Optimizing Time Delay for Cell Cycle Drug Response Model

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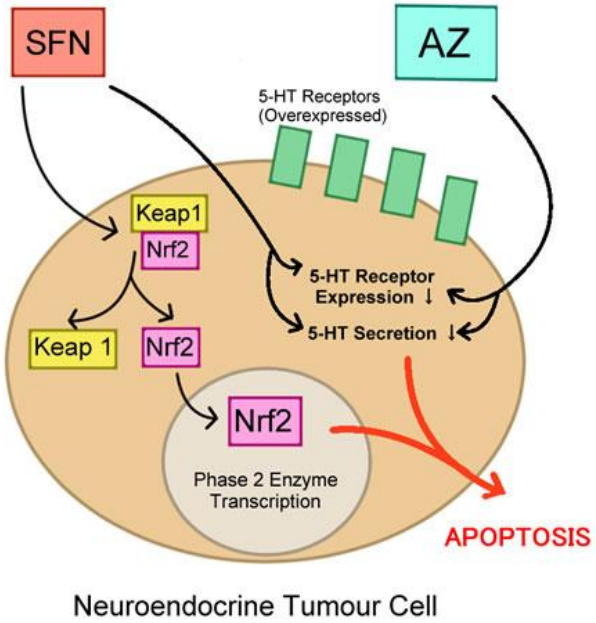
Meyer Lab (185 Project)

Identifying effective drug combinations

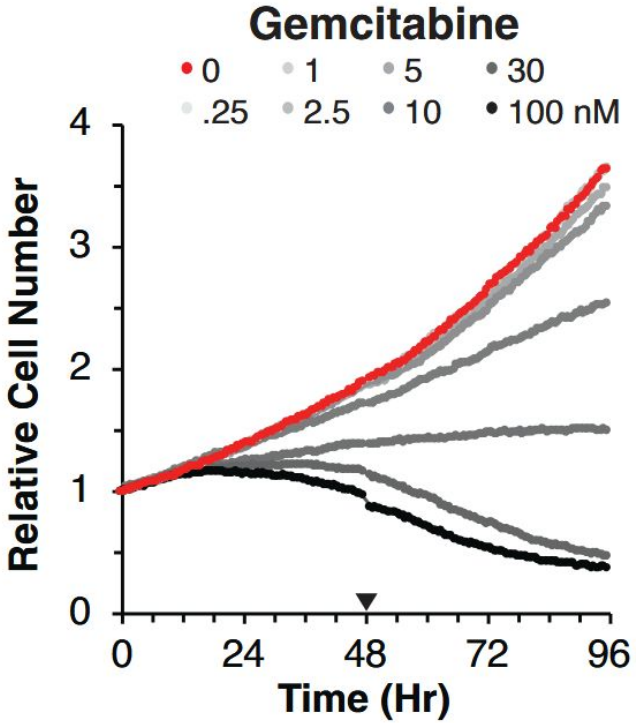
- Combinations can target key cancer pathways in additive way
- Identification is difficult due to complexity of pathways
- Meyer Lab approaches this with cell population modeling



Mokhtari RB et al. Oncotarget. 2017

Meyer Lab's cell cycle model

- Predicts cell population over time for insight into drug effects
- Ordinary Differential Equations (ODE)
- Explicit progression and death rates help with predictions for combinations
- "Linear Chain Trick": Time delay simulated with sub-phases



Gross SM et al. Nature Communications. 2023

G1

$$\frac{dG_{11,1}}{dt} = +2\beta_4 G_{24,5} - (\alpha_1 + \gamma_{1,1}) G_{11,1}$$

(sub-phases)

$$\frac{dG_{1k,1}}{dt} = +\alpha_{k-1} G_{1k-1,2} - (\alpha_k + \gamma_{1,k}) G_{1k,1}$$

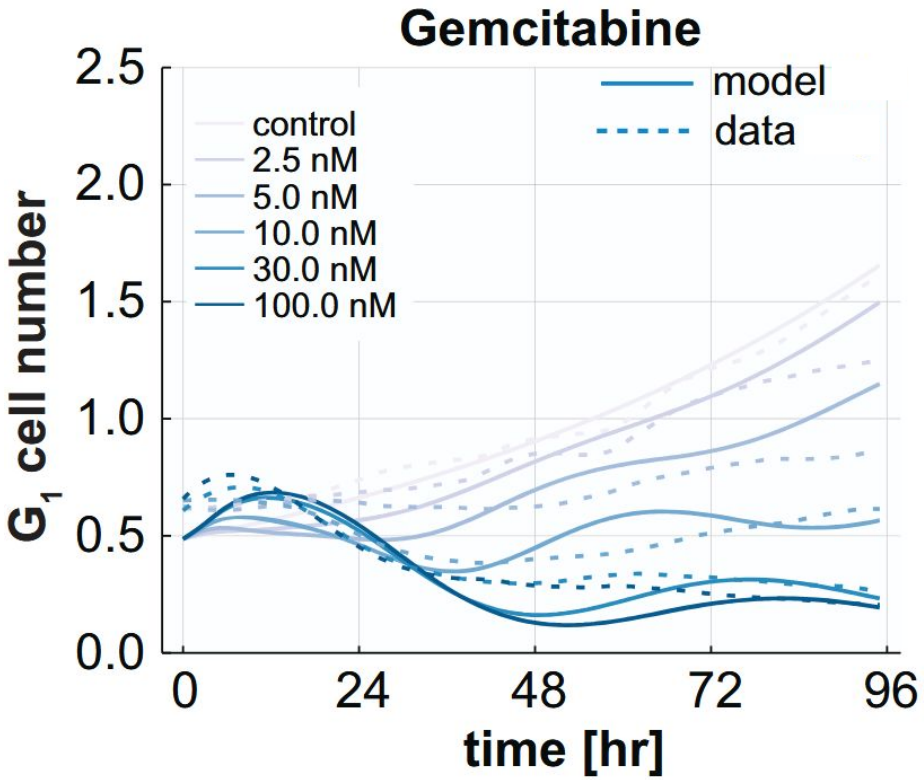
$$\frac{dG_{1k,2}}{dt} = +\alpha_k G_{1k,1} - (\alpha_k + \gamma_{1,k}) G_{1k,2} \; 1 \le k \le 4$$

S-G2

$$\frac{dG_{21,1}}{dt} = +\alpha_4 G_{14,2} - (\beta_1 + \gamma_{2,1}) G_{21,1}$$

$$\frac{dG_{2i,j}}{dt} = +\beta_i G_{2i,j-1} - (\beta_i + \gamma_{2,i}) G_{2i,j} \; 2 \le j \le 5 \; , 1 \le i \le 4$$

