Patient-specific prostate logical models allow clinical stratification of patients and personalized drug treatment

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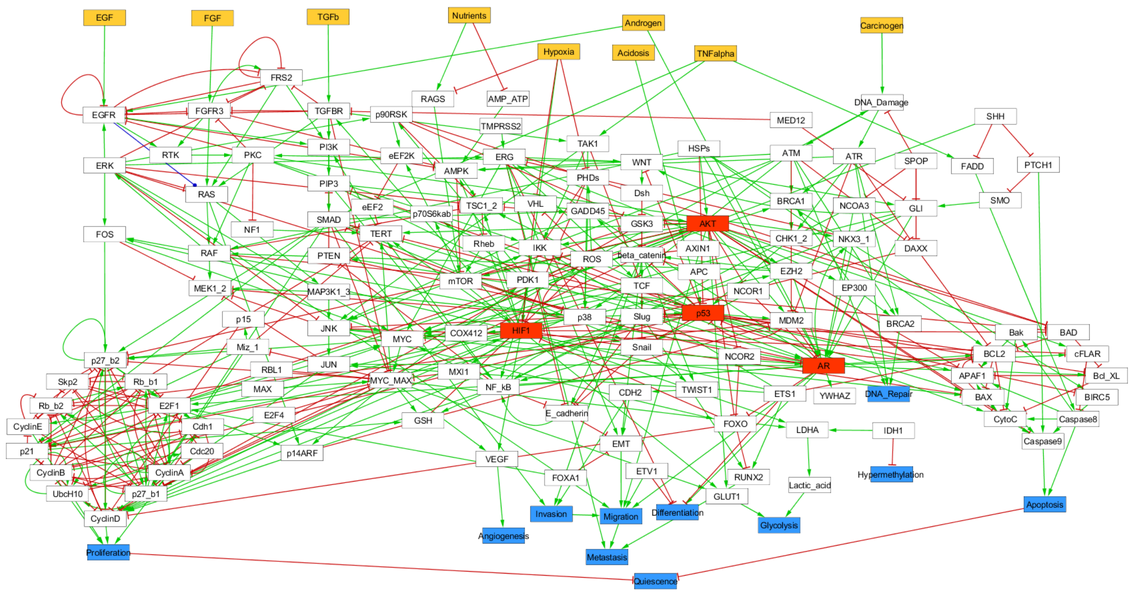
We developed a logical model that considers major pathways responsible for prostate cancer development. This model has been extensively tested *in silico* by studying all single and double mutants and its robustness using our pipeline of tools[1]. Additionally, we tailored our logical model to TCGA prostate cancer patients' and GDSC cell lines' data to capture their diversity of functioning and response to perturbations[2]. Finally, we simulated the effects of different drugs in prostate-specific cell lines models under different growth conditions in order to find proper combinations of drug concentrations in these cell lines.

Present results facilitate the use of logical models in personalized medicine, by allowing the instantiation of patient-specific models, and facilitates the study of patient-specific drug treatments that depend on the specific patient's response.

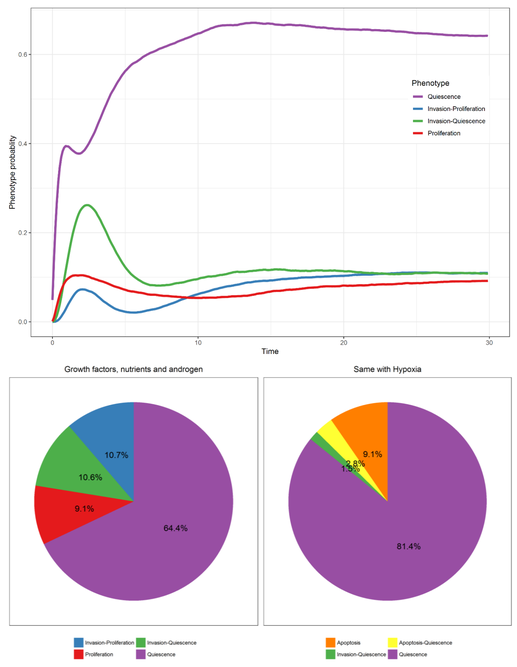
Prostate cancer Boolean model



Information from pathway databases[3] and literature[4] was integrated in a prostate-specific model that accounts for 148 nodes and 498 edges.

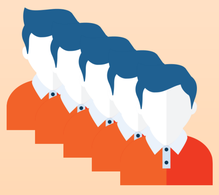
The use of **MaBoSS**[5,6], a tool that uses Monte-Carlo kinetic algorithm to perform **continuous time stochastic simulations on logical models**, allowed for semi-quantitative evaluation of the model's phenotypes and perturbations.

