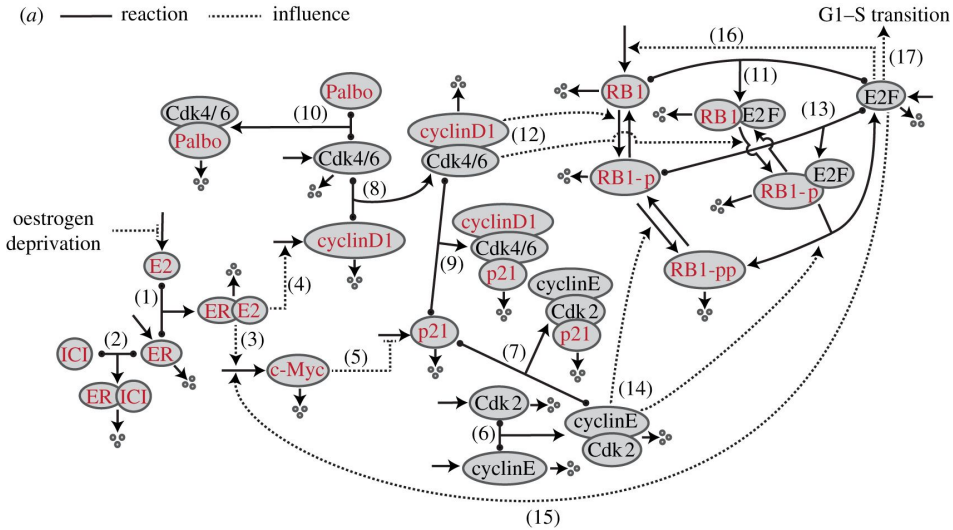
Mathematical Modeling of breast cancer cells in response to endocrine therapy and Cdk4/6 inhibition



Andrea Tonina e Gloria Lugoboni
30/01/2024

He Wei, Demas Diane M., Conde Isabel P., Shajahan-Haq Ayesha N. and Baumann William T. 2020, Mathematical modelling of breast cancer cells in response to endocrine therapy and Cdk4/6 inhibitionJ. R. Soc. Interface.

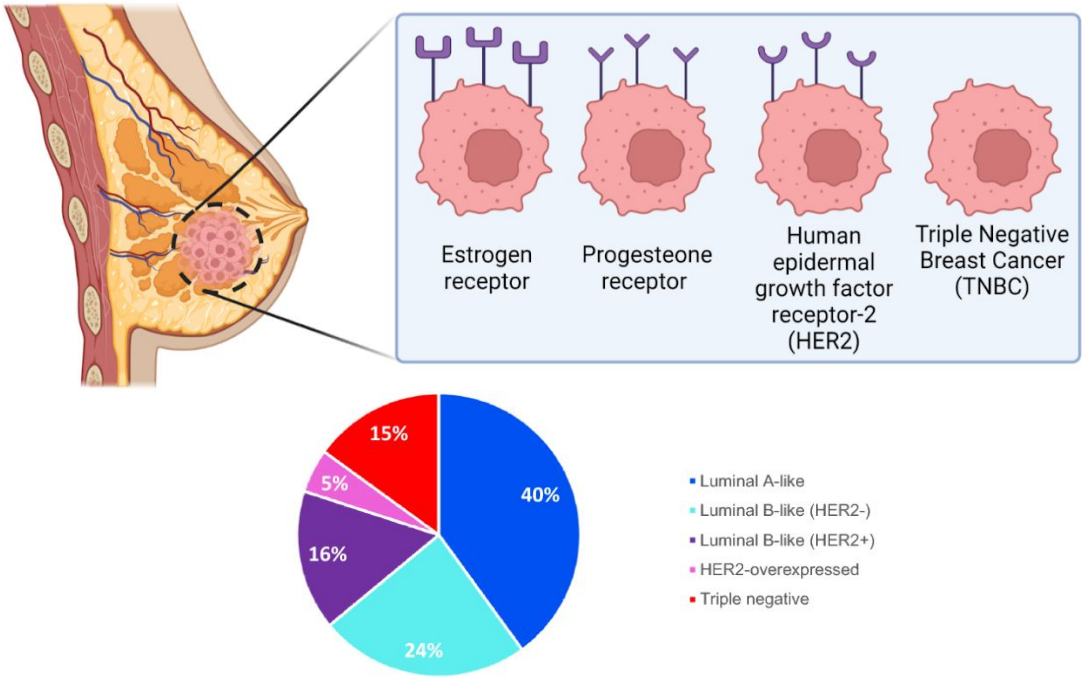
Introduction

- Breast cancer
  - General overview
- Endocrine therapies and Cdk4/6 inhibition
  - Cyclin-dependent kinases Cdk4/6 and Palbociclib
  - Endocrine therapies