Example of model prediction vs experimental data



Gross SM et al. Nature Communications. 2023

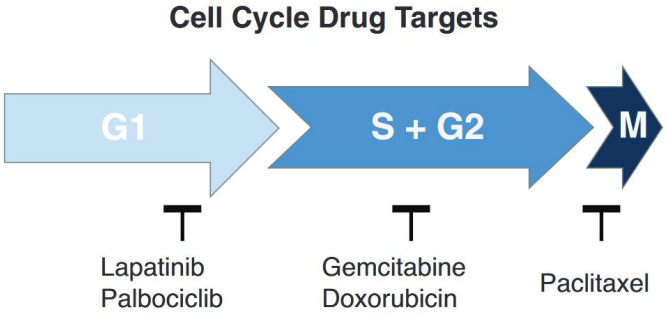
Pros and cons of original model

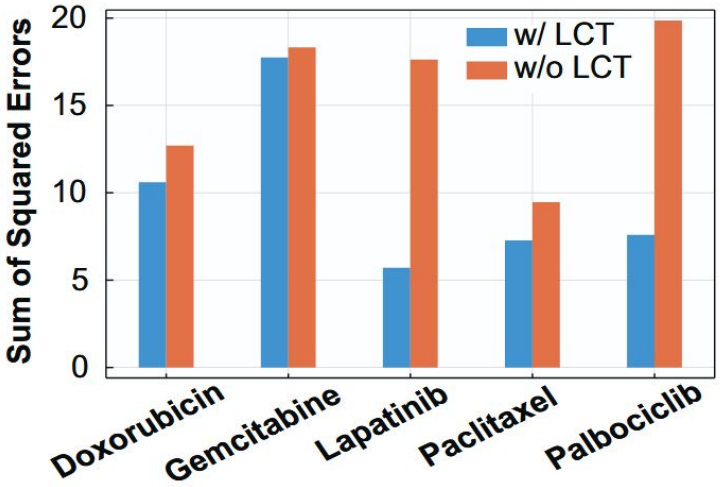
Pros:

- Time delay (LCT) reduces error across all drugs

Cons:

- Error remains high for S-G2 drugs
- High error can negatively affect treatment predictions





Gross SM et al. Nature Communications. 2023

Hypothesis: Unoptimized time delay might cause high error

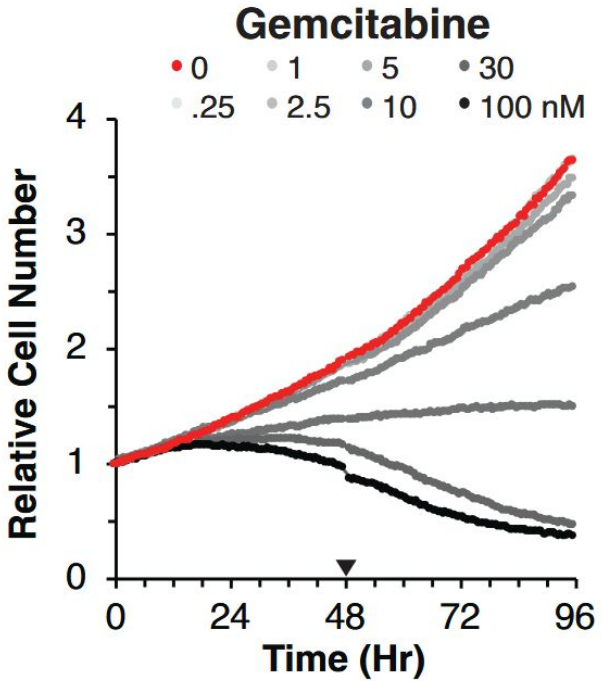
- Number of sub-phases kept the same across all drugs
- Current number of sub-phases might not be optimal for S-G2 drugs

Goal: Optimizing Time Delay

Can time delay from the number of sub-phases be adjusted so the model will have lower error for S-G2 drugs?

Experimental cell data

- Tracked cell population over 96 hours
- Varied concentrations across different drugs
- Focusing on three drugs:
  - Lapatinib (G1 drug)
  - Doxorubicin, Gemcitabine (S-G2 drugs)



Gross SM et al. Nature Communications. 2023

Baseline ODE model setup

- Phases: G1 and S-G2

- G1 = 8 sub-phases
- G2 = 20 sub-phases

- α, β = progression rate
- γ_1, γ_2 = death rate

$$\frac{dG_{11,1}}{dt} = +2\beta_4 G_{24,5} - (\alpha_1 + \gamma_{1,1}) G_{11,1}$$

$$\frac{dG_{1k,1}}{dt} = +\alpha_{k-1} G_{1k-1,2} - (\alpha_k + \gamma_{1,k}) G_{1k,1}$$

$$\frac{dG_{1k,2}}{dt} = +\alpha_k G_{1k,1} - (\alpha_k + \gamma_{1,k}) G_{1k,2} \; 1 \le k \le 4$$

