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

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Computational Systems Biology of Cancer group

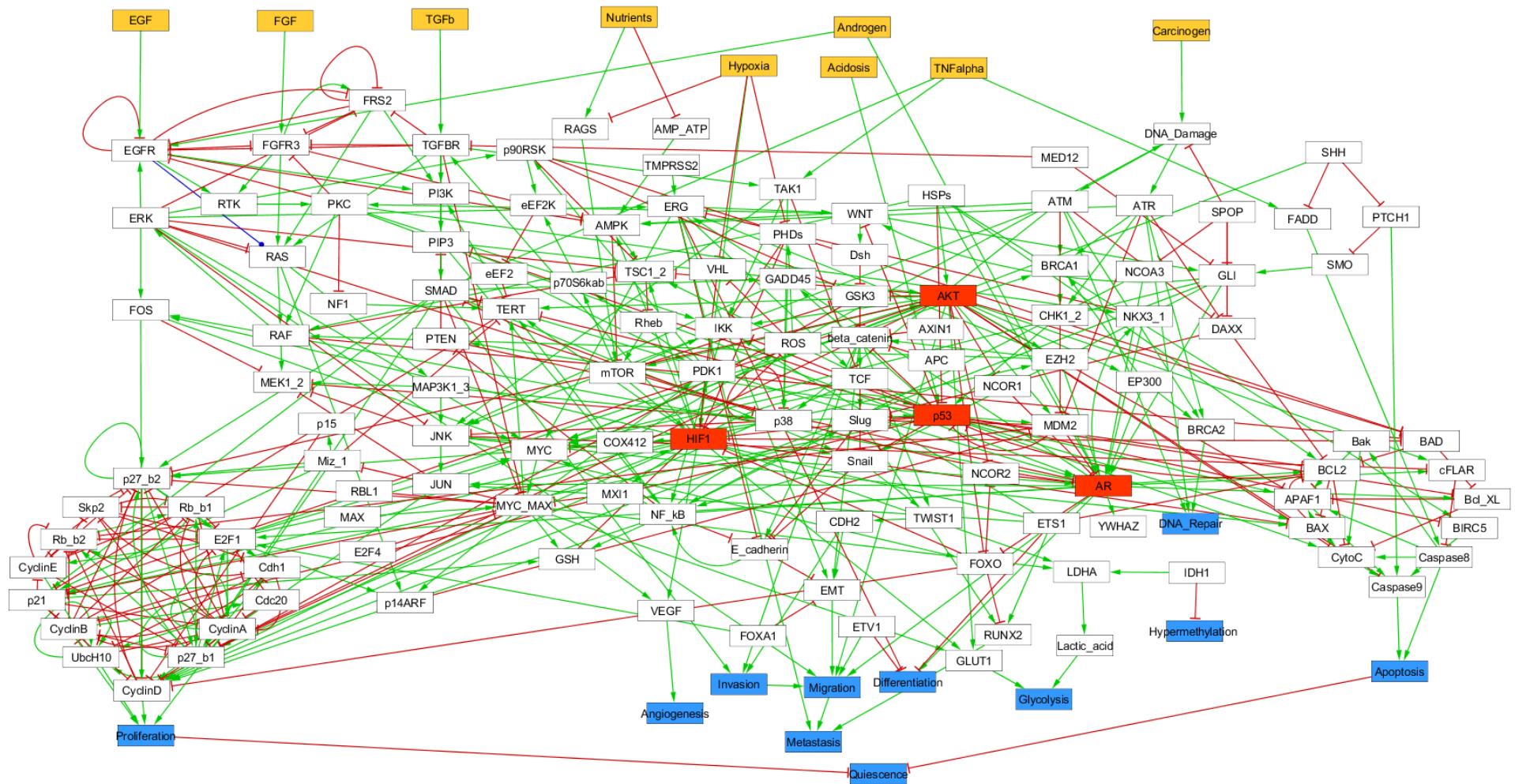
Institut Curie

8th September 2018, ECCB18, W6, Athens, Greece

Prostate cancer Boolean model

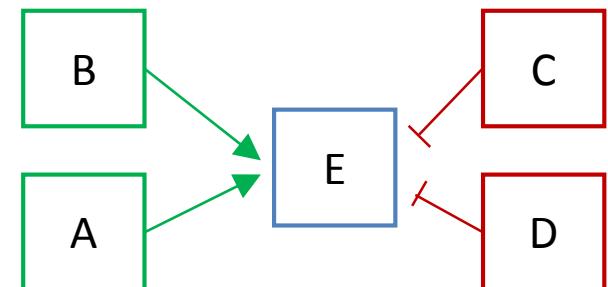
148 nodes; 498 edges; 322 genes

9 inputs; 11 outputs



Simulating logical rules

- Logical model = network + **logical rules**
- Set of discrete variables as **abstractions of activity level**
 - linked by logical rules as **signed interactions**
- Convenient way to model regulatory and **signalling networks**
 - Allows integration of literature & heterogeneous data
 - Provides **qualitative analysis**
- Standard logical rules:
 - $E \leftarrow (A \mid B) \& !(C \mid D)$
- Solutions are **attractors** (stable states and limit cycles)
 - We developed a tool to **assign probabilities** to these solutions
 - Applies Gillespie algorithm on the **state transition graph** using **asynchronous** updates and allows for **semi-quantitative** simulations
 - Stoll et al. (2012). *BMC Syst Biol*; Stoll et al. (2017). *Bioinformatics*



