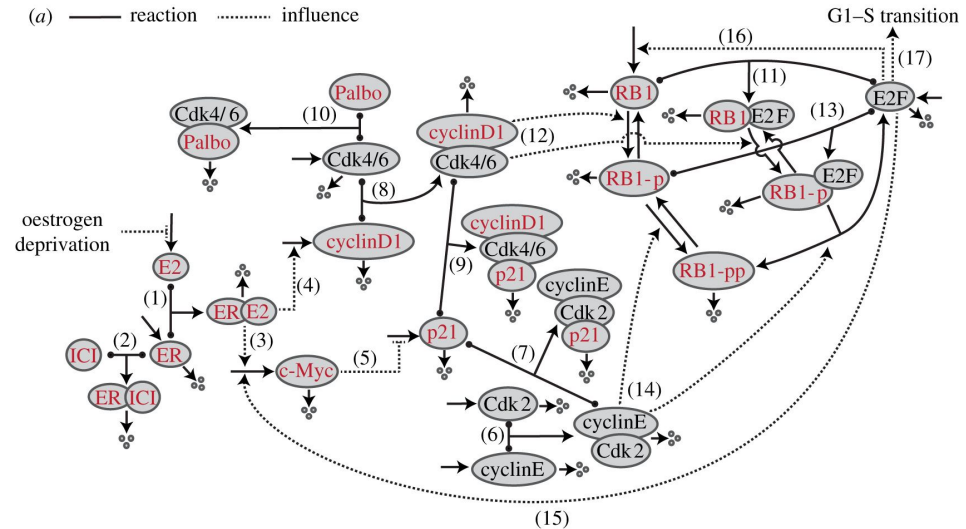


# Mathematical Modeling of breast cancer cells in response to endocrine therapy and Cdk4/6 inhibition

Andrea Tonina e Gloria Lugoboni  
30/01/2024

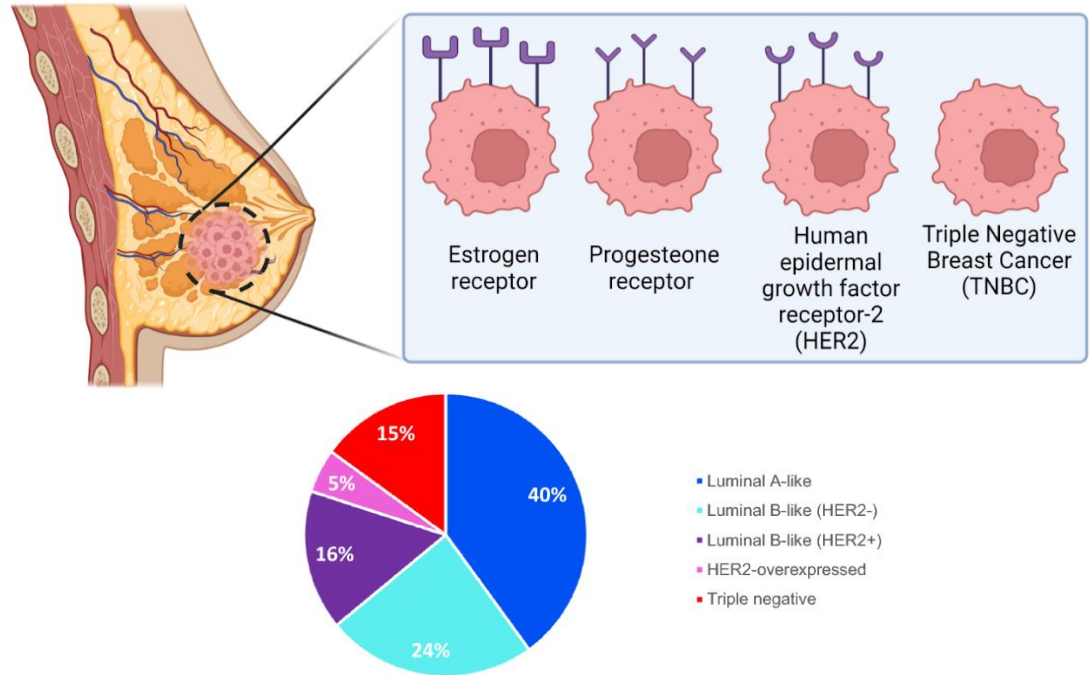


# Introduction

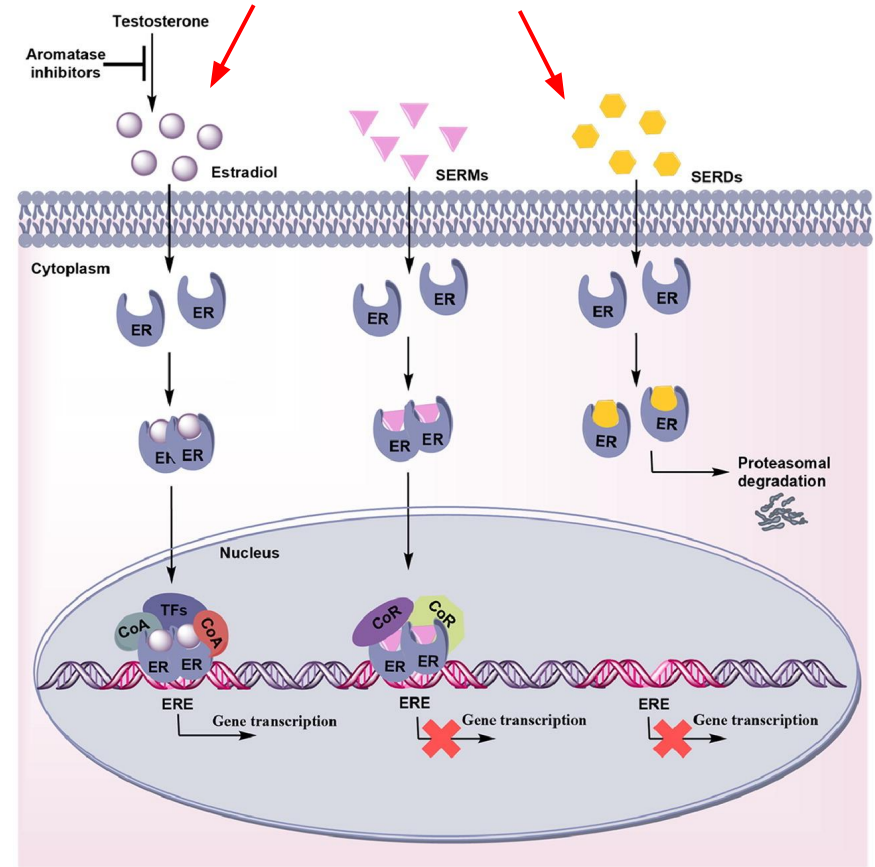
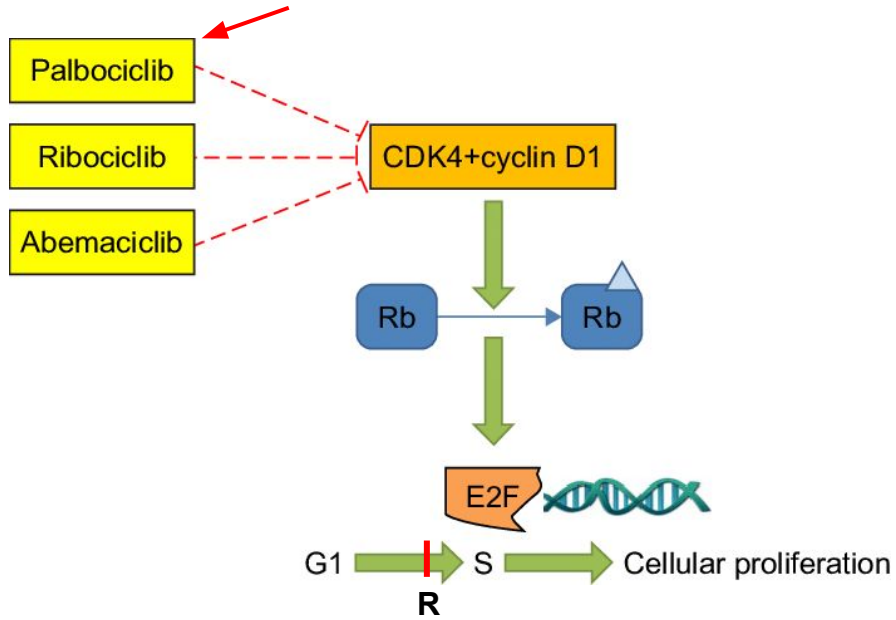
- Breast cancer
  - General overview
- Endocrine therapies and Cdk4/6 inhibition
  - Cyclin-dependent kinases Cdk4/6 and Palbociclib
  - Endocrine therapies