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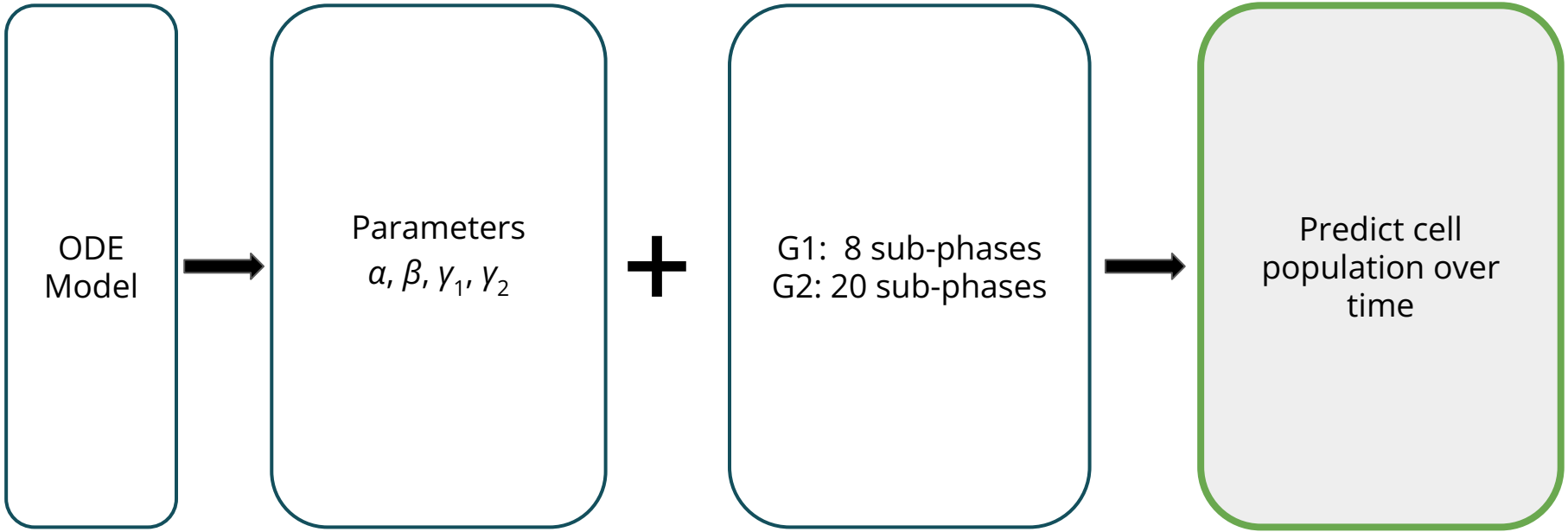
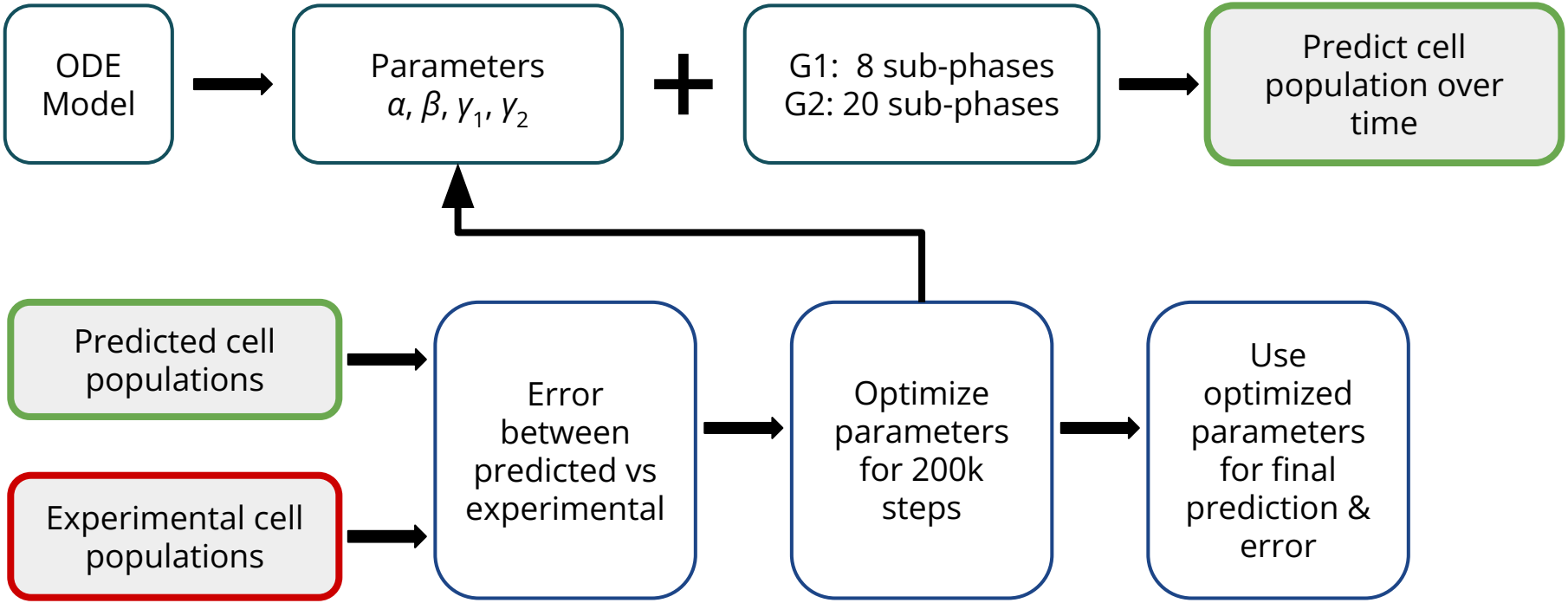
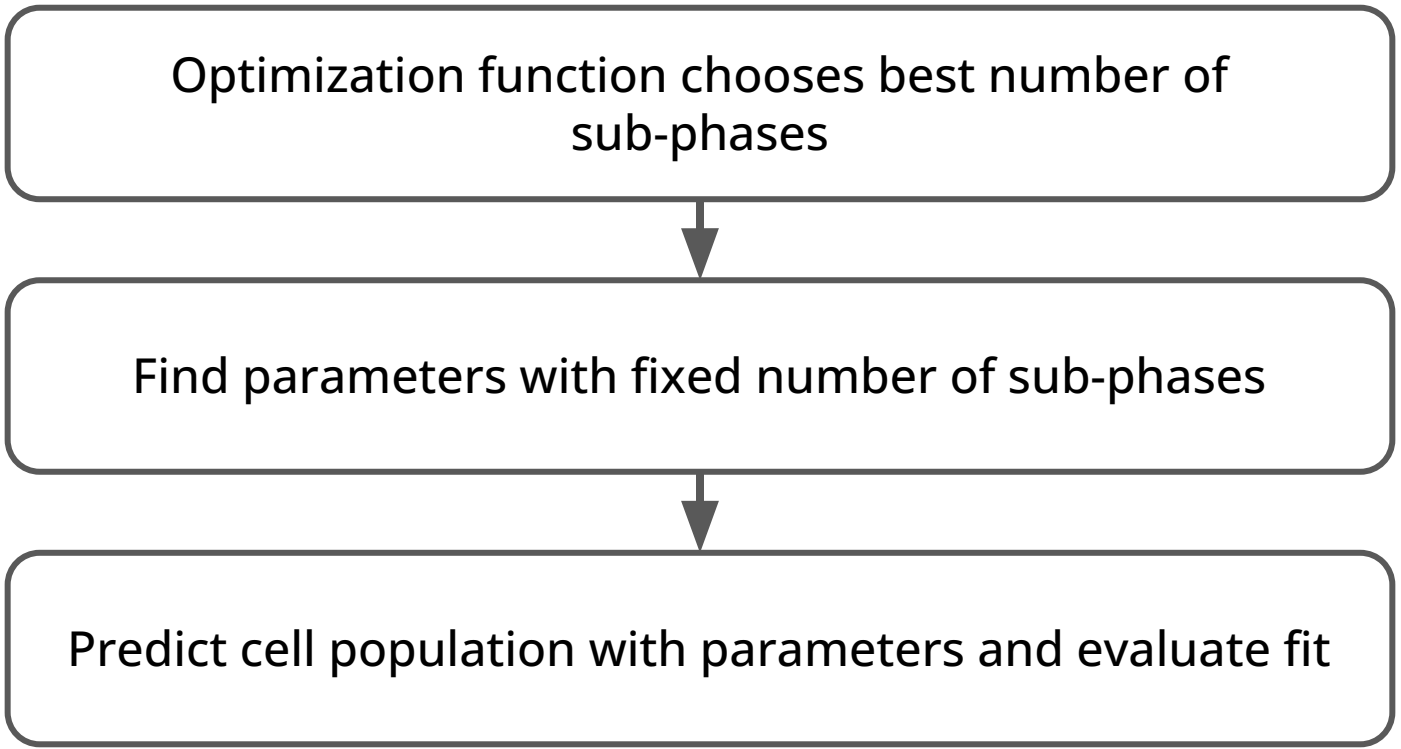
Baseline ODE predictions