Breast cancer

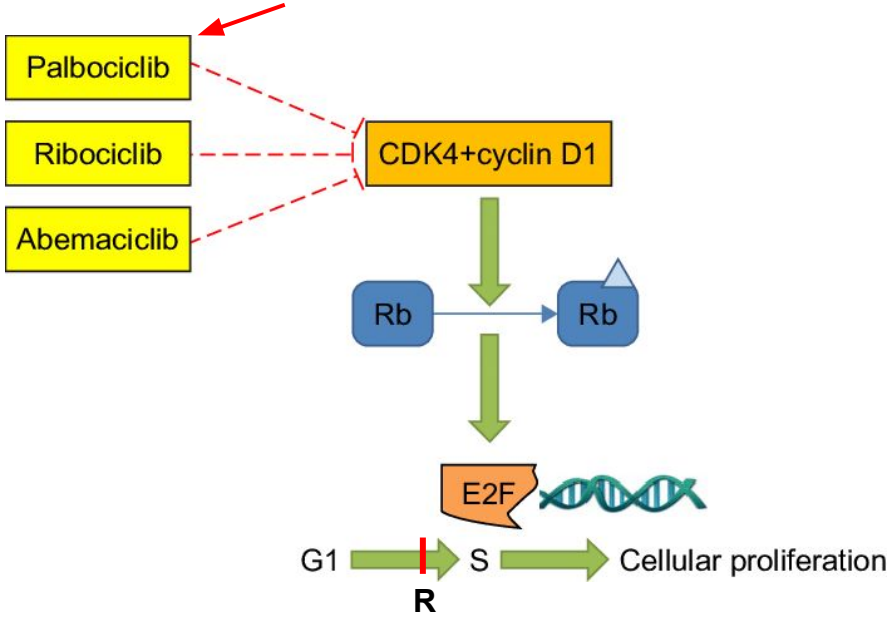
- One of the most common cancer of this generation

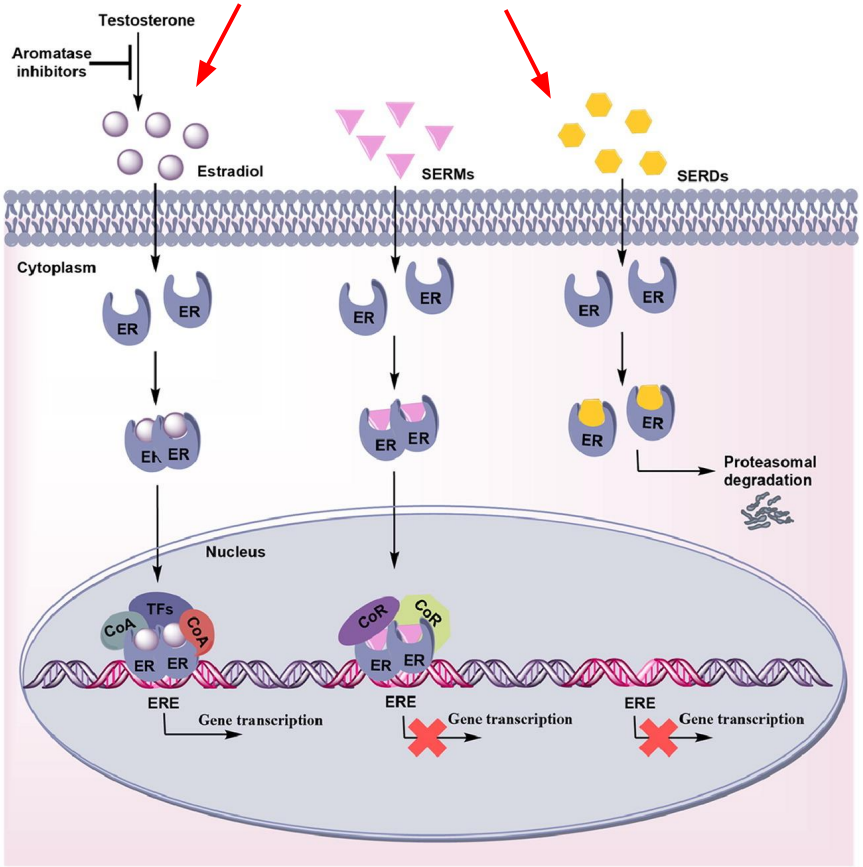
- Divided into 5 main subtypes based on gene expression
  - Luminal A and Luminal B are ER-positive (aberrant proliferation)



Chitkara, A., Mesa-Eguiagaray, I., Wild, S.H. et al. Reproductive history differs by molecular subtypes of breast cancer among women aged ≤ 50 years in Scotland diagnosed 2009–2016: a cross-sectional study. Breast Cancer Res Treat
QBRI Insights: Breast Cancer and the Importance of Awareness