Gillespie algorithm allows of stochastic simulations



Conditions

Nutrients

50%

Androgen

50%

GFs

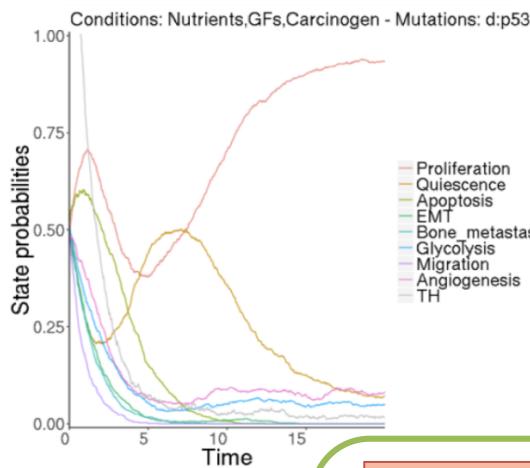
50%

Carcinogen

10%

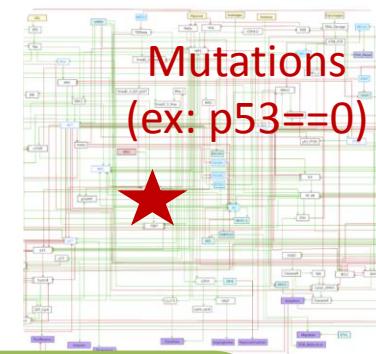
Hypoxia

10%



Stochastic trajectories

Signalling pathways



Probabilities
based on 1000
trajectories

Apoptosis

10%

Proliferation

23%

Quiescence

67%

EMT

0%

Metastasis

0%

Angiogenesis

10%

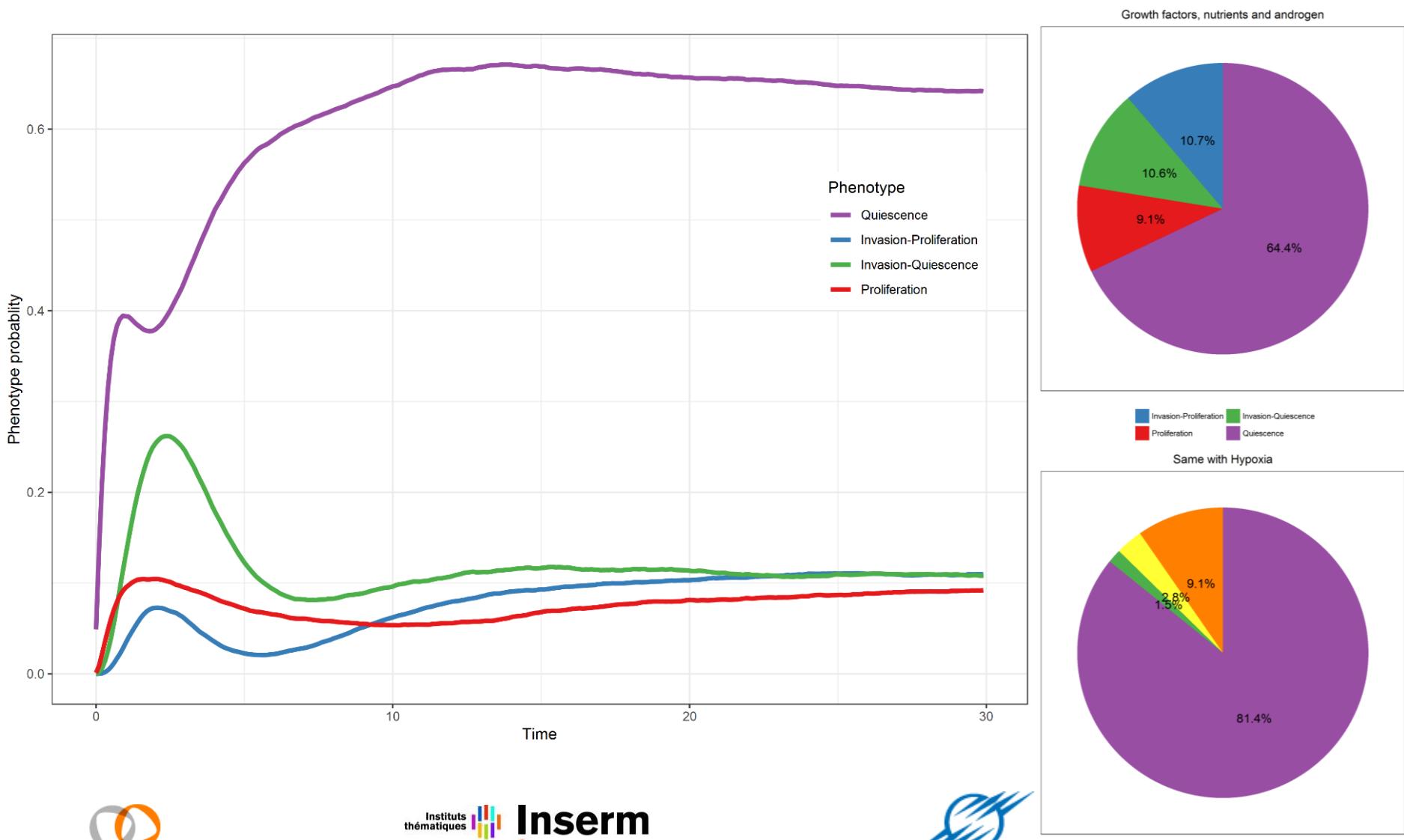
DNA repair

5%

Migration

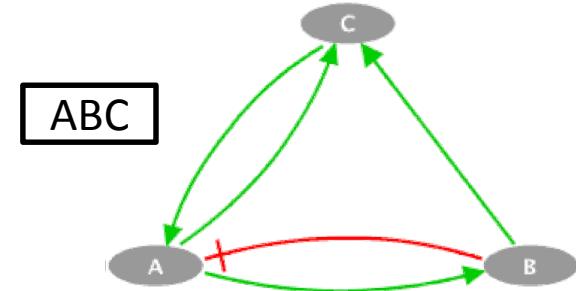
0%