From a set of initial conditions, the solutions can be represented in different forms: a **probability** of network states equivalent to the **asymptotic solutions** of the stochastic simulations, or **time evolution** of the nodes of interest. These probabilities can be used to **compare wild type and mutant models**.



Patient-specific Boolean models

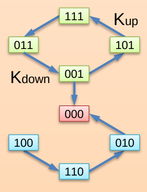
The model provides a support to **incorporate multi-omics patient-specific molecular data**, encoded as different variables of the modelling framework. Molecular data from 333 **TCGA prostate samples** and 1029 **GDSC cell lines** (8 prostate) were incorporated in different variables of the modelling framework using our methodology[2].



Data from TCGA and GDSC

Data:

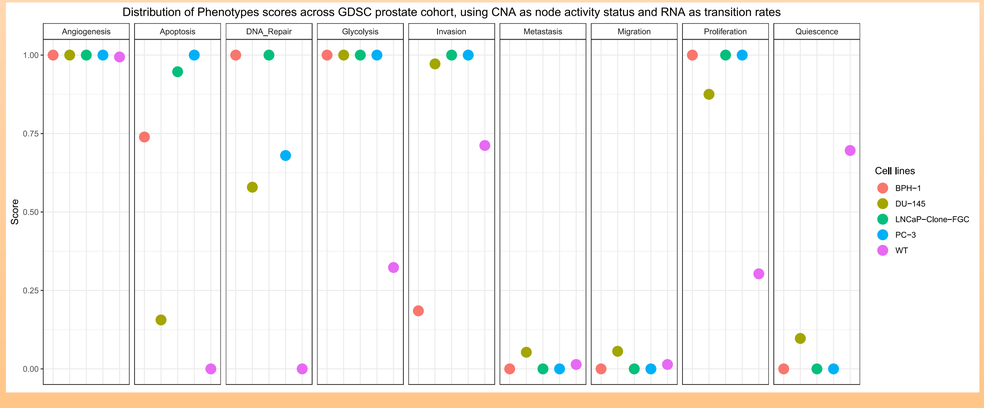
- Mutations
- Copy Number Variations
- RNA expression
- Protein data



state transition graph

Modelling framework:

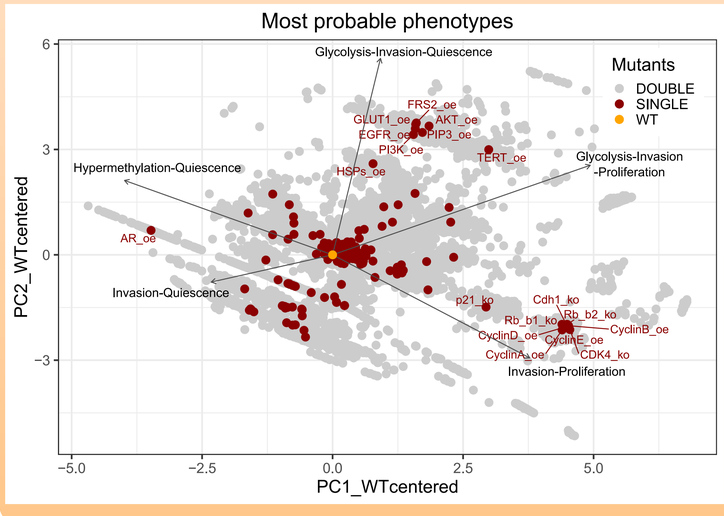
- Node activity status = mutants
- Initial conditions = growth media conditions or experimental setup
- Transitions rates = gene's ability to activate or deactivate

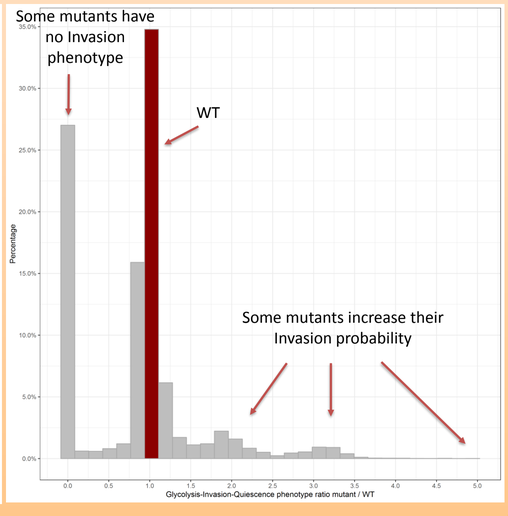


High-throughput mutant study

Using our pipeline[1], we studied **all single and double mutants** of **LNCaP-cell-line-specific Boolean model**. These 38089 different models were simulated using MaBoSS resulting in phenotypes probabilities for each one of them. The **genetic interaction study** explores the combined effect of double mutations on phenotypes' probabilities in comparison to wild type and single mutants' ones[7].