# 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)



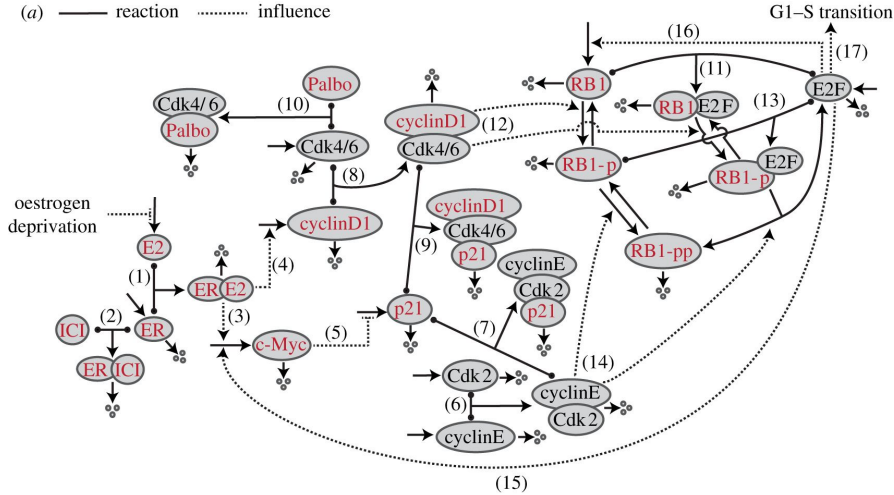
# Therapies



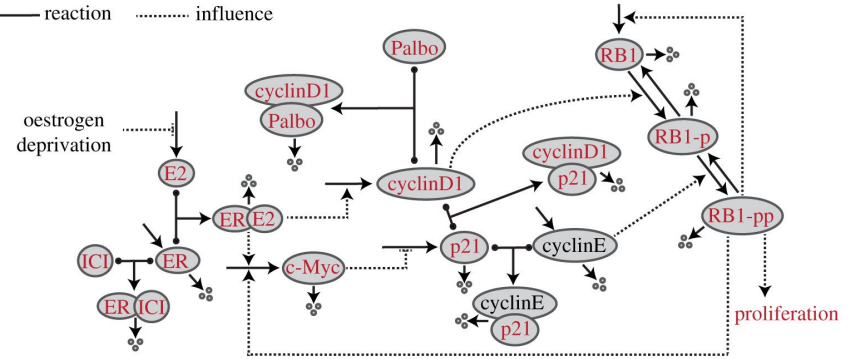
Abemaciclib: A CDK4/6 inhibitor for the treatment of HR+/HER2- advanced breast cancer, Silvia Corona et al, Drug Design Development and Therapy Volume 12, 2018  
 Hitisha K. Patel, Teeru Bihani, Selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs) in cancer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