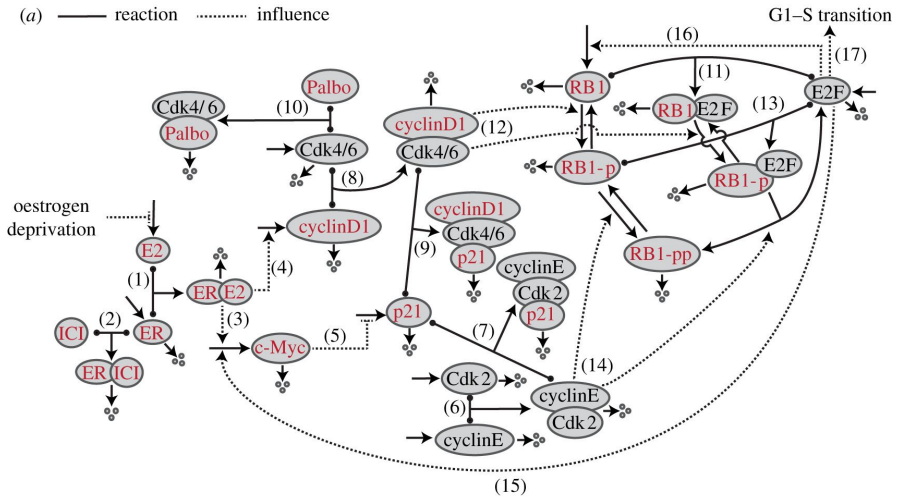
Therapies

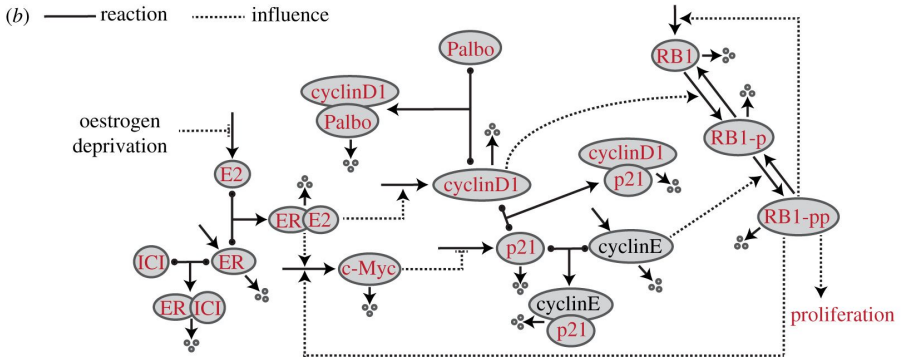




Abemaciclib: A CDK4/6 inhibitor for the treatment of HR+/HER2- advanced breast cancer, Silvia Corona et al,Drug Design Development and Therapy Volume 12, 2018
Hitisha K. Patel, Teeru Bihani, Selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs) in cancer treatment, Pharmacology & Therapeutics, 2018

Model structure





Model description: 14 ODE of first order, 16 variables, 62 parameters

Our implementation

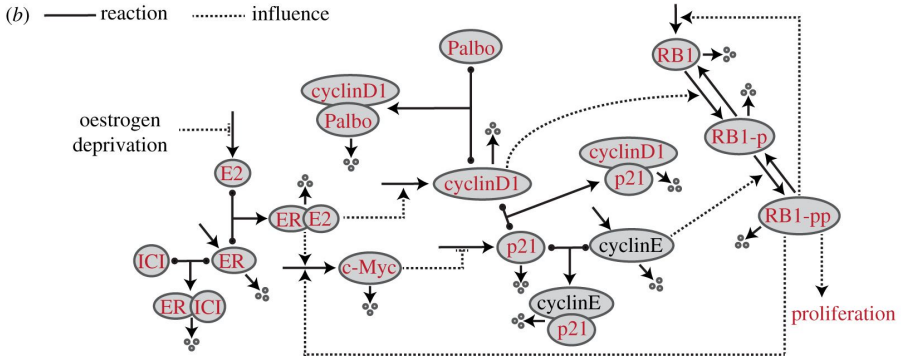
Deterministic approach

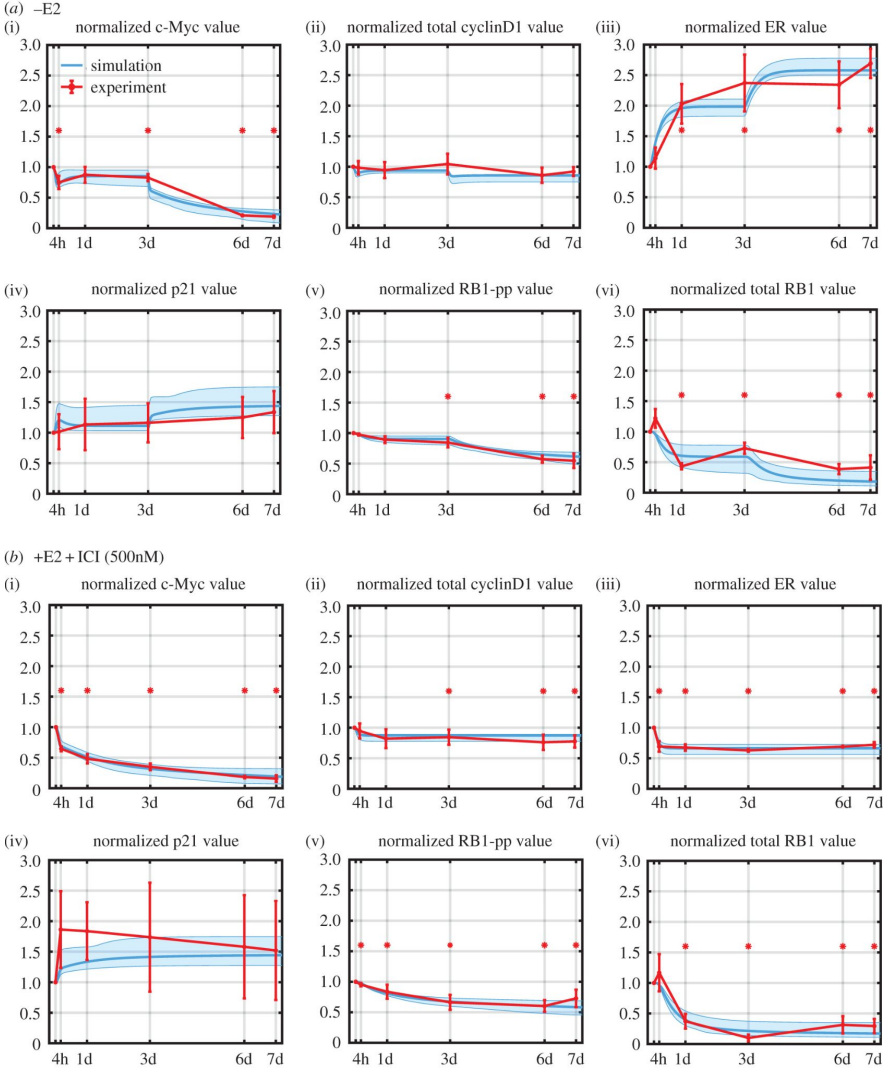
- ODE solver: ode23s
- Initial states and parameters were obtain from the original paper