Prostate cancer Boolean model time trajectories and populations' dynamics

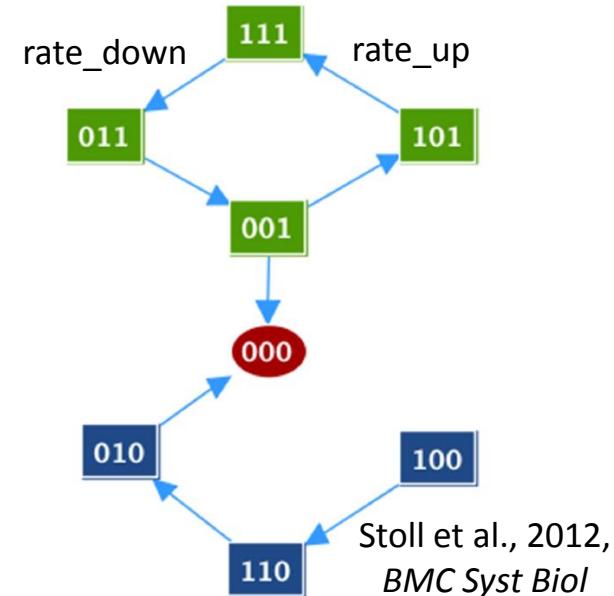


Model instantiation to patients' profiles

- Choosing the proper **data type** in the proper **model variable**
- Modelling framework:
 - **Node states** = mutants → Discrete
 - **Initial conditions** = growth media conditions or experimental setup
 - **Transitions rates** = Gene's ability to activate or deactivate → Continuous
- Data types:
 - CNA
 - Mutations } **Easily Boolean**
 - Expression: RNA and/or proteins } **Easily continuous**