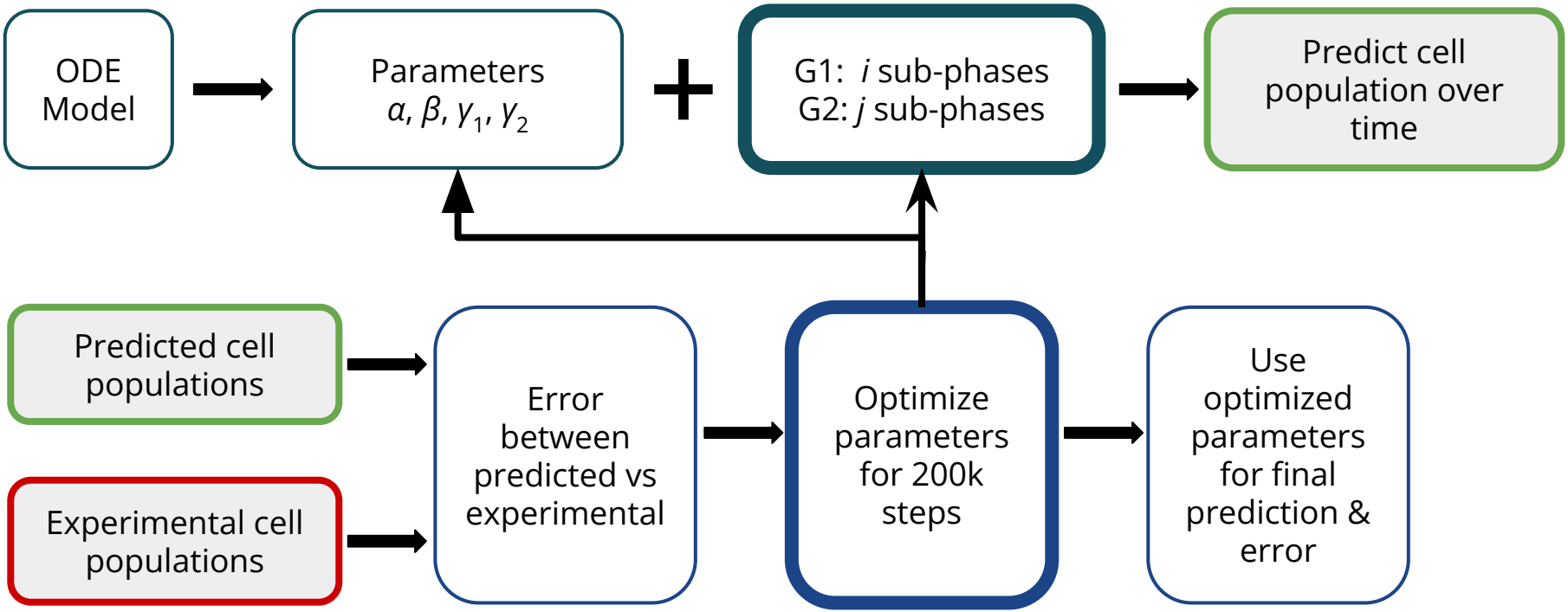
Baseline ODE fitting: minimizing error



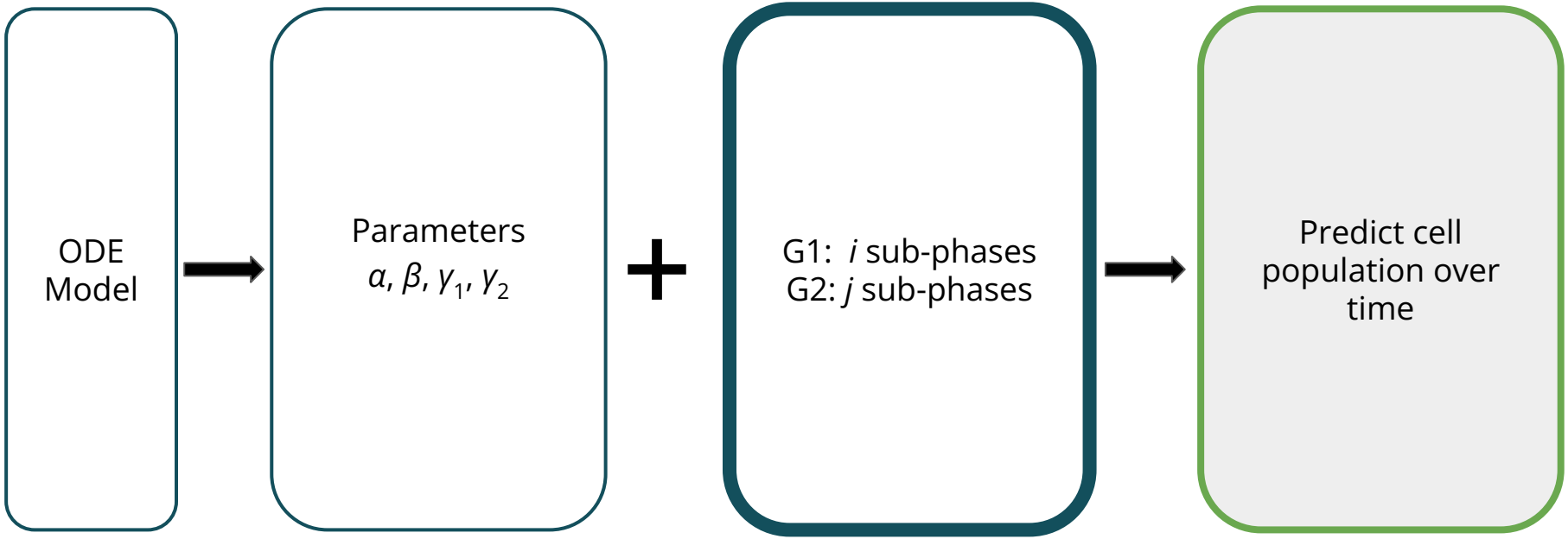
Experiment Pipeline



Altered ODE pipeline: Optimizing sub-phases

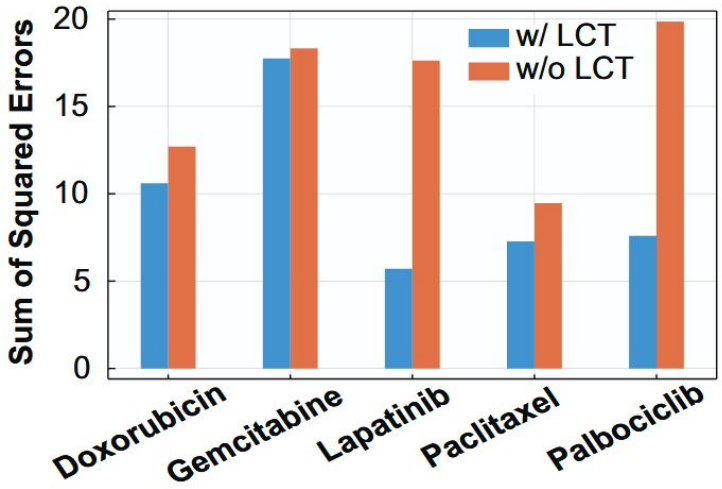


Altered ODE pipeline: Predictions with new sub-phases

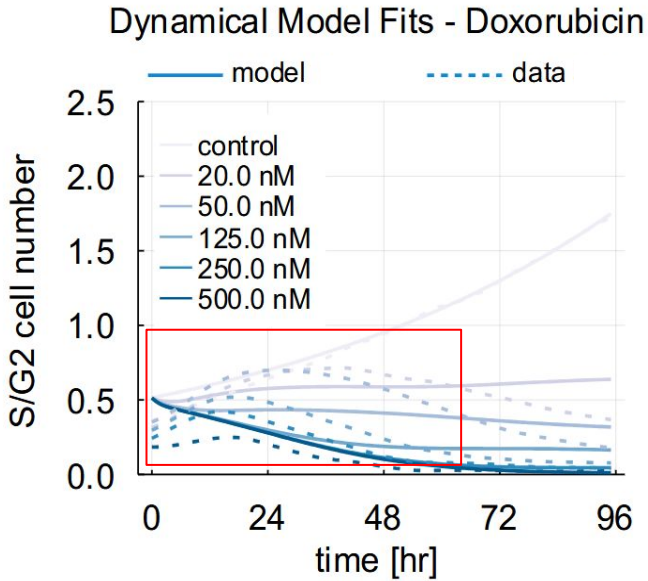


Evaluating fit

- Compare errors of optimized model predictions to original



- Compare qualitative fit e.g. similar oscillations



