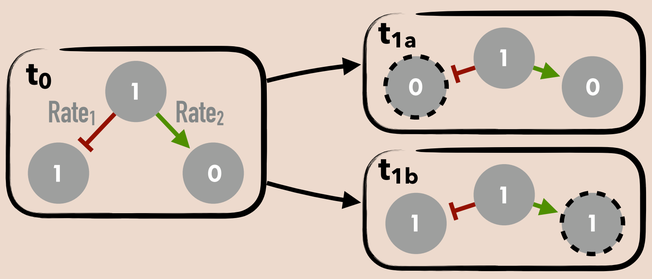
Abstract

Logical models of cancer pathways are typically built by mining the literature and they are usually generic as they apply for large cohorts and do not capture the heterogeneity of patient. We present here a novel framework to **tailor logical models to a patient's tumor**. This methodology enables comparisons between the model simulations and the individual clinical data.

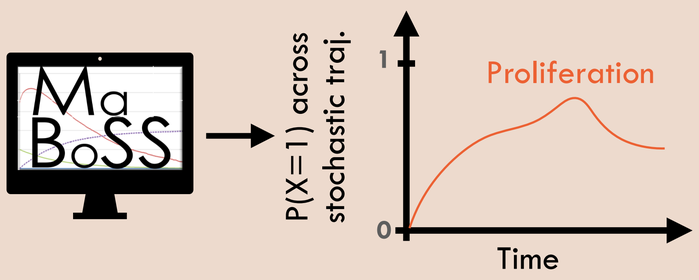
Our approach focuses on integrating mutations, copy number alterations (CNA), and expression data to logical models. These **omics data, after appropriate processing, can be incorporated in the model modifying the activity of the node, the initial conditions or the transition rates**, as defined in MaBoSS, a tool performing stochastic simulations of logical models. As a first proof of concept, omics data from breast-cancer patients is integrated into several logical models to derive **phenotypic outputs that correlate with clinical read-outs such as survival**, with better performances combining both mutations and expression data. All in all, we aim to **combine the mechanistic insights of logical modeling with multi-omics data integration** to provide patient-relevant models to physicians, enabling precision medicine.

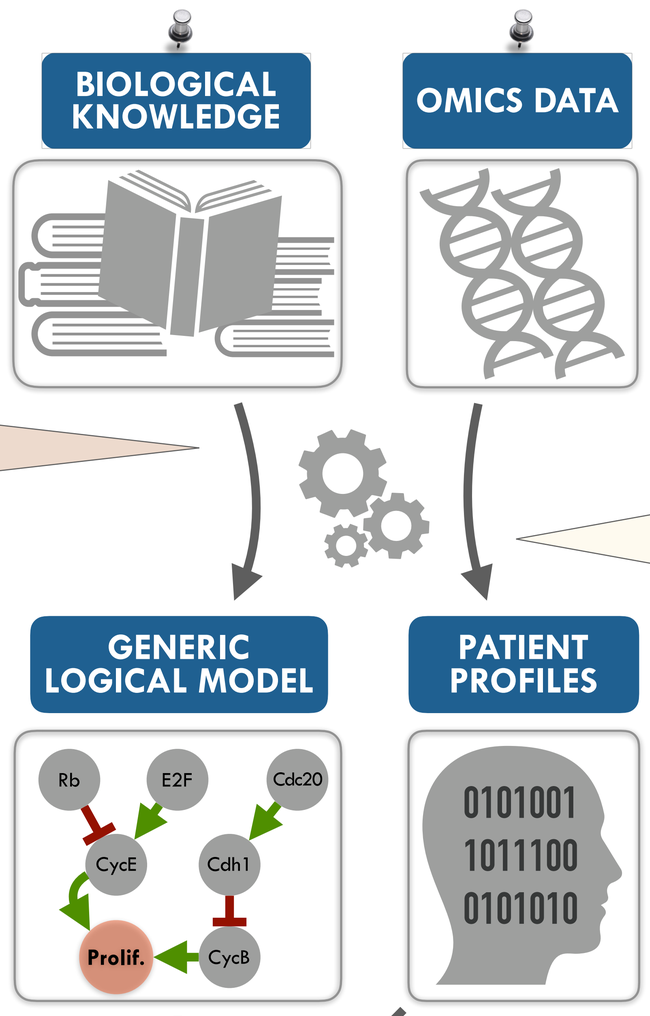
Logical Modelling

- **Principles**: discrete variables as abstractions of activity level. Logical rules as signed interactions. Stochastic updates based on $Rate_{1/2}$