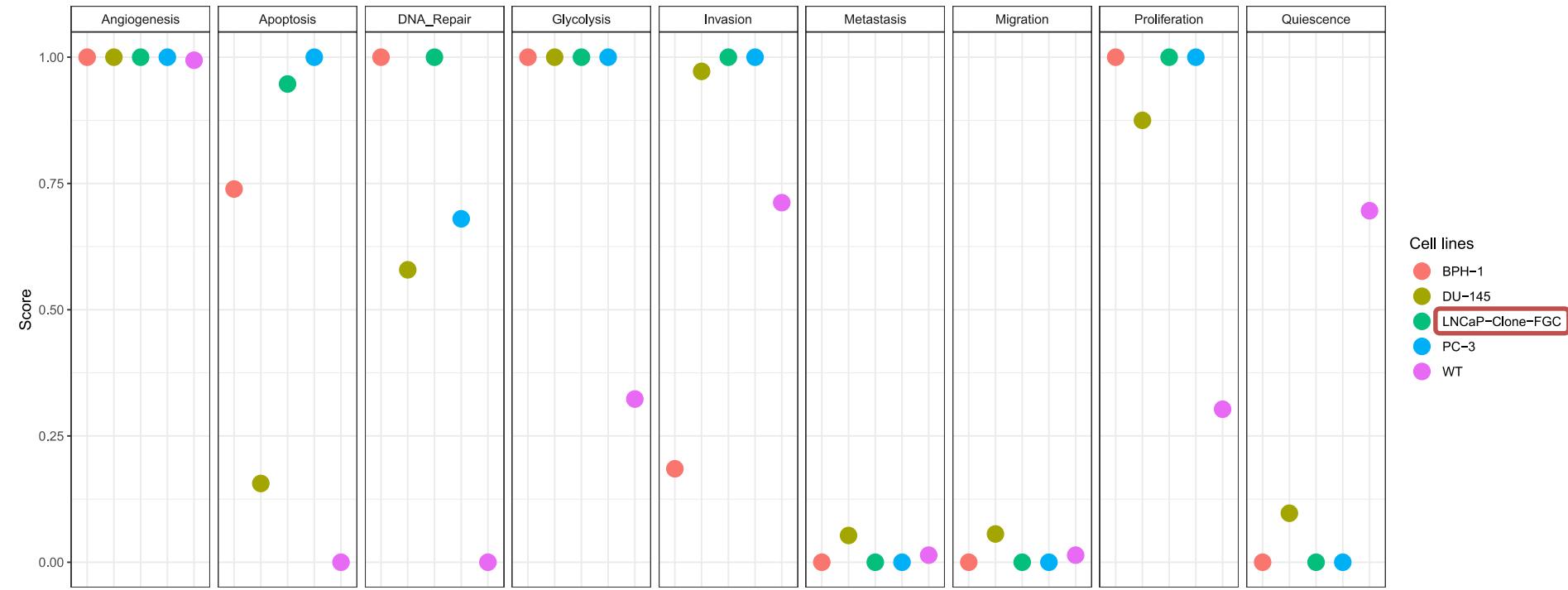
Boolean state transition graph



Cell-line-specific Boolean models

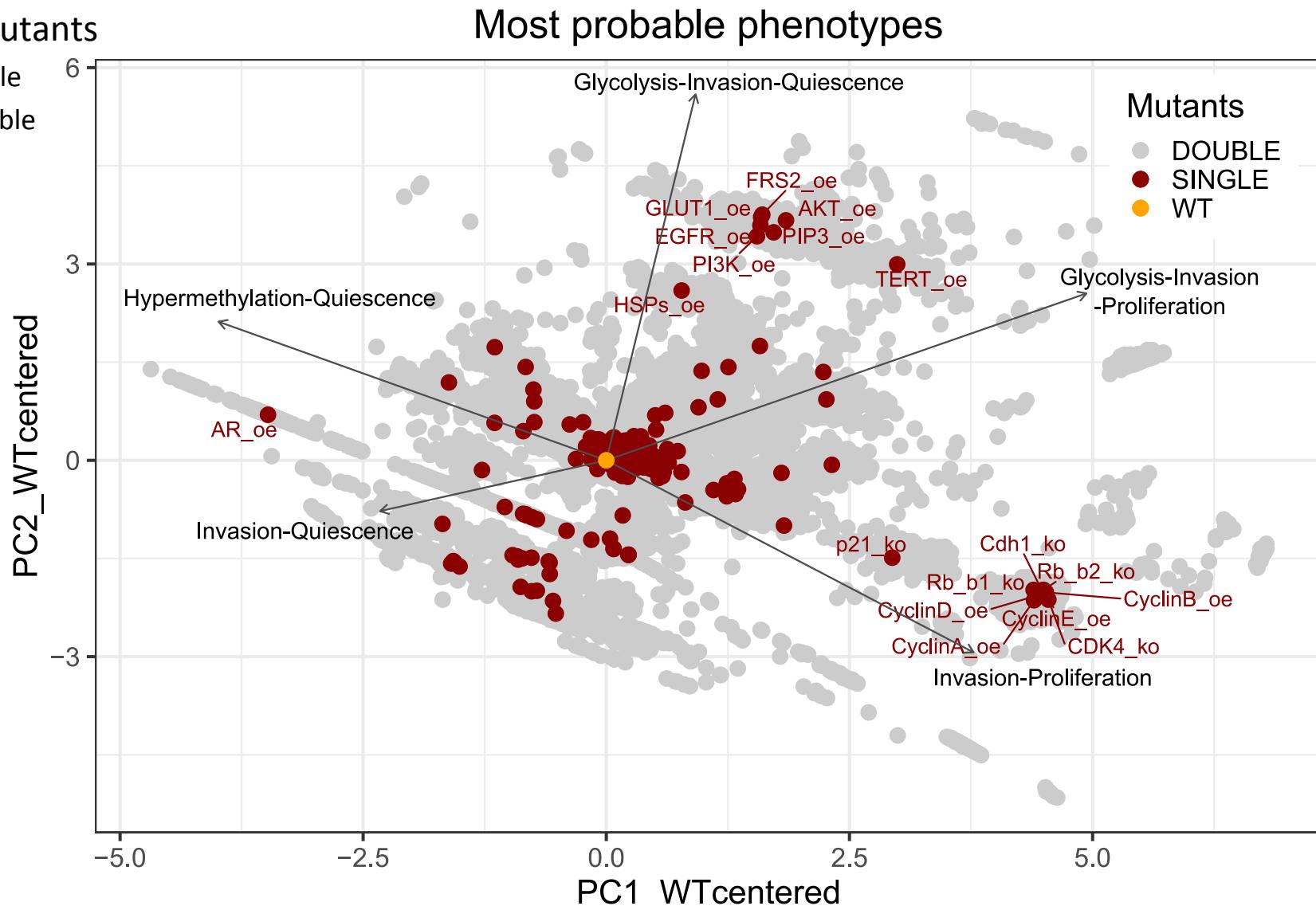
- GDSC cohort
- CNA as node activity
- RNA as transition rates
- 4 prostate cell lines have CNA and RNA
 - BPH-1 is a benign prostate hyperplasia
- WT is non-instantiated model