Stochastic approach

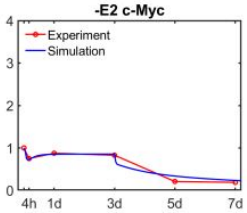
- ODE were converted into a set of reactions
- Deterministic rates converted into stochastic rates
- RSSA

Results 1: The proposed model structure can largely explain the experimental data

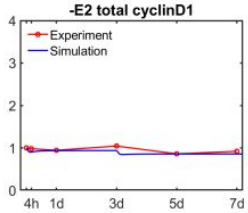




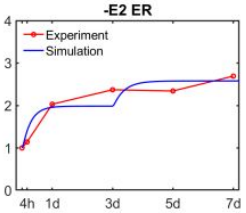
Our results



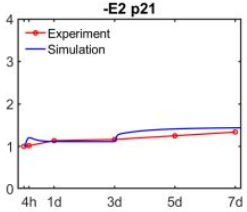
(a) *normalized c-Myc value*



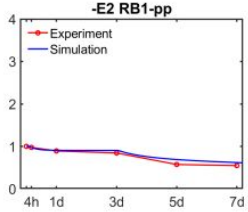
(b) *normalized total cyclinD1 value*



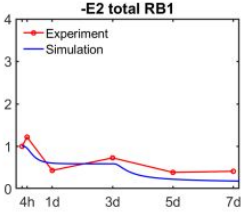
(c) *normalized ER value*



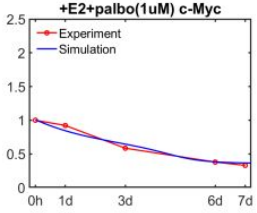
(d) normalized p21 value



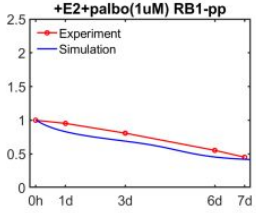
(e) normalized RB1-pp value



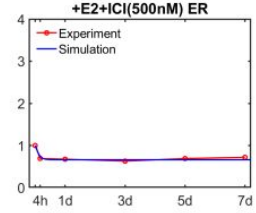
(f) normalized total RB1 value