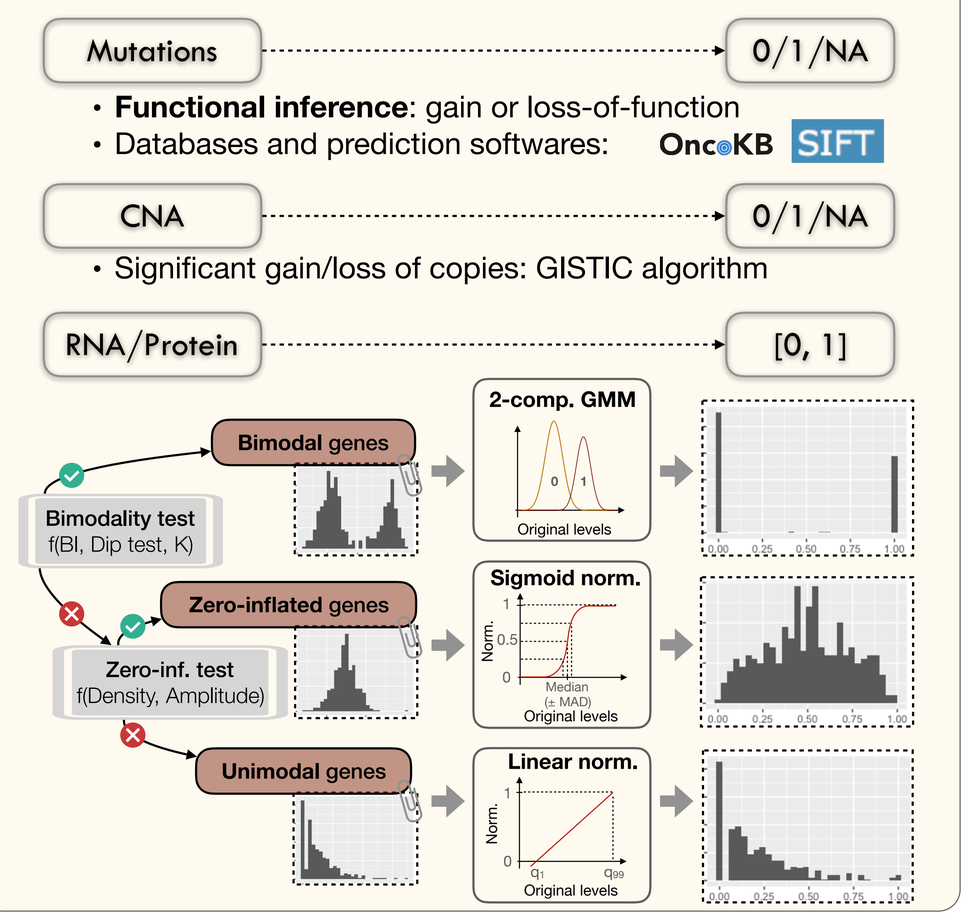


- **Design**: models based on maps, interaction networks and literature
- **Simulation**: time trajectories of output probabilities based on stochastic trajectories[1]