Distribution of Phenotypes scores across GDSC prostate cohort, using CNA as node activity status and RNA as transition rates

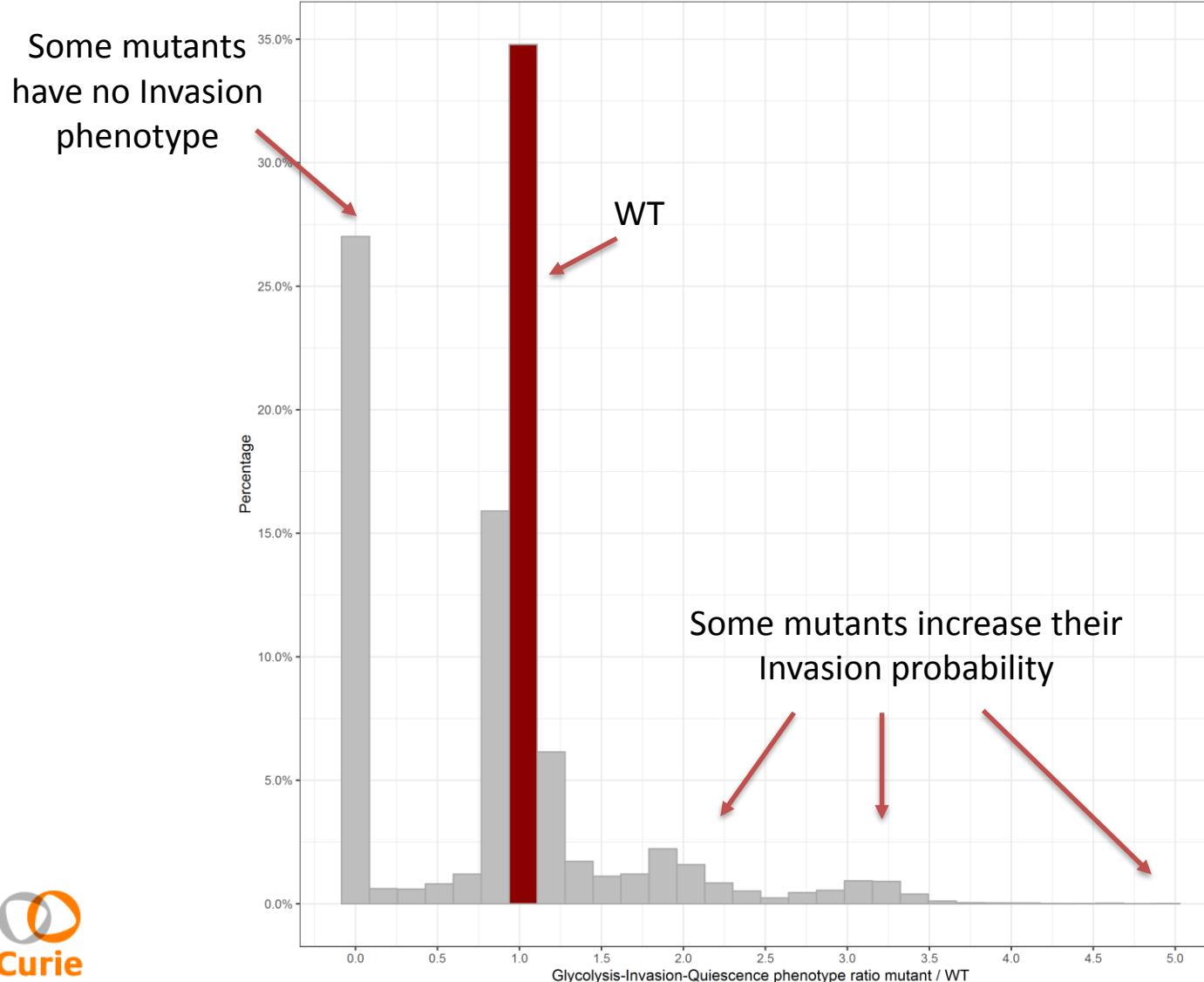


