Building a Boolean model of signaling pathways altered in prostate cancer

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Introduction

The aim of this work is to build **Boolean models** to simulate specifically prostate cancer in individual patients or clones. That way, we seek to understand by which means the cells become cancerous and propose appropriate drug interventions to **personally treat** the patient.

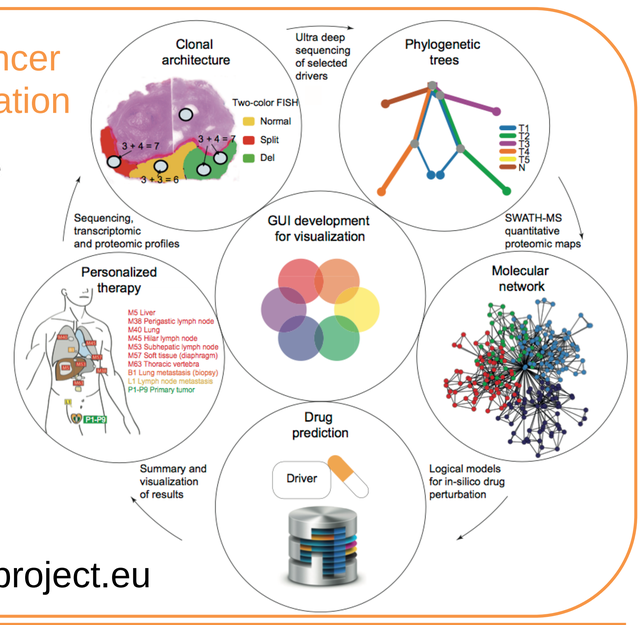
This involves the following steps:

- build a **network of the signaling pathways** that include frequently altered genes in prostate cancer,
- identify **new molecular processes** to complement the network, in particular with **gene set quantification**, and **search detailed interactions** supported by literature relevant in these pathways,
- derive **a Boolean model** describing the network dynamics in specific contexts, and estimate **time evolution of phenotypic probabilities** with MaBoSS.

PrECISE — Personalized Engine for Cancer Integrative Study and Evaluation

This work is part of PrECISE, a project which studies prostate cancer and aims at:

- Elucidating clone-specific tumorigenic mechanisms
- Suggesting adequate therapeutic interventions based on personalized molecular and clinical information
- Validating these suggestions in prospective cohorts and a panel of prostatic cell lines
- Developing PrECISE into deployable software tool: user-friendly interface accessible to the clinical research community



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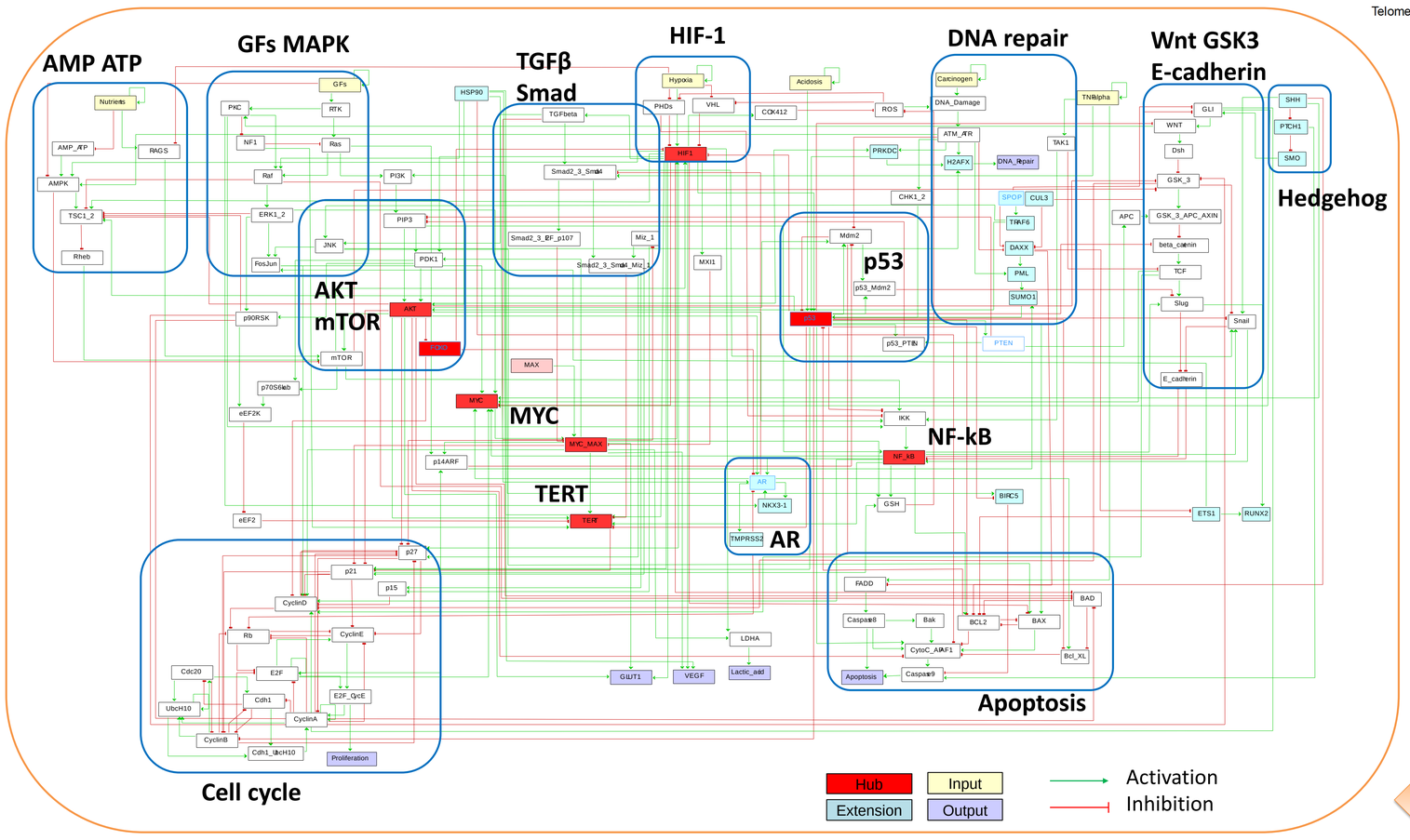
Building a regulatory map of prostate cancer

A published model [1] is extended using both pathway databases and the literature, and is made more specific to our cohort of patient data by applying gene set quantification methods.