Our pipeline can also perform many more analyses, such as to study the **robustness of the model** logical rules to highlight "weak" rules whose alteration abolishes a given phenotype.

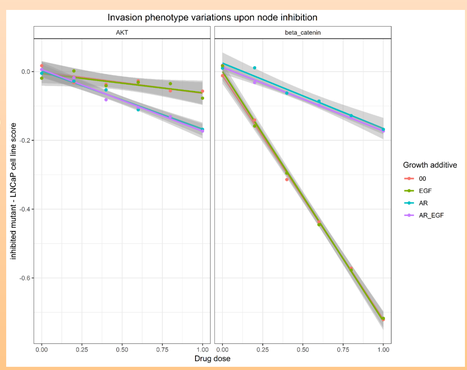


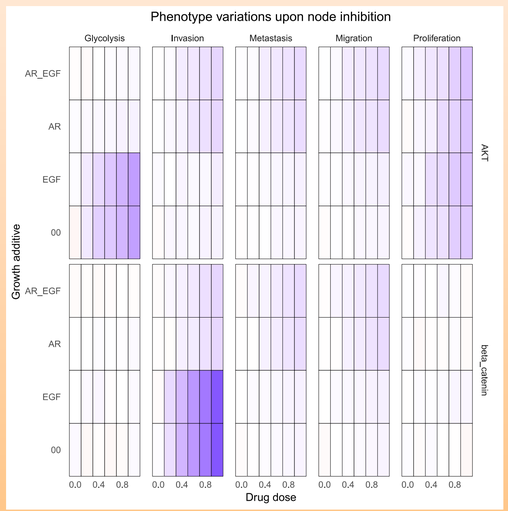


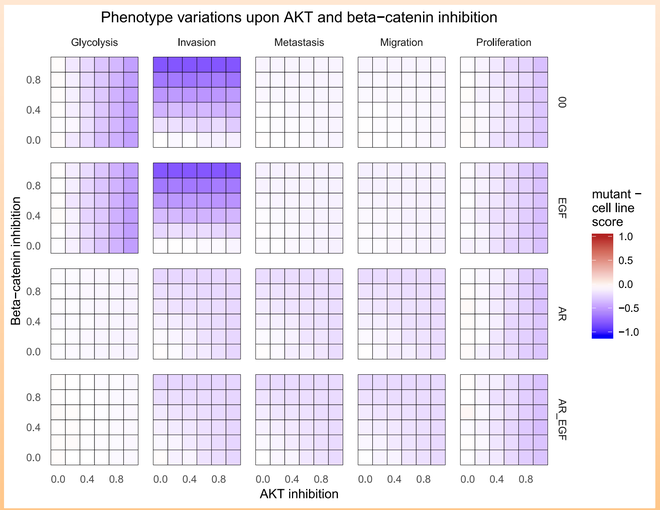
Drug simulations of cell-line-specific Boolean models

Taking advantage of MaBoSS[5,6] and its **population probabilities**, the model's node activity status can be **forced to have a continuous value** simulating the effect of a given drug.

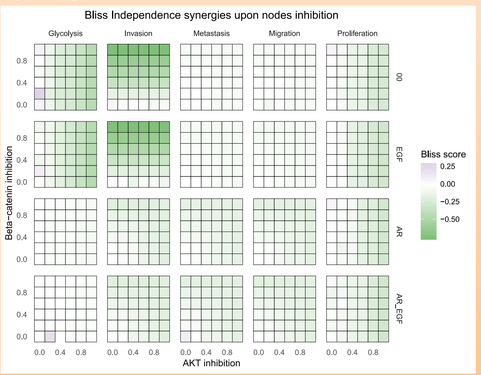
As an example using LNCaP-cell-line-specific Boolean model, we have simulated **drugs that interfere with the status of AKT and beta-catenin** to study their effect on several **phenotypes relevant to cancer**, such as Invasion, Glycolysis and Proliferation.







As in the case of the mutant study, we can also simulate the **combined effect** of these inhibitions and **uncover cell-lines- and patient-specific drug synergies**.



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Acknowledgements

PrECISE,
AMX scholarship (JB)