High-throughput mutant study of LNCaP-specific Boolean model

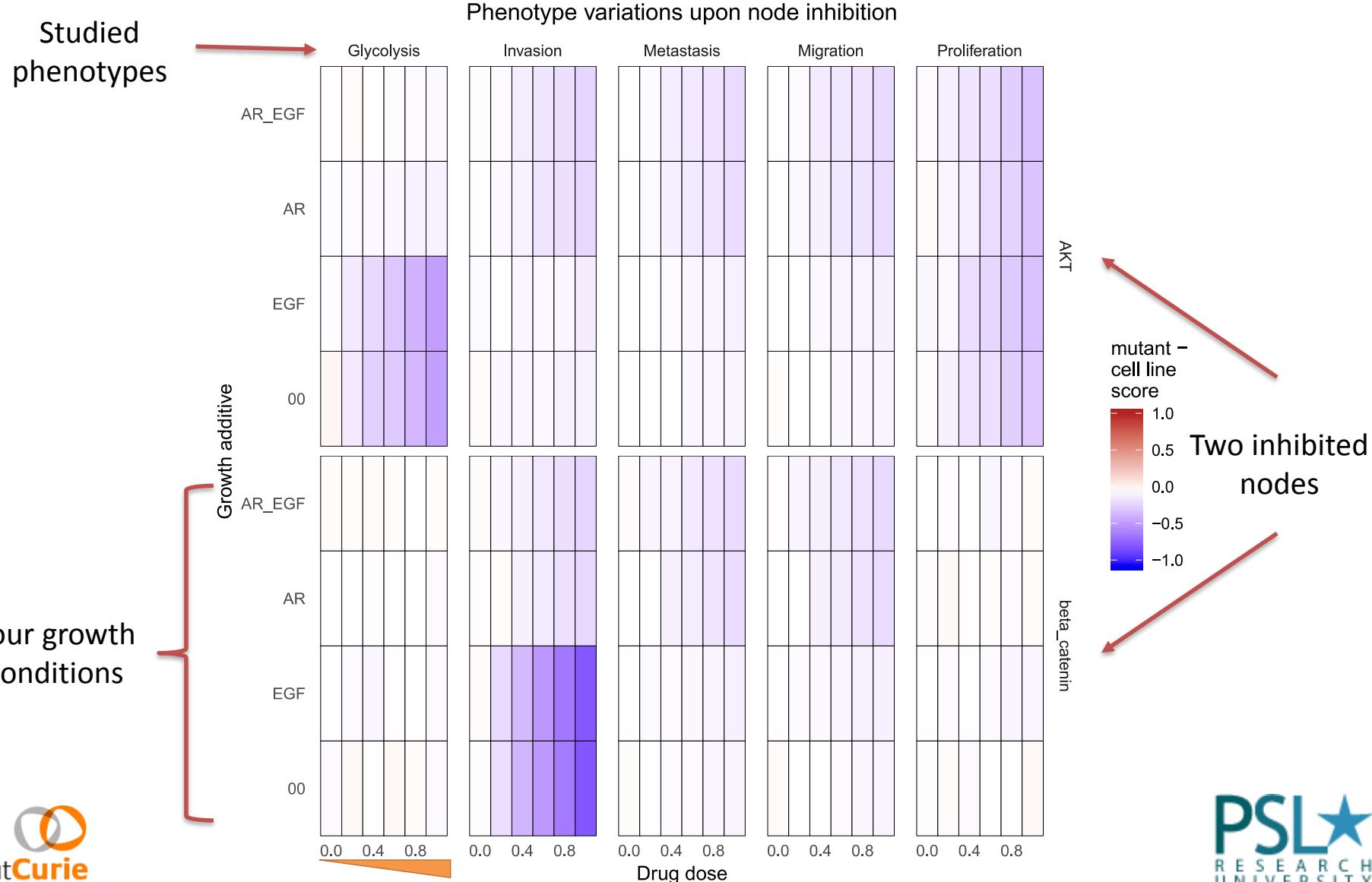
- >38k mutants



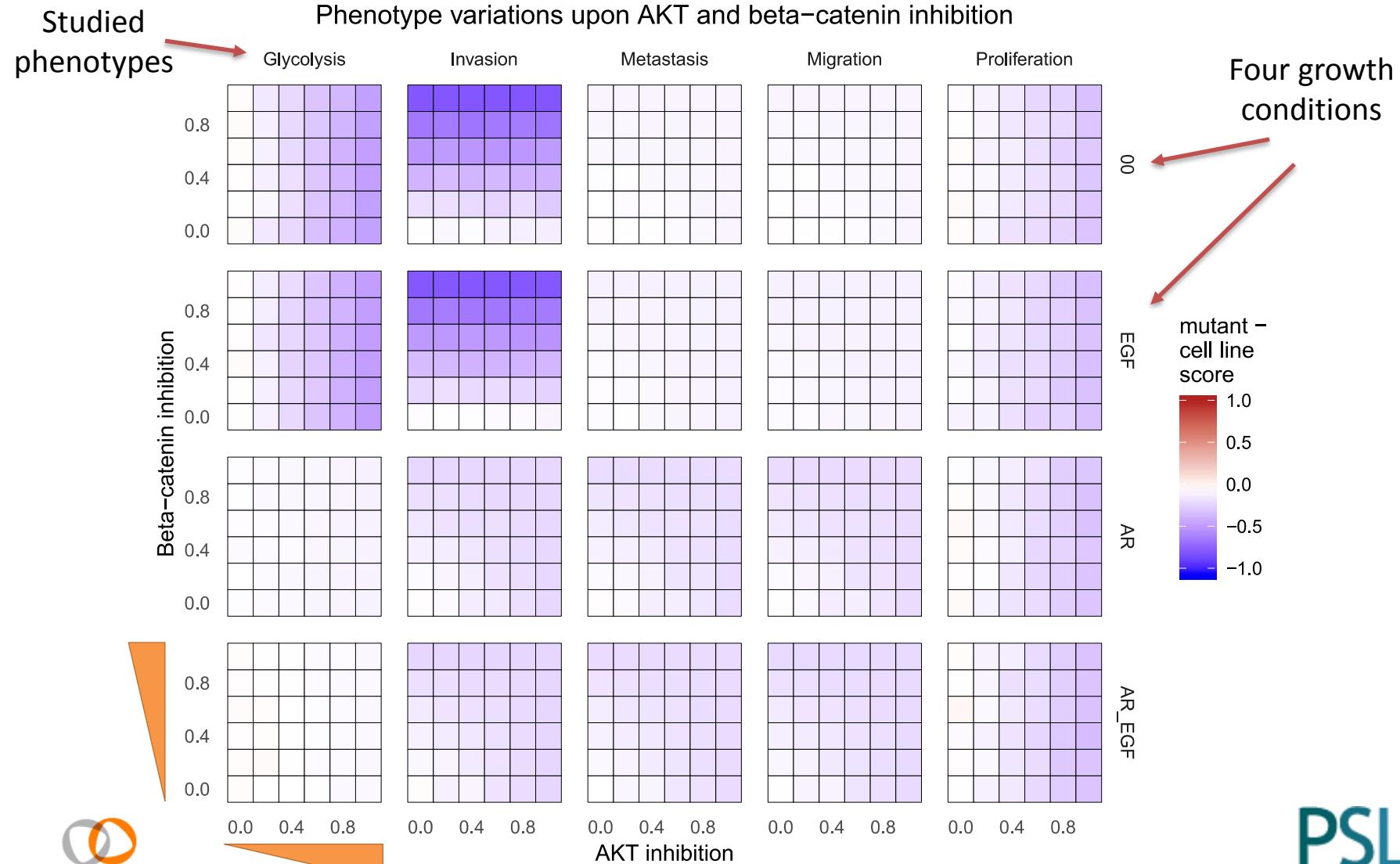
High-throughput mutant study of LNCaP-specific Boolean model