# Model structure

(a) — reaction ..... influence



(b) — reaction ..... influence



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

# Our implementation

## Deterministic approach

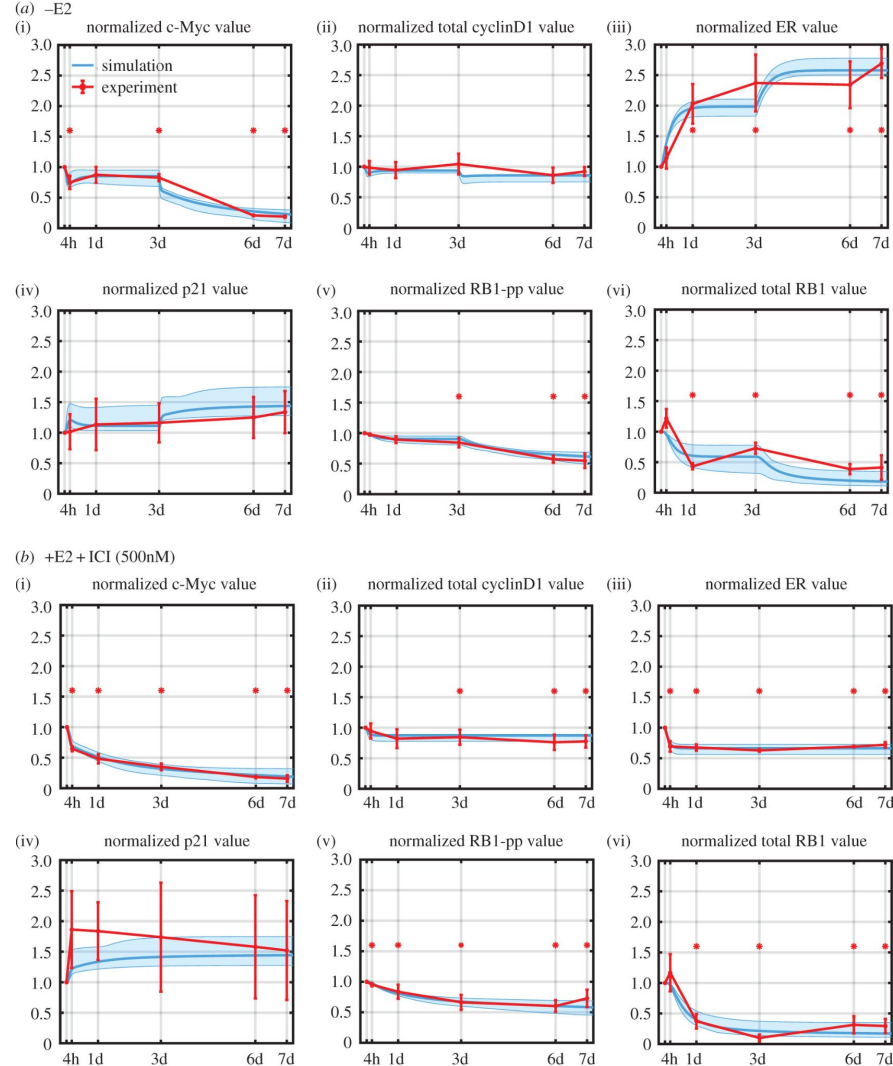
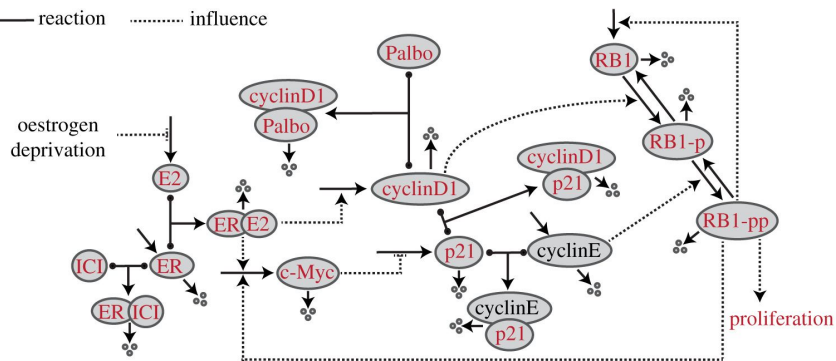
- ODE solver: ode23s
- Initial states and parameters were obtain from the original paper

## Stochastic approach

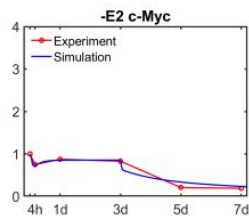
- ODE were converted into a set of reactions
- Deterministic rates converted into stochastic rates
- RSSA