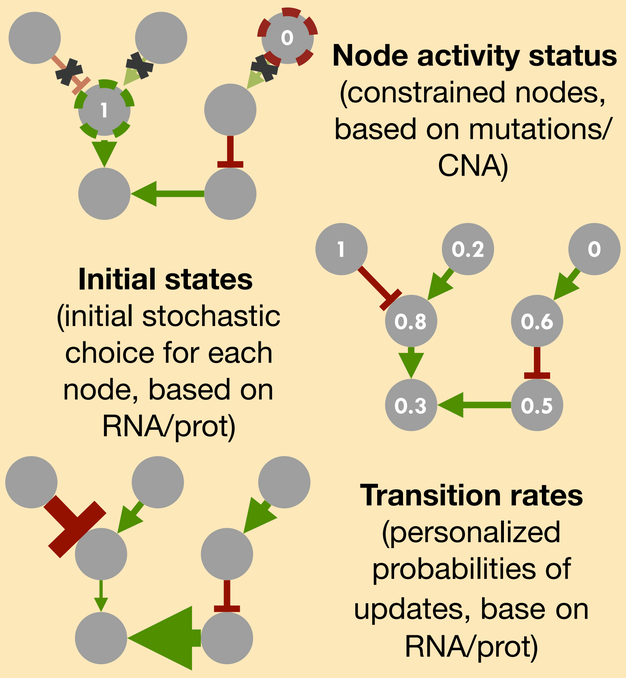


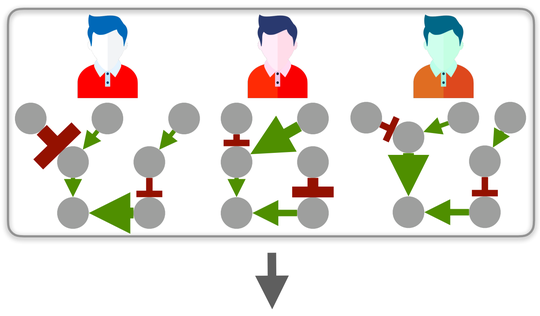


Generation of Patient Profiles



Model Specification





Clinical Analysis

- Different logical models and omics data combinations

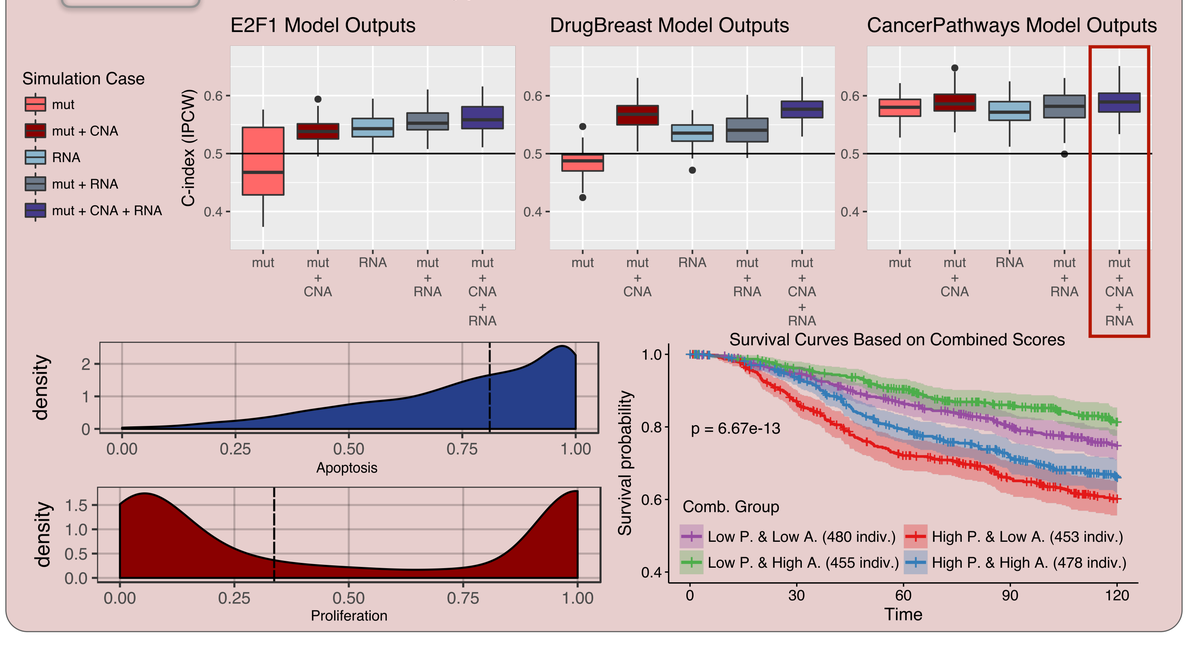
Table 1: Logical models survey

Models	E2F1[2]	DrugBreast[3]	CancerPathways[4]
Number of nodes	35	73	98
Phenotypic outputs	EMT	Prolif. & Apop.	Prolif. & Apop.
Breast-specific	☑	☑	☐

Table 2: METABRIC4 cohort, ~2000 breast-cancer patients

Data types and their use	Mutations	CNA	RNA
Node activity status	☑	☑	☐
Initial states	☐	☐	☑
Transition rates	☐	☐	☑

- Different behaviours depending on the model
- On average, performance improvement with integration of several data types, i.e. mutations/CNA/RNA



Perspectives

- Instantiation of cell-line specific models
- Implement drug effect predictions modelling drug actions on personalized models

References

[1]Stoll et al. Bioinformatics. 2017
[2]Khan et al. Nat. Commun. (2017)
[3]Zanudo et al. Cancer Conv. 2013
[4]Fumia et al, PLoS One. 2017
[5]Curtis et al. Nature. 2012

Contact & Code

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