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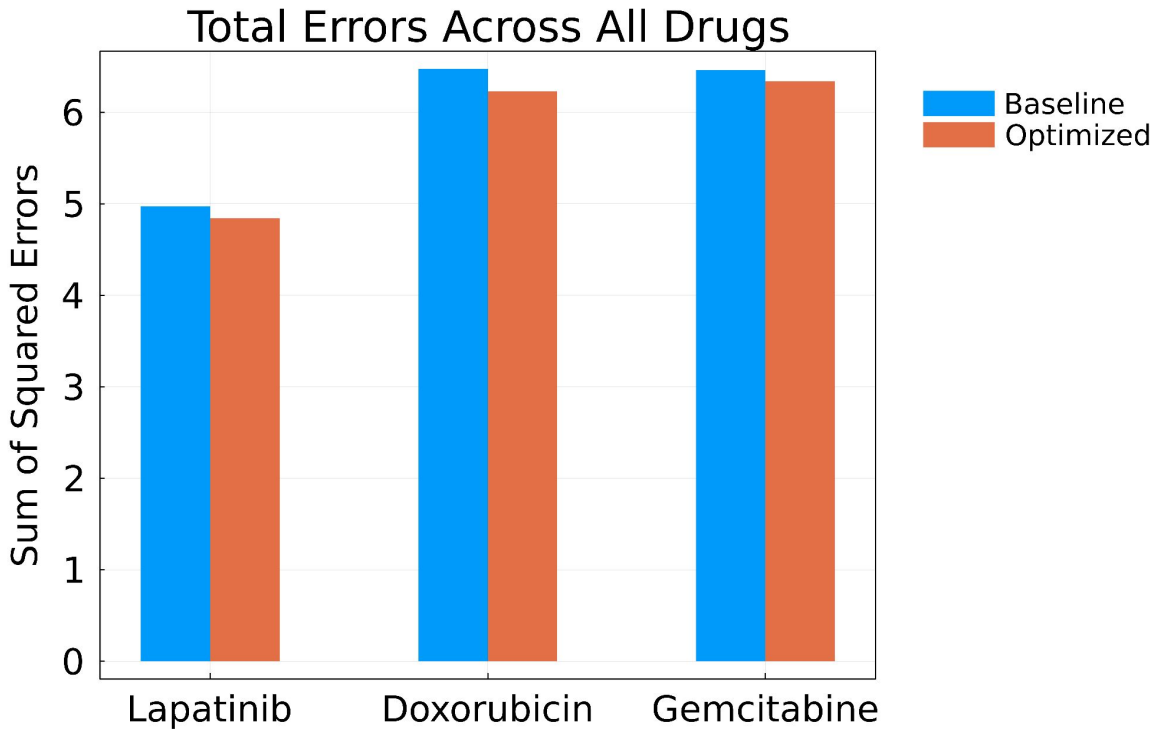
Results: Changes to sub-phases

Drug	G1 sub-phases	S-G2 sub-phases
Baseline	8	20
Lapatinib (G1)	**4**	20
Doxorubicin (S-G2)	**4**	**28**
Gemcitabine (S-G2)	**4**	**24**

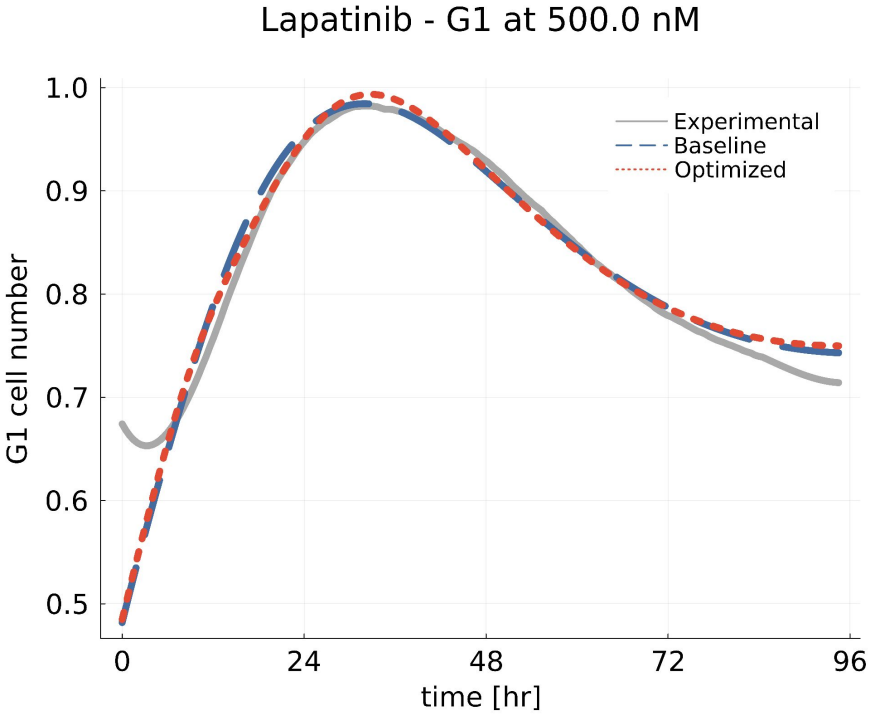
- Changes to sub-phases support hypothesis

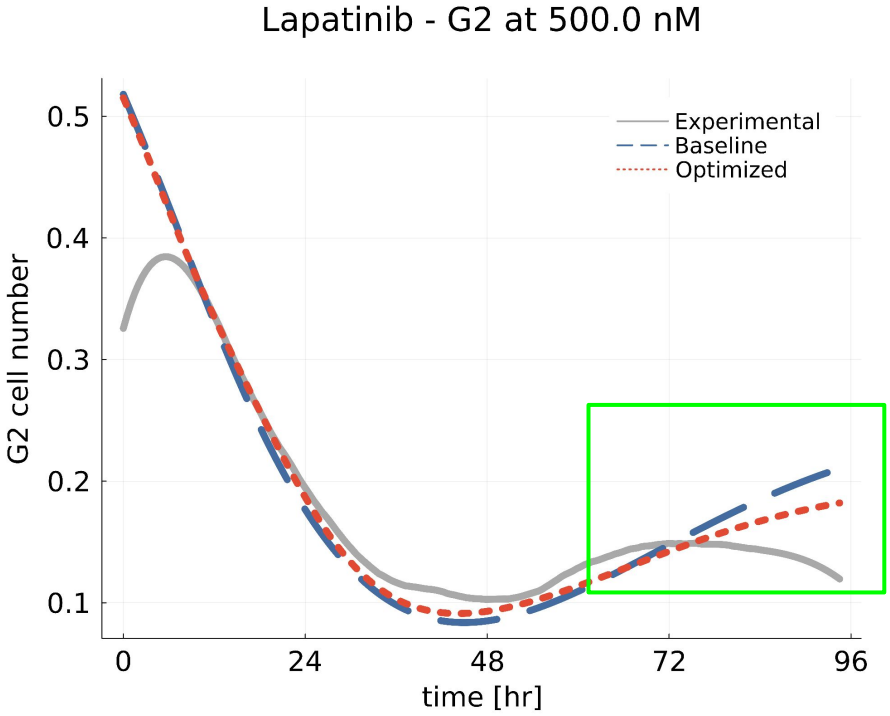
Comparing errors between models

- Improvements across all drugs
- Only minor changes to error due to optimizing sub-phases