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

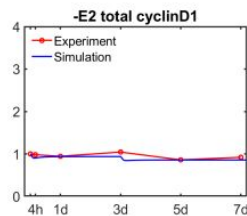
(b) — reaction ..... influence



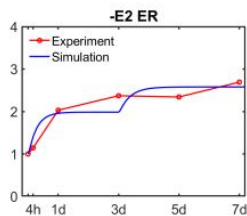
# Our results



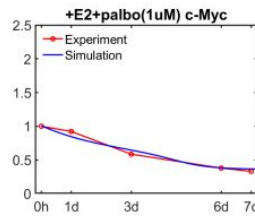
(a) *normalized c-Myc value*



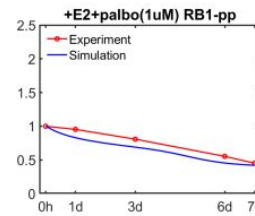
(b) *normalized total cyclinD1 value*



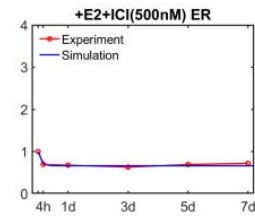
(c) *normalized ER value*



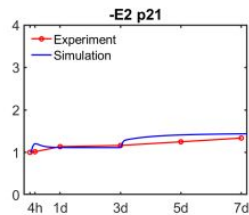
(g) *normalized c-Myc value*



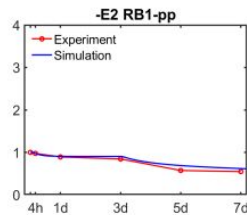
(h) *normalized total RB1-pp value*



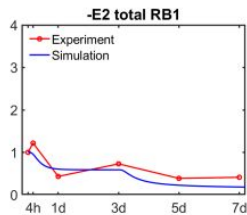
(i) *normalized ER value*



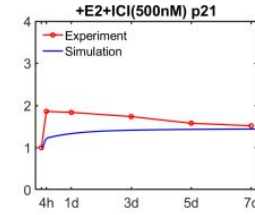
(d) *normalized p21 value*



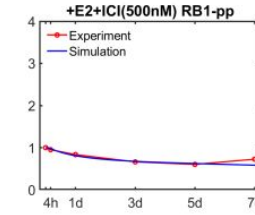
(e) *normalized RB1-pp value*



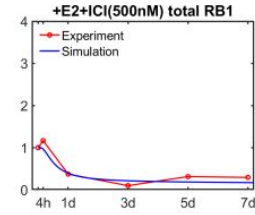
(f) *normalized total RB1 value*



(j) *normalized p21 value*



(k) *normalized RB1-pp value*



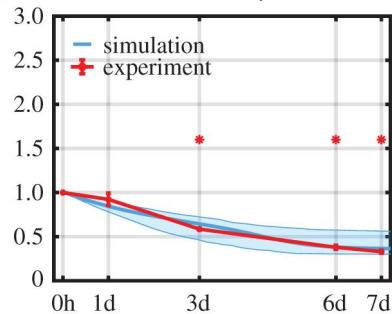
(l) *normalized total RB1 value*



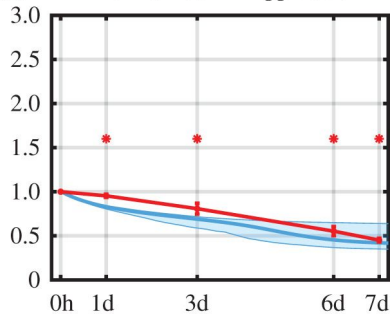
## Results 2: Adding a new drug to the model requires limited new data

+E2 + palbo (1  $\mu$ M)