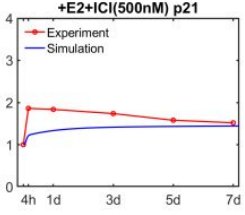
(g) *normalized c-Myc value*



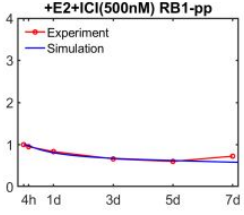
(h) *normalized total cyclinD1 value*



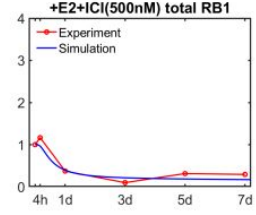
(i) *normalized ER value*



(j) normalized p21 value

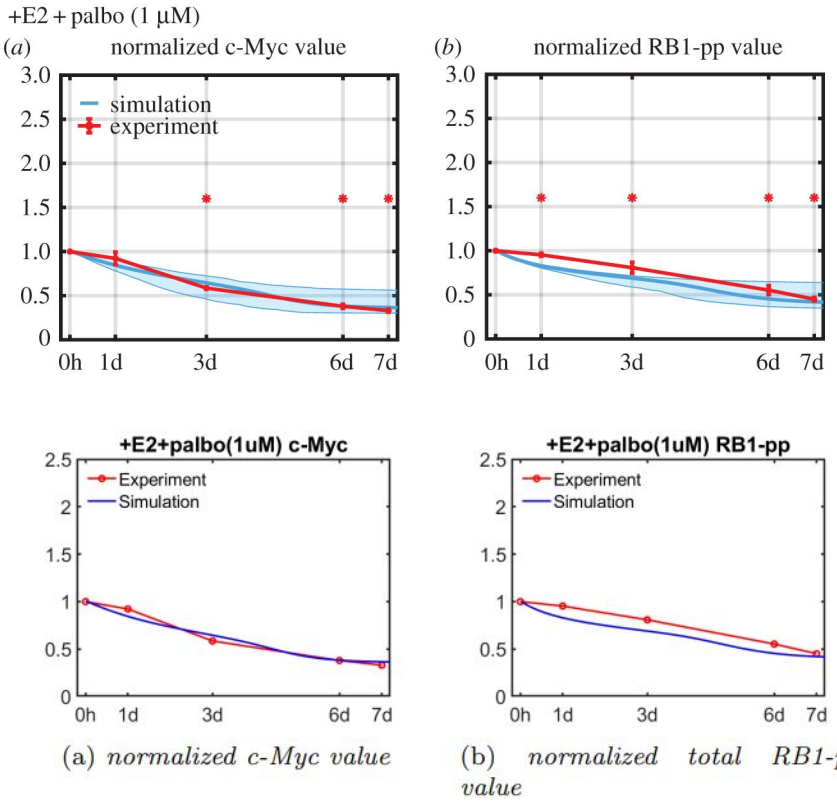


(k) normalized RB1-pp value

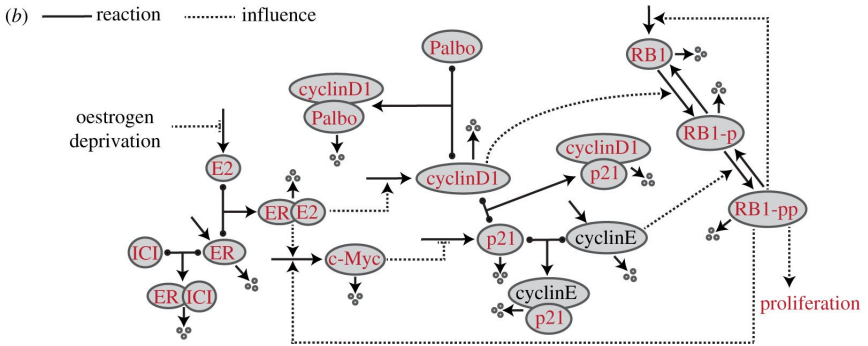


(l) normalized total RB1 value

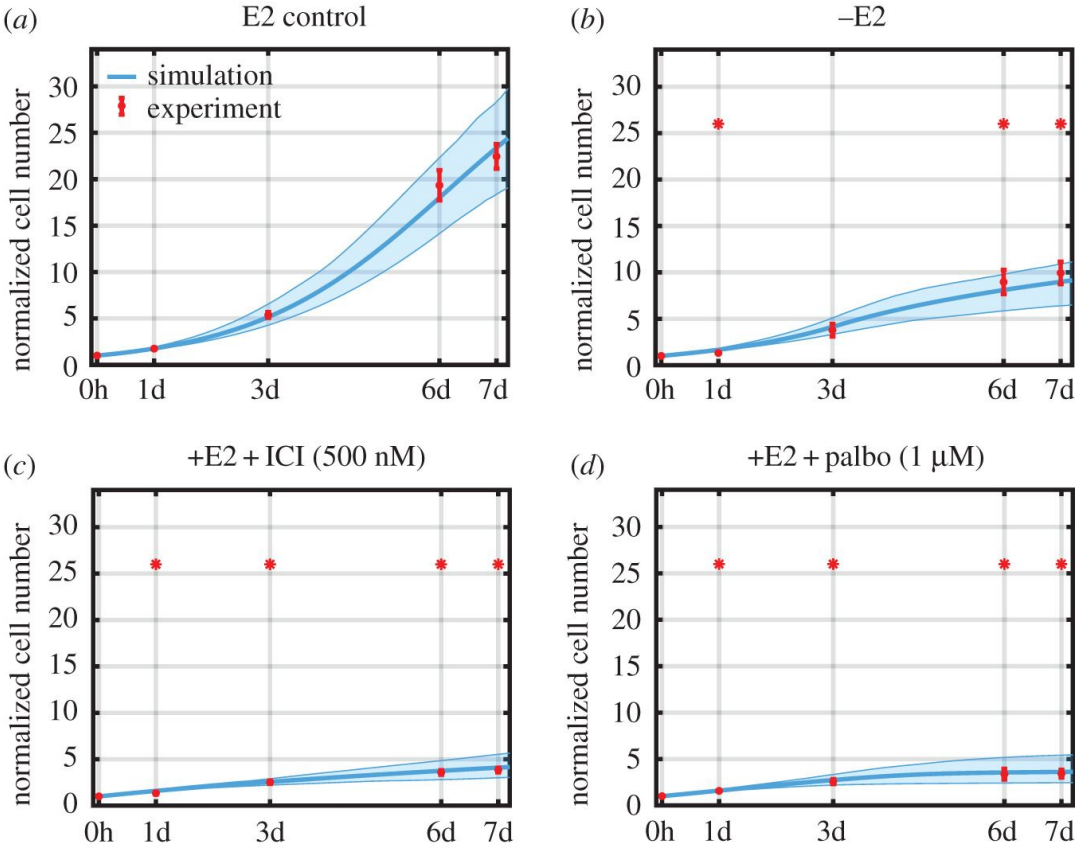
Results 2: Adding a new drug to the model requires limited new data



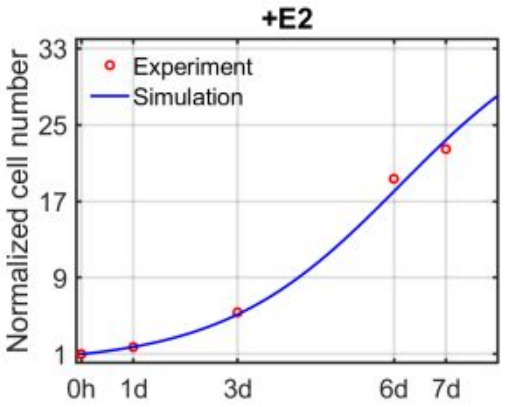
(a) *normalized c-Myc value* (b) *normalized total RB1-pp value*



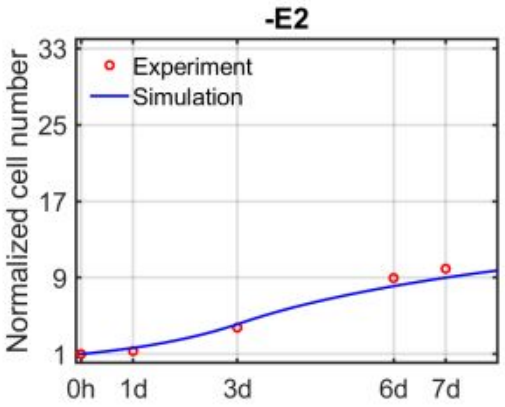
Results 3: The proliferation results can be explained by the RB1-pp level



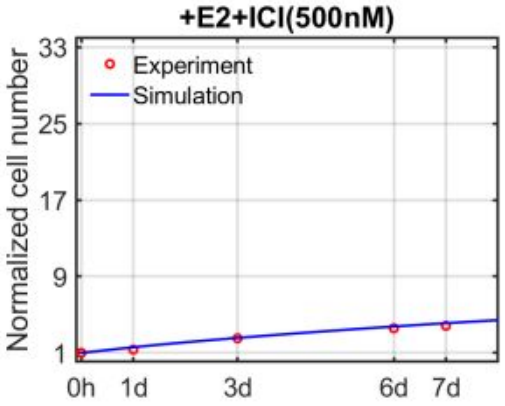
Our results:



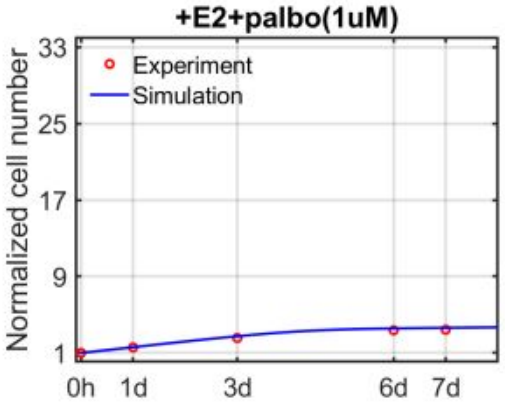
(a) *E2 control*



(b) *-E2*



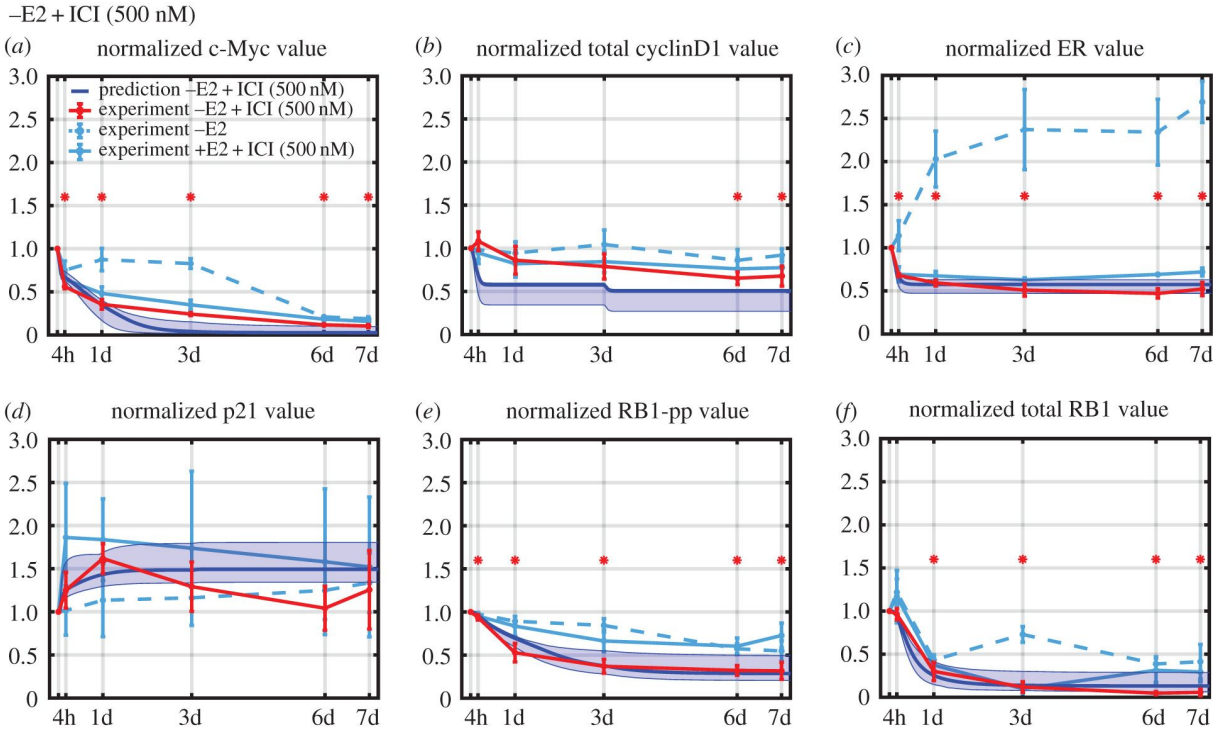
(c) *+E2+ICI*



(d) *+E2+palbo*

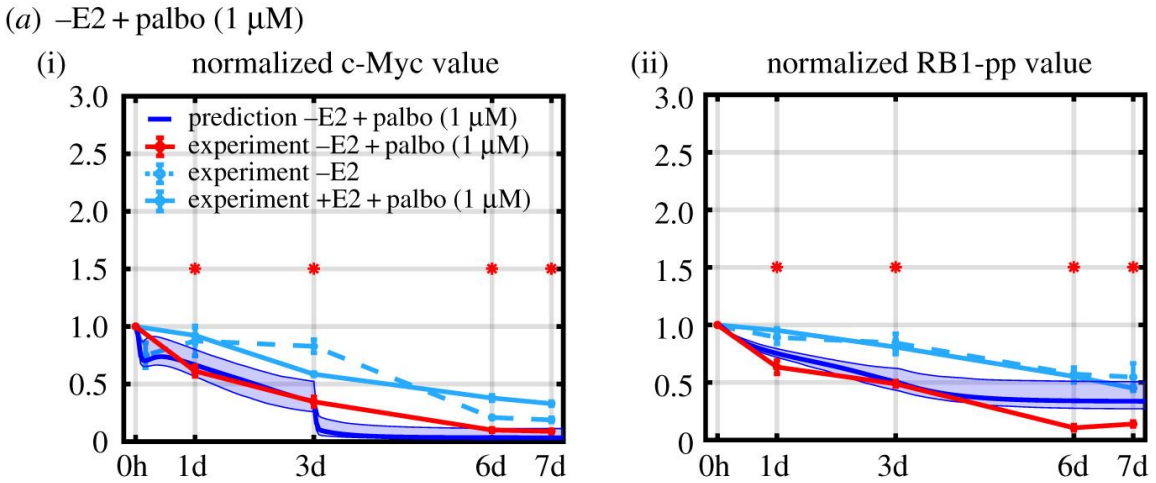
Results 4:

The model can predict the effect of combination treatment



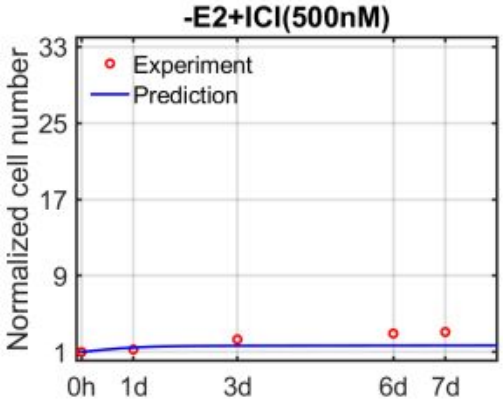
Results 4:

The model can predict the effect of combination treatment

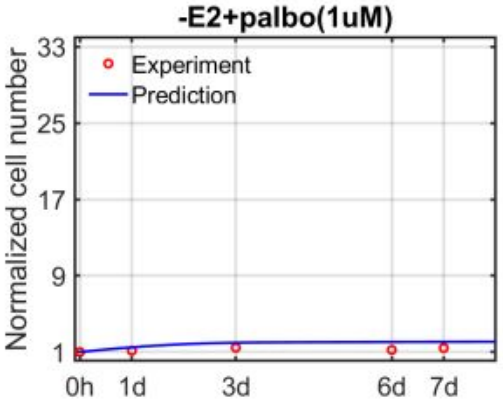


Our result:

On proliferation levels with combination of therapies

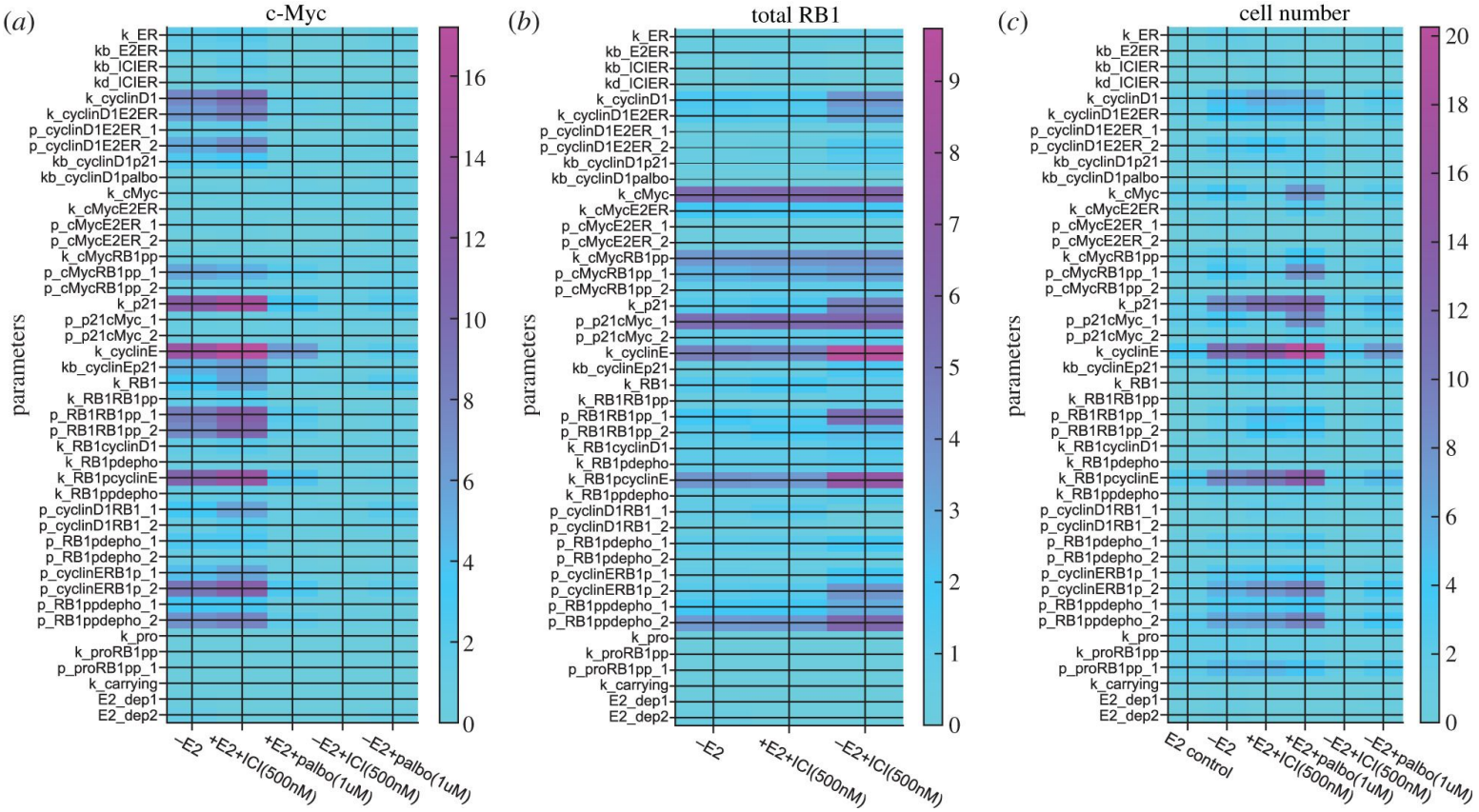


(a) *-E2+ICI*

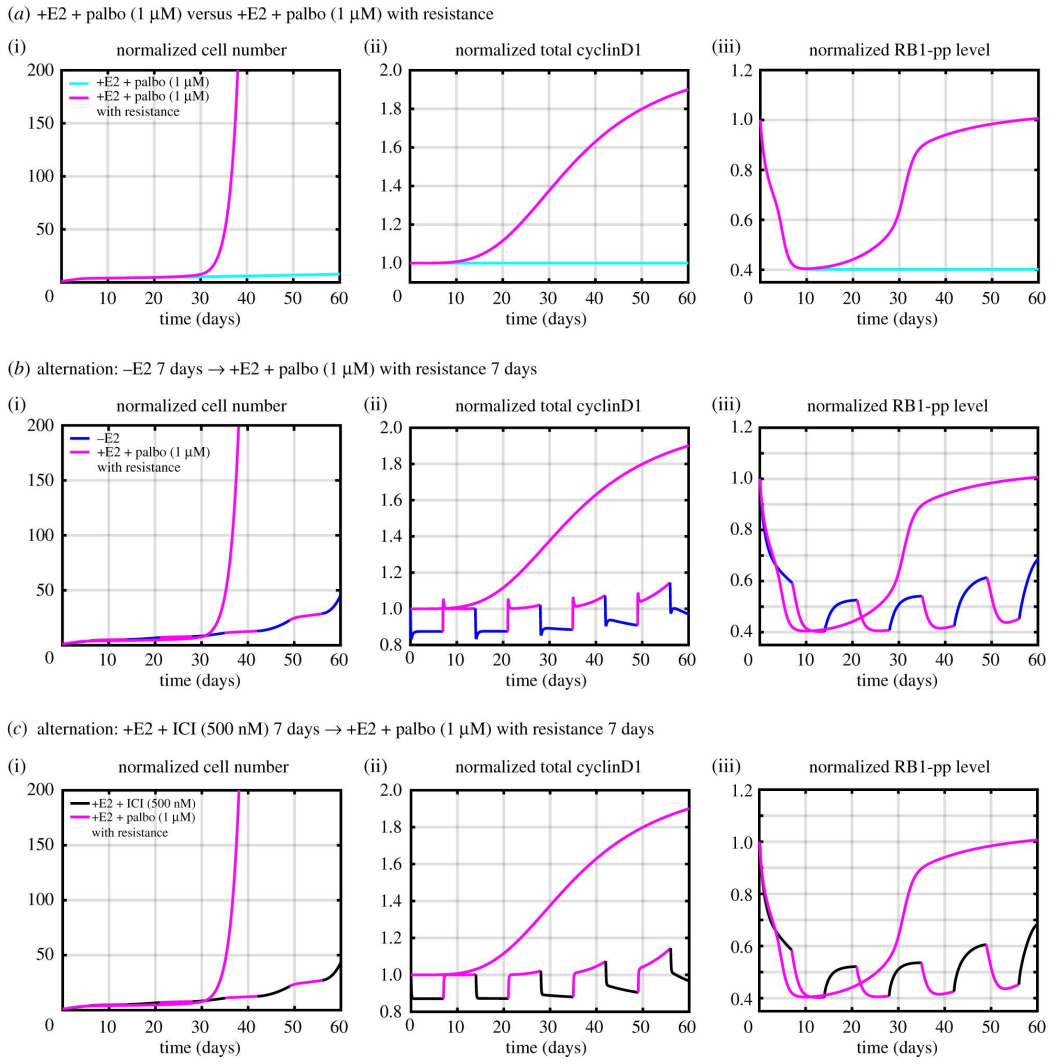


(b) *-E2+Palbo*

Results 5: Local sensitivity analysis of protein levels and proliferation



Results 6: The model can be used to explore the effect of sequential therapies

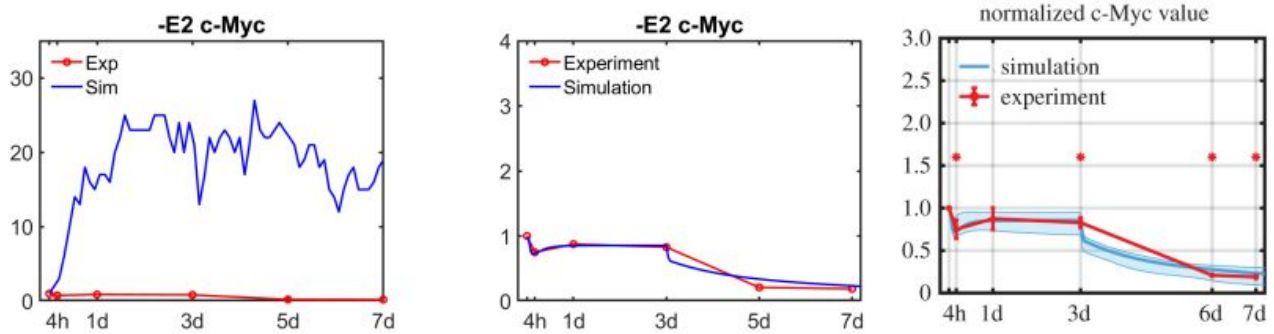


Discussion:

- Mathematical model is able to describe the aberrant ER signaling that takes place in these cancer cells

- The model was found to be predictive for cell proliferation and protein levels regulating ER signaling, both in terms of monotherapies and combined therapies

- Make assumptions on the predictive ability of the model regarding the utilization of cycle therapies in the context of resistance onset



(a) *Stochastic simulation* (b) *Deterministic simulation* (c) *Original paper*

Figure 14: Comparison between the results of the stochastic simulation, the deterministic simulation, and the original paper in terms of the levels of the proteins c-Myc.