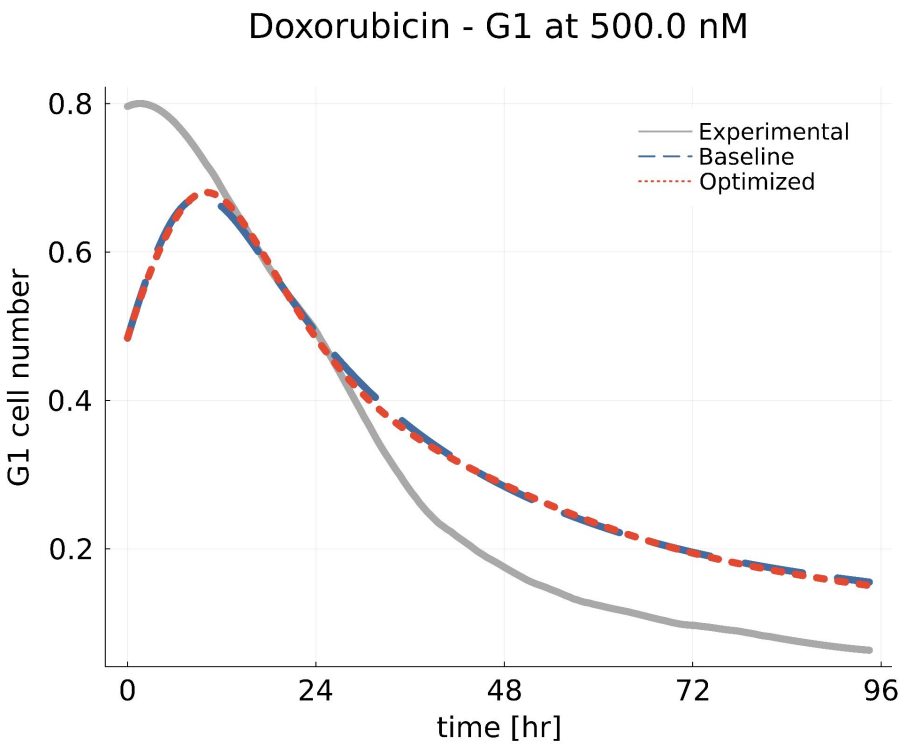


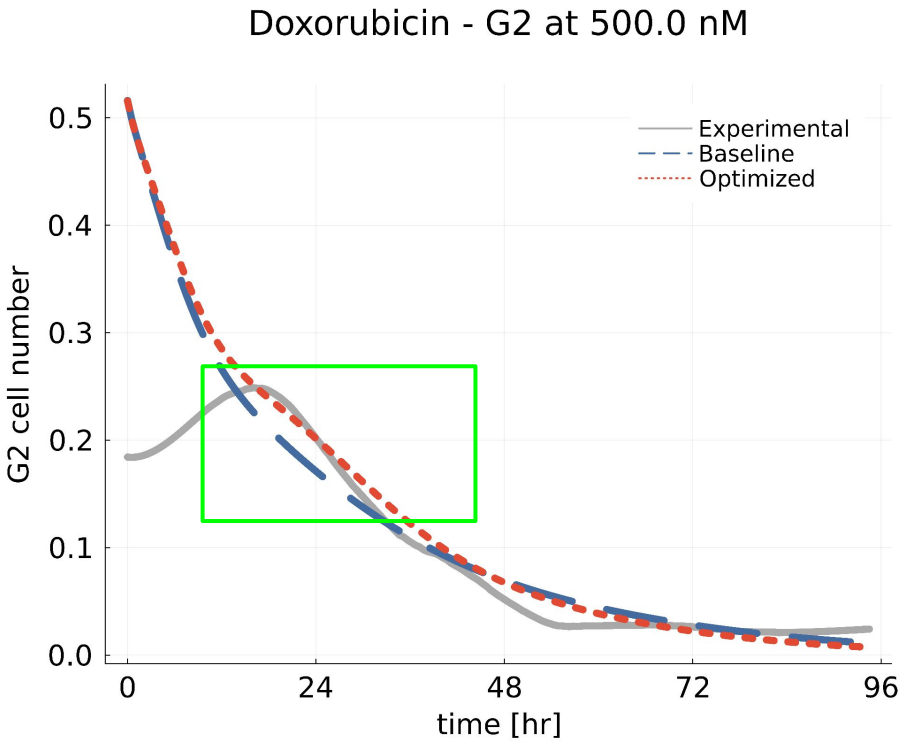
Lapatinib: Qualitative comparisons at highest dosage