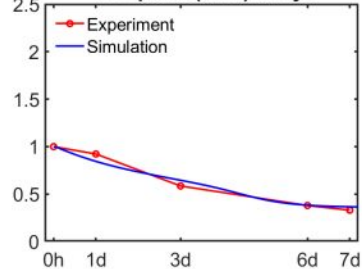
(a) normalized c-Myc value



(b) normalized RB1-pp value

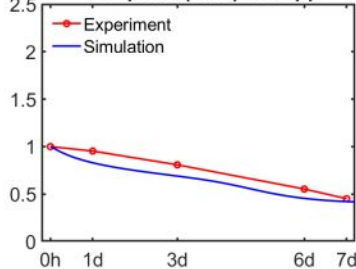


+E2+palbo(1uM) c-Myc

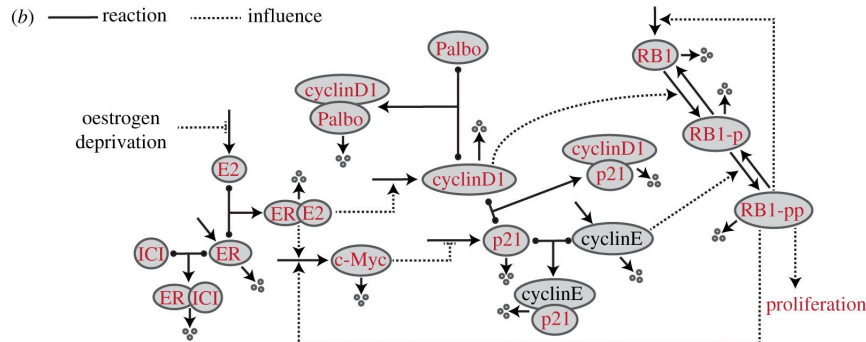


(a) normalized c-Myc value

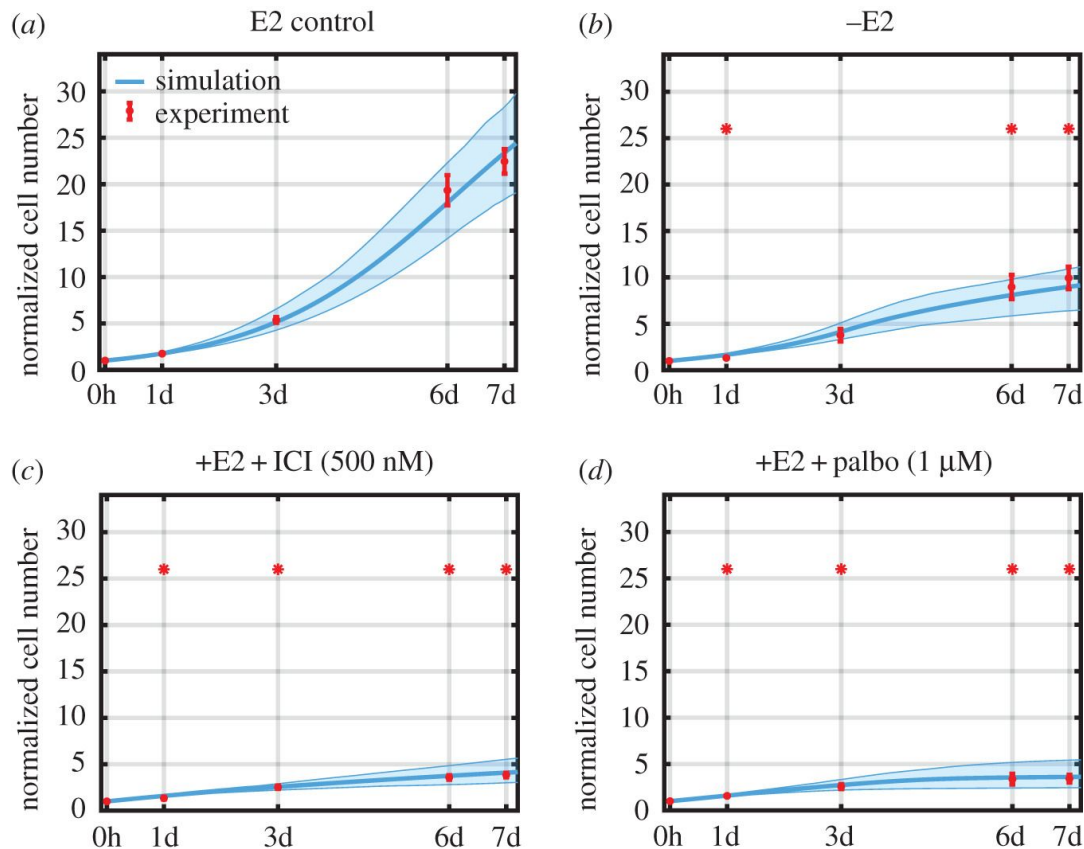
+E2+palbo(1uM) RB1-pp



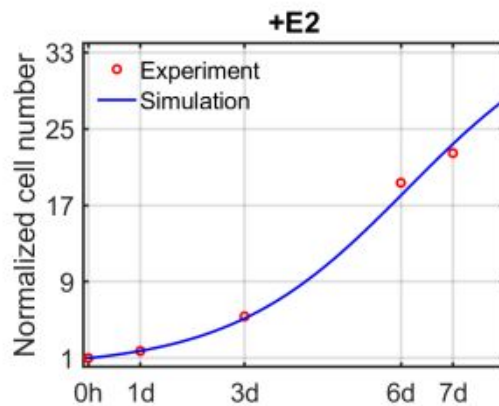
(b) normalized total RB1-pp value



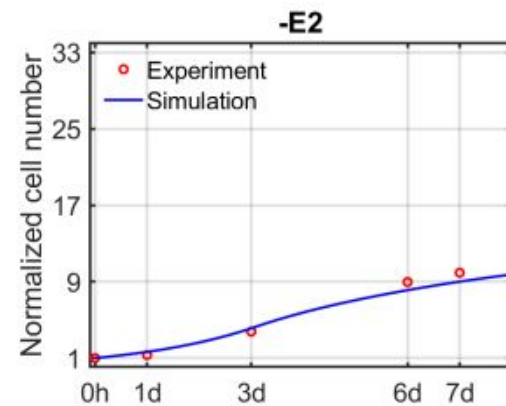
# Results 3: The proliferation results can be explained by the RB1-pp level



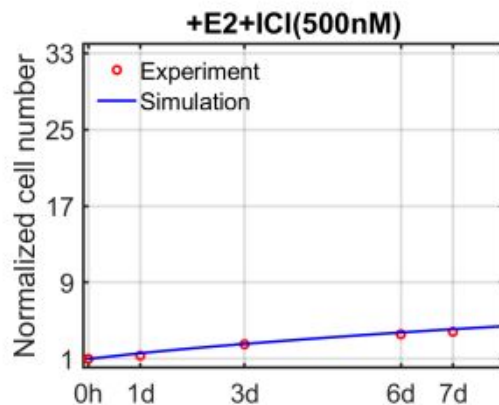
# Our results:



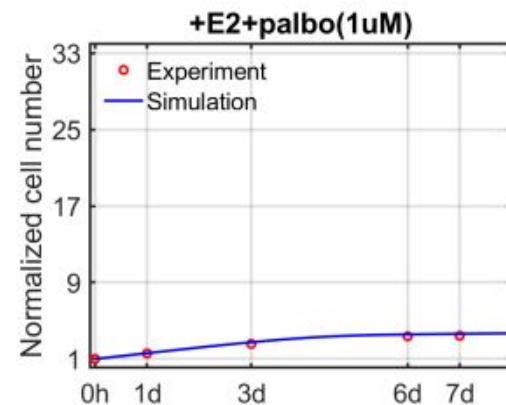
(a) *E2 control*



(b) *-E2*



(c) *+E2+ICI*



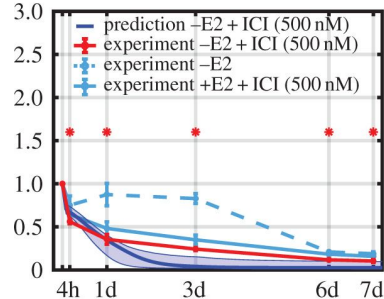
(d) *+E2+palbo*

# Results 4:

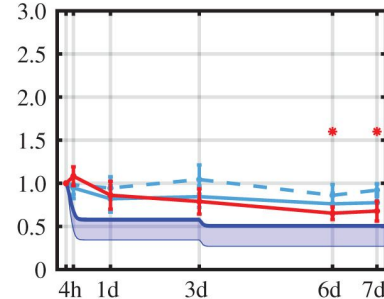
The model can predict the effect of combination treatment

-E2 + ICI (500 nM)

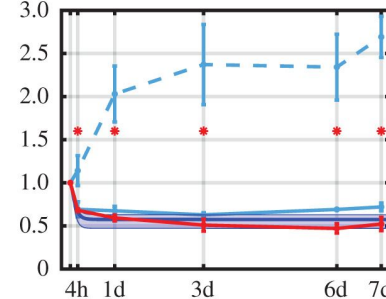
(a) normalized c-Myc value



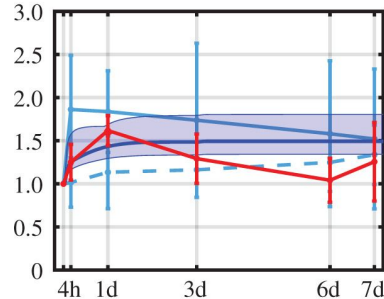
(b) normalized total cyclinD1 value



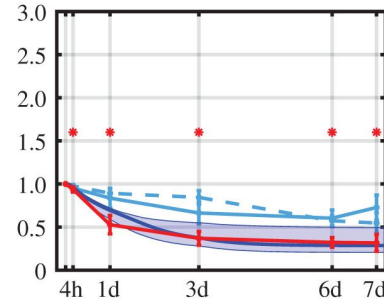
(c) normalized ER value



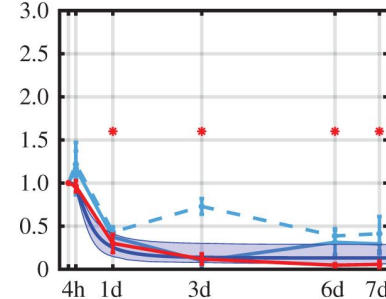
(d) normalized p21 value



(e) normalized RB1-pp value



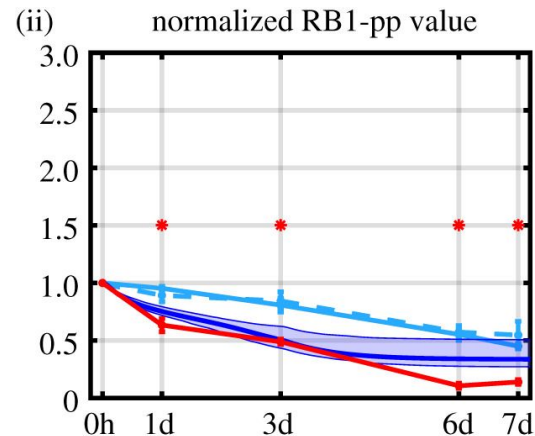
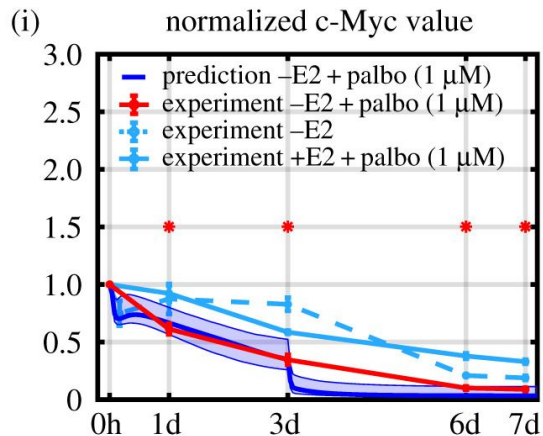
(f) normalized total RB1 value



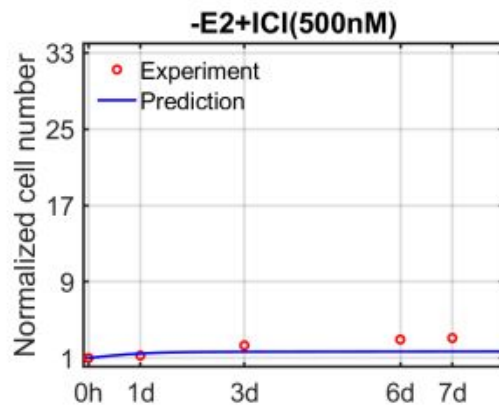
## Results 4:

The model can predict the effect of combination treatment

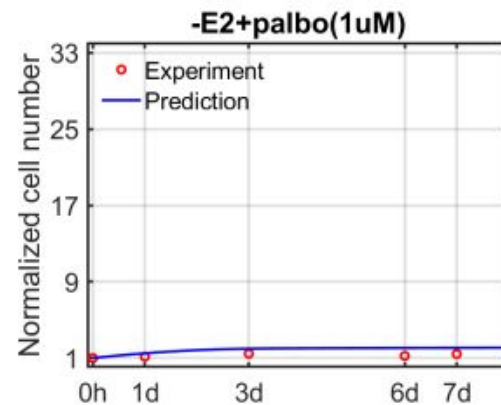
(a) -E2 + palbo (1  $\mu$ M)



**Our result:**  
On proliferation  
levels with  
combination of  
therapies

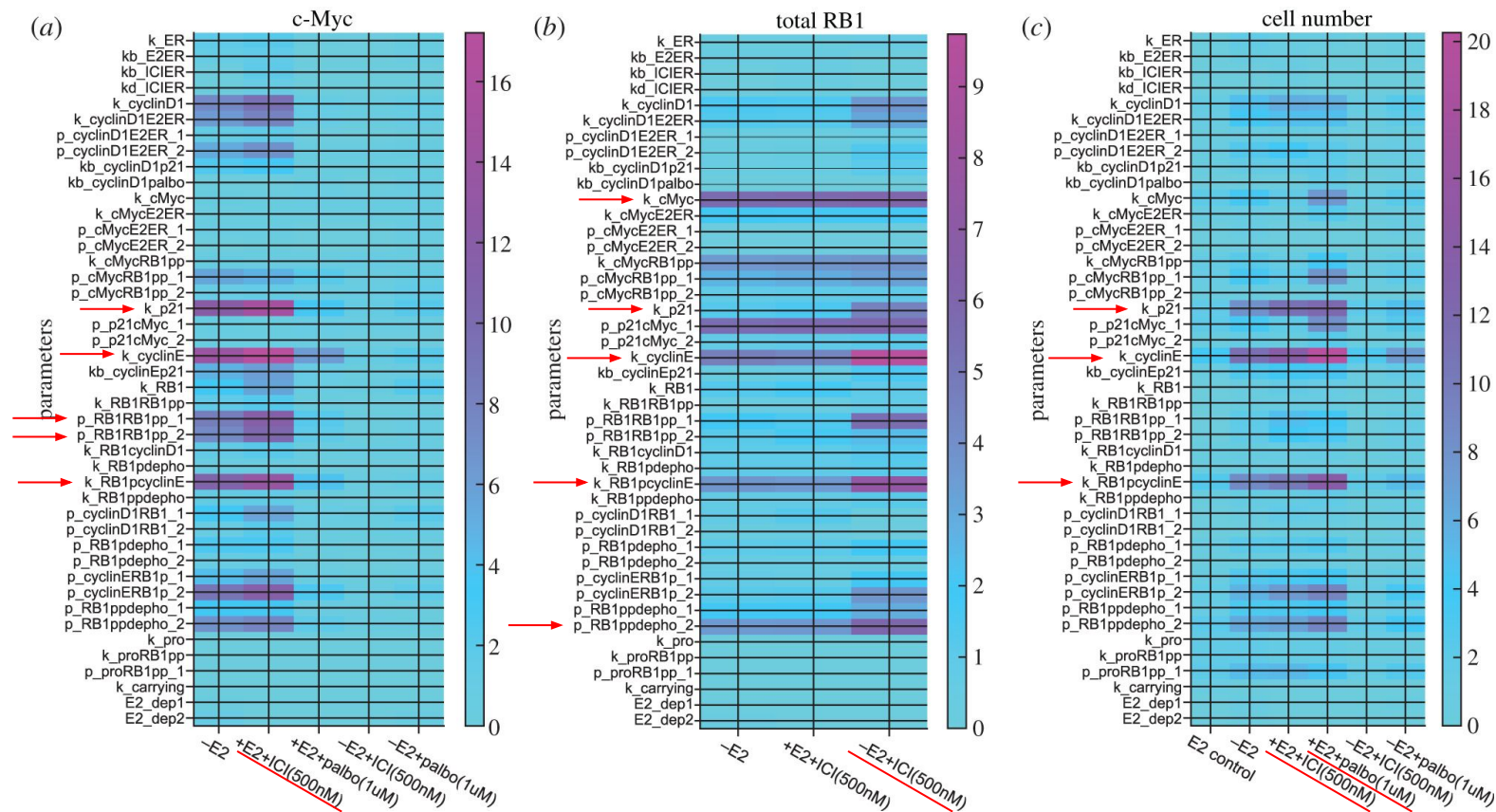


(a)  $-E2+ICI$



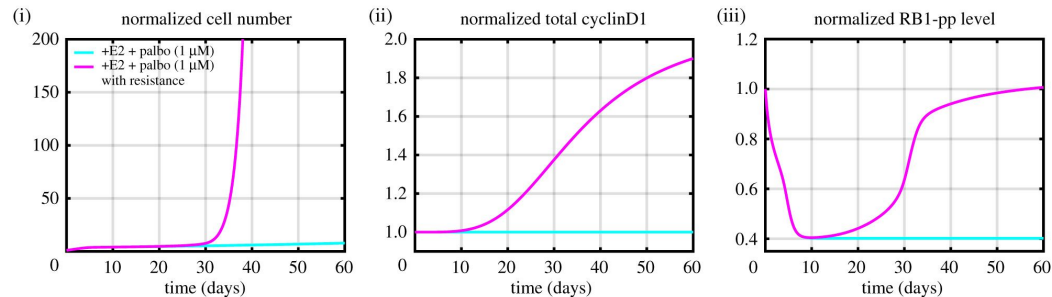
(b)  $-E2+Palbo$

# Results 5: Local sensitivity analysis of protein levels and proliferation

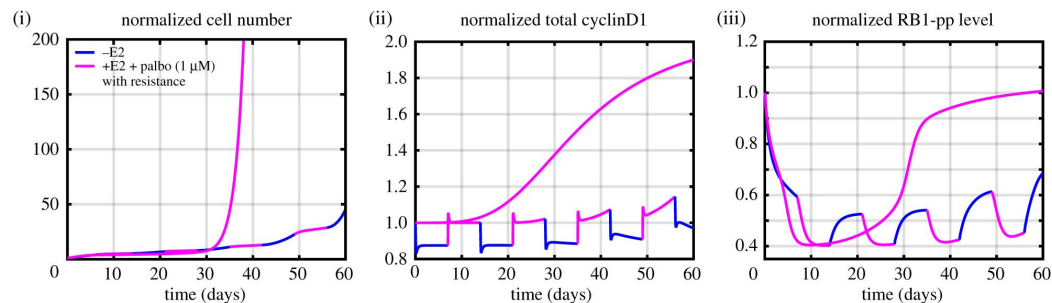


# Results 6: The model can be used to explore the effect of sequential therapies

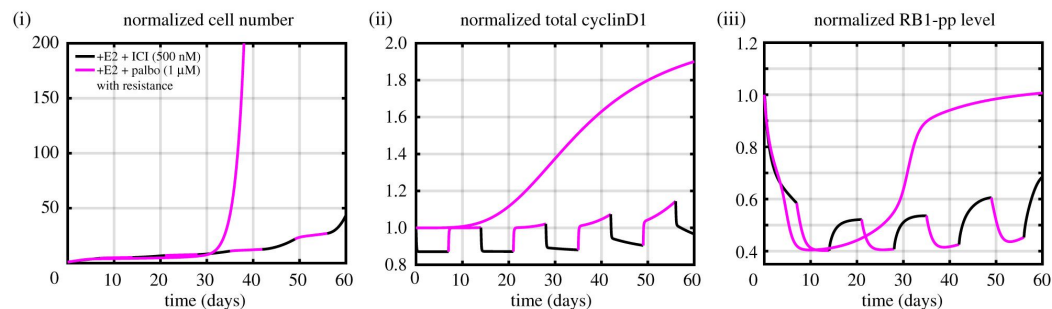
(a) +E2 + palbo (1  $\mu$ M) versus +E2 + palbo (1  $\mu$ M) with resistance



(b) alternation: -E2 7 days  $\rightarrow$  +E2 + palbo (1  $\mu$ M) with resistance 7 days



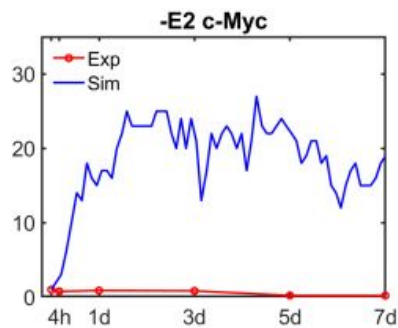