Drug simulations of LNCaP-specific Boolean model

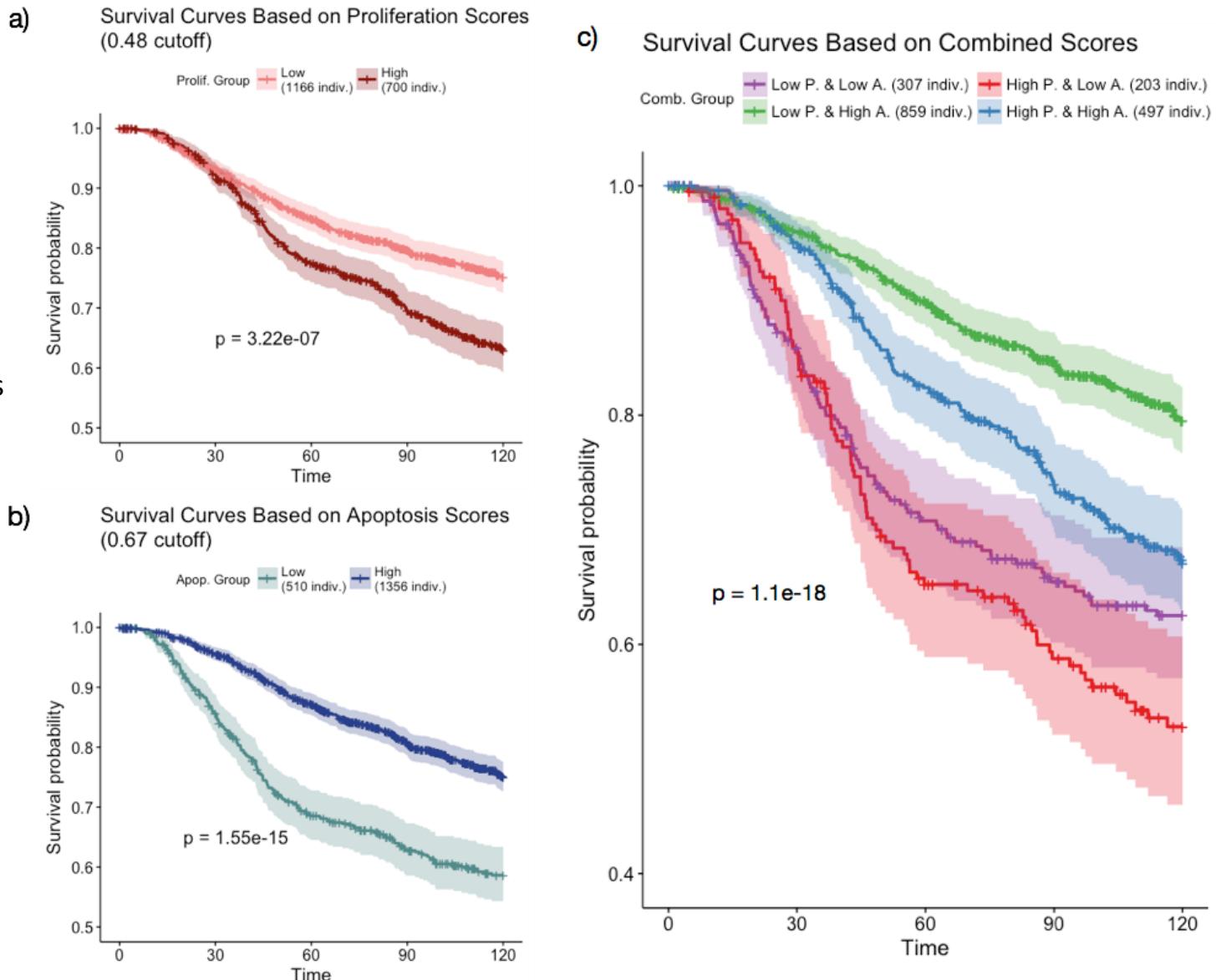


Drug simulations of LNCaP-specific Boolean model



Phenotypes correlate with clinical data: METABRIC models vs survival data

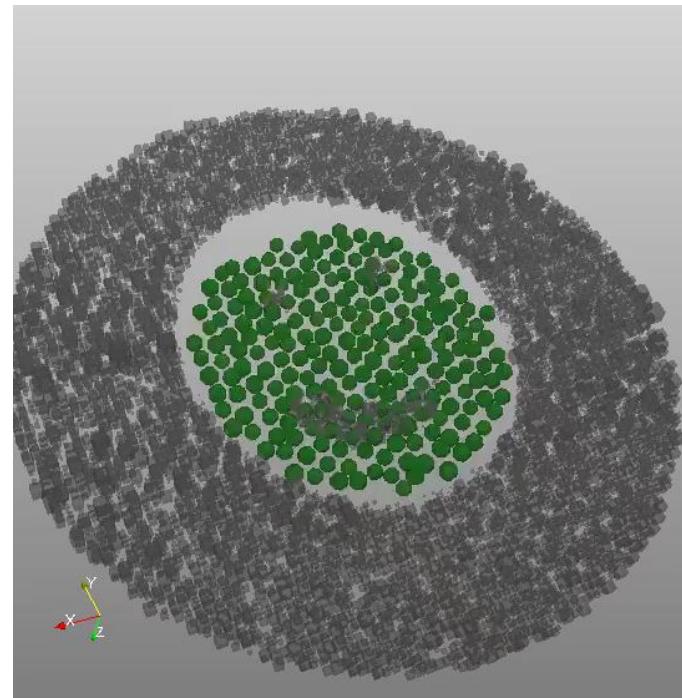
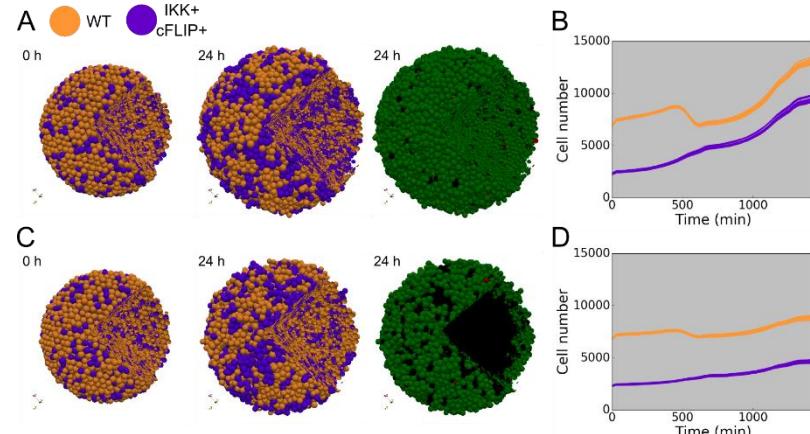
- Generic cancer model
 - Fumiā et al., 2013, PLoS ONE
- Breast cancer data
 - CNA + mutations + RNA
 - Survival data



Perspective: multi-scale modelling

- Patient-specific clonal heterogeneity
- PhysiBoSS: a multi-scale agent based modelling framework integrating physical dimension and cell signalling
 - Boolean model embedded in an agent-based model
 - Letort et al., *Bioinformatics*, 2018, bty766

- Proliferative cells
- Apoptotic cells
- NonACD cells
- Quiescent cells



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- Multi-scale modelling
 - Gaelle Letort, poster P_Sy011
 - *Bioinformatics*, 2018, bty766
- Instantiation of Boolean models
 - Jonas Béal, poster P_Sy023
 - *Frontier in Physiology*, under review



- High-throughput mutant study
 - Montagud et al, *Briefings in Bioinformatics*, 2017, bbx163



- Drug simulations of prostate-cell-line-specific Boolean models
 - Poster P_Sy022

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