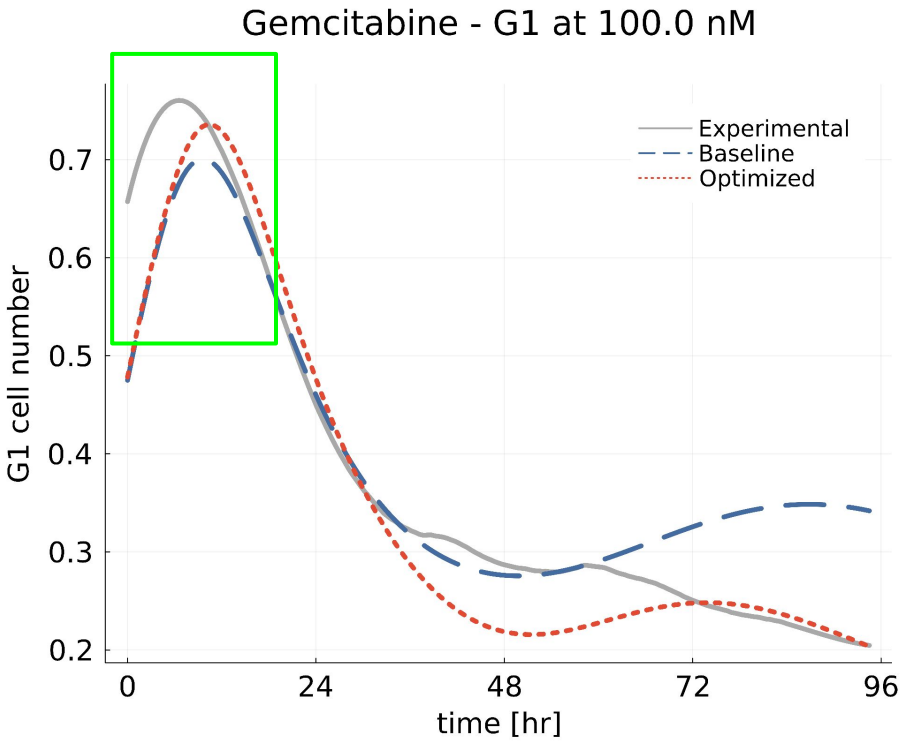


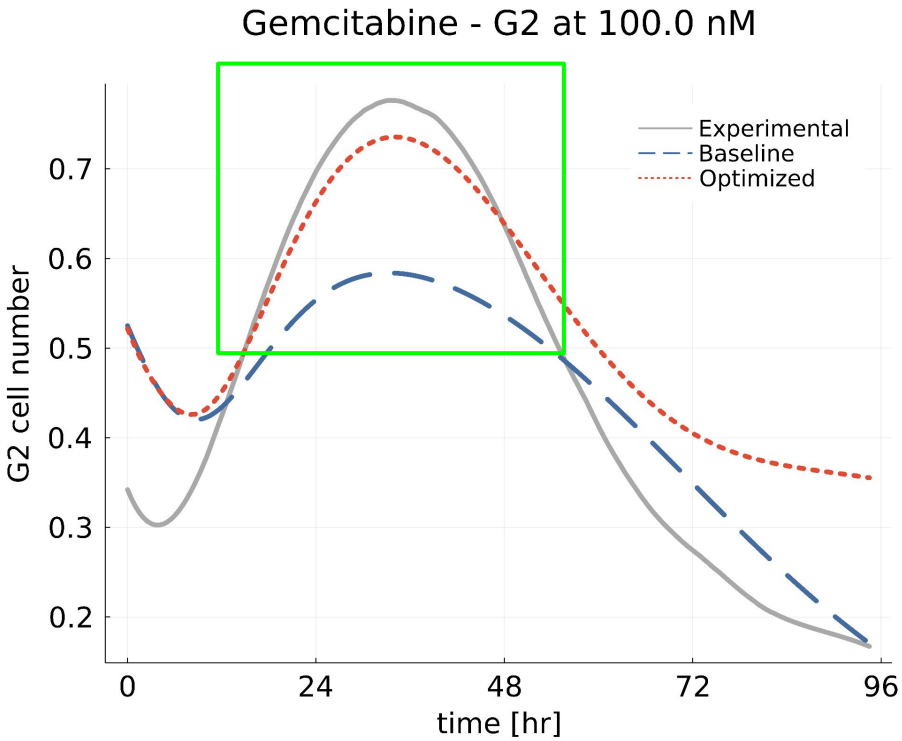
Doxorubicin: Qualitative comparisons at highest dosage





Gemcitabine: Qualitative comparisons at highest dosage





Summary of results

- All three drugs had a minor decrease to their errors
- Lapatinib and Doxorubicin only visually improved slightly
- Gemcitabine seems to visually capture the dynamics much better as well as decreasing error

Conclusion: Improving cancer treatment predictions

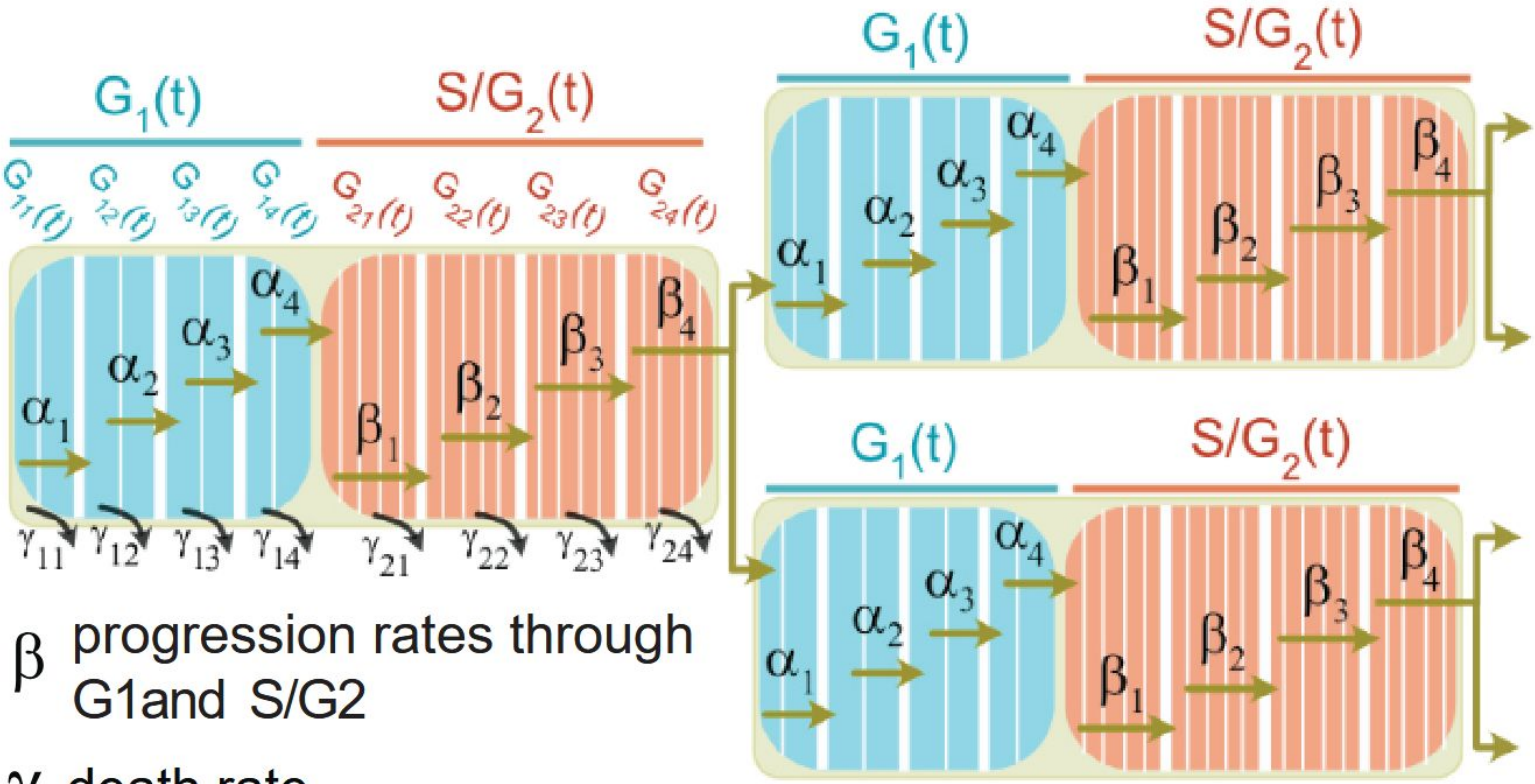
- Changing sub-phases is a simple change that improves the model's ability to capture population dynamics for S-G2 drugs
- Optimized number of sub-phases offers additional insight
- Other aspects of time delay can be an area of improvement for the model
- **Improvements to the model allow for better insights into drug effects, guiding our ability to find effective combinations for cancer**