(c) alternation: +E2 + ICI (500 nM) 7 days  $\rightarrow$  +E2 + palbo (1  $\mu$ M) with resistance 7 days



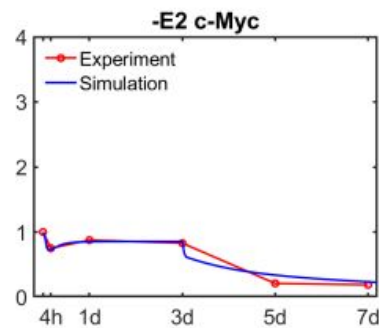


# Discussion:

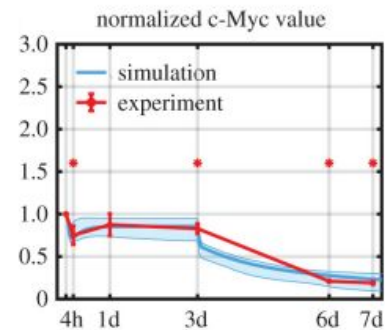
- Mathematical model is able to describe the aberrant ER signaling that takes place in these cancer cells
- The model was found to be predictive for cell proliferation and protein levels regulating ER signaling, both in terms of monotherapies and combined therapies
- Make assumptions on the predictive ability of the model regarding the utilization of cycle therapies in the context of resistance onset



(a) *Stochastic simulation*

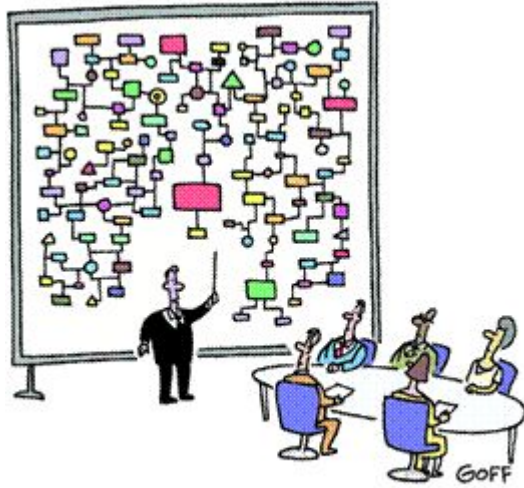


(b) *Deterministic simulation*



(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.



"And that's why we need a computer."

# Thank you!