Published networks and models

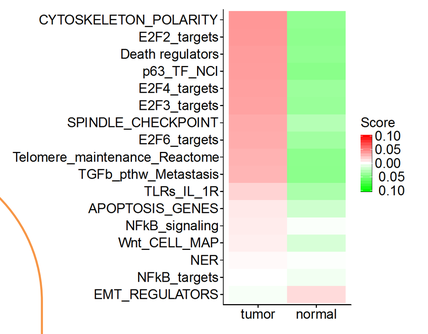
Public pathway databases, literature



Regulatory network for prostate cancer

Datasets (TCGA + PrECISE)

Significant pathways are identified from a predefined list of gene sets.



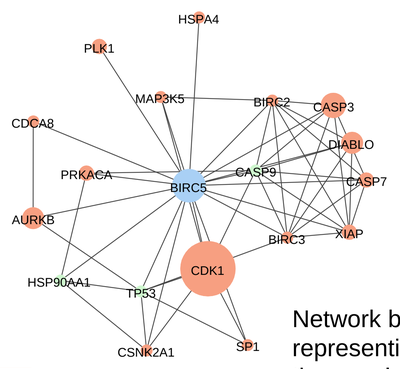
Pathway activity computed with **ROMA** from protein expression datasets in prostate samples

ROMA [2] is a gene set quantification tool that can estimates pathway activity score and dispersion in multiple samples.

Hot spot (top contributing) **genes** are selected.

Example: BIRC5 top contributing gene in « death regulators »

Interactions linking novel nodes with the map are retrieved with **Pypath.**



Network built with **Pypath**, representing all neighbors of the novel node BIRC5 (blue) in Omnipath, with the nodes already included in the network colored in green

Pypath is a Python module for building molecular interaction networks. It is linked to **OmniPath** [3], a comprehensive collection of literature curated human signaling pathways.

Network extension

Dynamical model of prostate cancer

- Building a logical model based on the regulatory map

The influence network is translated into a Boolean model. Each node can take two values 0 or 1 and is updated according to a logical rule associated to it, which takes into account the activity of its inputs. The inputs are linked with the logical operators AND, OR or NOT.

- Stochastic simulations

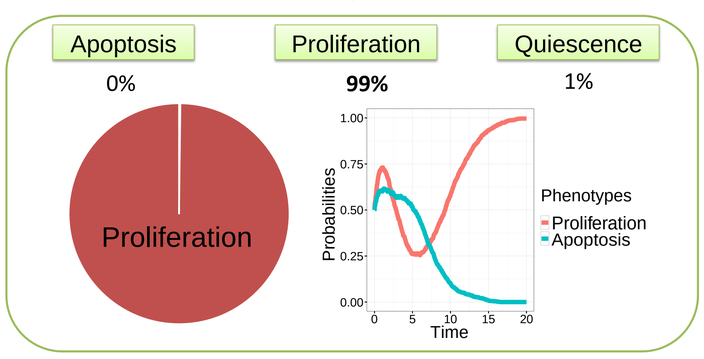
From a set of initial conditions, the logical model is simulated stochastically using **MaBoSS** software. The solutions can be represented in different forms: a probability of network states equivalent to **the asymptotic solutions** of the stochastic simulations, or **time evolution** of the nodes of interest.

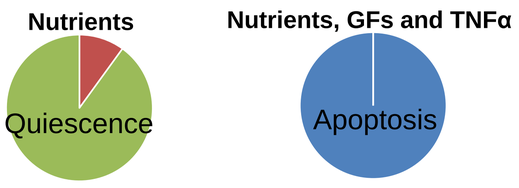
MaBoSS [4] is a probabilistic framework based on continuous time Markov chains, used to estimate time evolution of state probabilities in logical models.

Inputs

Nutrients	Hypoxia	GFs	Carcinogen	Acidosis
1	0	1	0	0

Outputs





Prospects

- Cell-specific data fitting

Phosphoproteomics data will be generated by PrECISE partners and used to automatically fit the model to cell types with CellNOpt [5].

- Patient-specific model instantiation

The genetic profile of each patient can be encoded in the model as **mutations** or **initial states**. According to the initial conditions or altered genes, the probabilities of the phenotypes will vary and inform on the possible consequences of each modification on the cells.

- Drug simulation

The **effect of several drugs** on the model can be simulated and compared to experimental observations.

Predictions made under this framework are intrinsically accompanied by a **mechanistic explanation** and can provide a support to incorporate **patient-specific molecular data.**

References

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[5] C Terfve, T Cokelaer, A MacNamara, D Henriques, E Goncalves, MK Morris, M van Iersel, DA Lauffenburger, J Saez-Rodriguez. CellNOptR: a flexible toolkit to train protein signaling networks to data using multiple logic formalisms. *BMC Systems Biology, 2012, **6**:133*

Acknowledgements

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Tools

www.pypath.omnipathdb.org
https://maboss.curie.fr
https://github.com/sysbio-curie/Roma