References

Mokhtari RB et al. Combination therapy in combating cancer. Oncotarget. 2017;8(23):38022–38043. https://doi.org/10.18632/oncotarget.16723

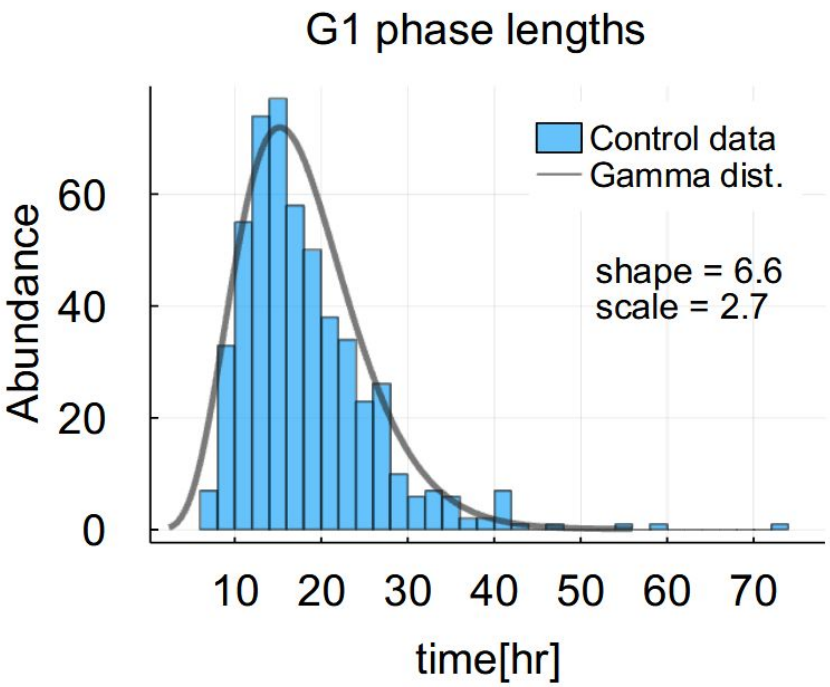
Gross SM et al. Analysis and modeling of cancer drug responses using cell cycle phase-specific rate effects. Nature Communications. 2023;14(1):3450. https://doi.org/10.1038/s41467-023-39122-z

LCT model of phase progression



α β progression rates through G1and S/G2

γ death rate


G1 phase lengths
Control data
Gamma dist.
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Abundance
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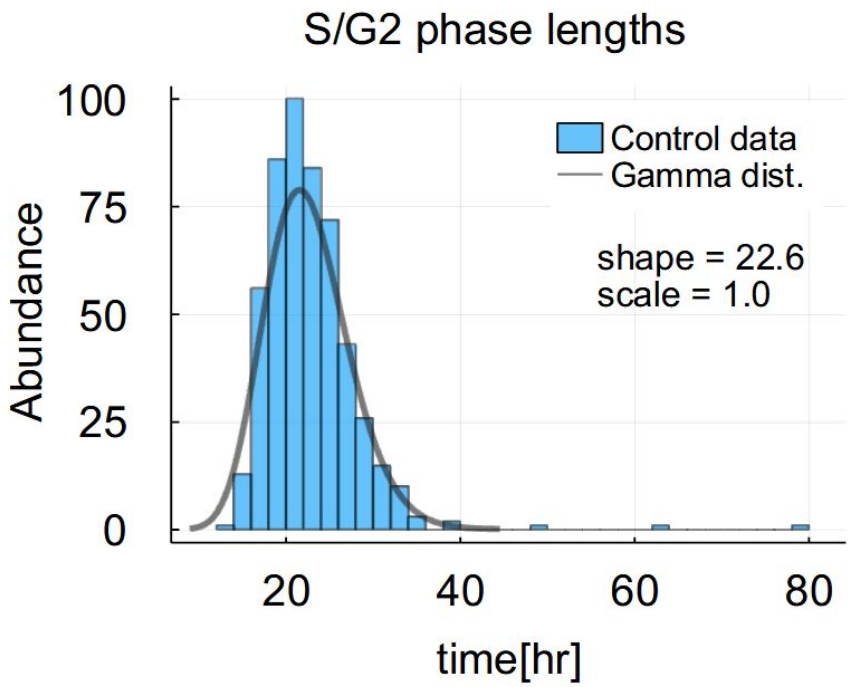
20
40
60
10
20
30
40
50
60
70
time[hr]


S/G2 phase lengths
Control data
Gamma dist.
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scale = 1.0
Abundance
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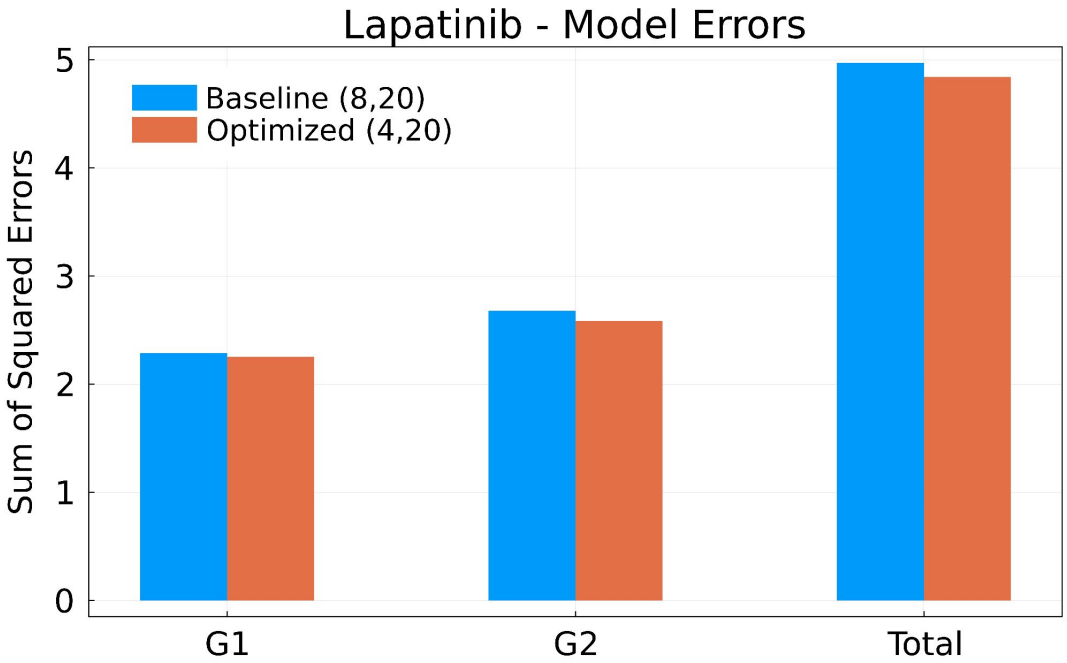
25
50
75
100
20
40
60
80
time[hr]

Overall errors across the three drugs

Drug	Baseline Error	Optimized Error	% Improvement
Lapatinib	4.97	4.84	**2.62%**
Doxorubicin	6.47	6.23	**3.80%**
Gemcitabine	6.46	6.34	**1.90%**

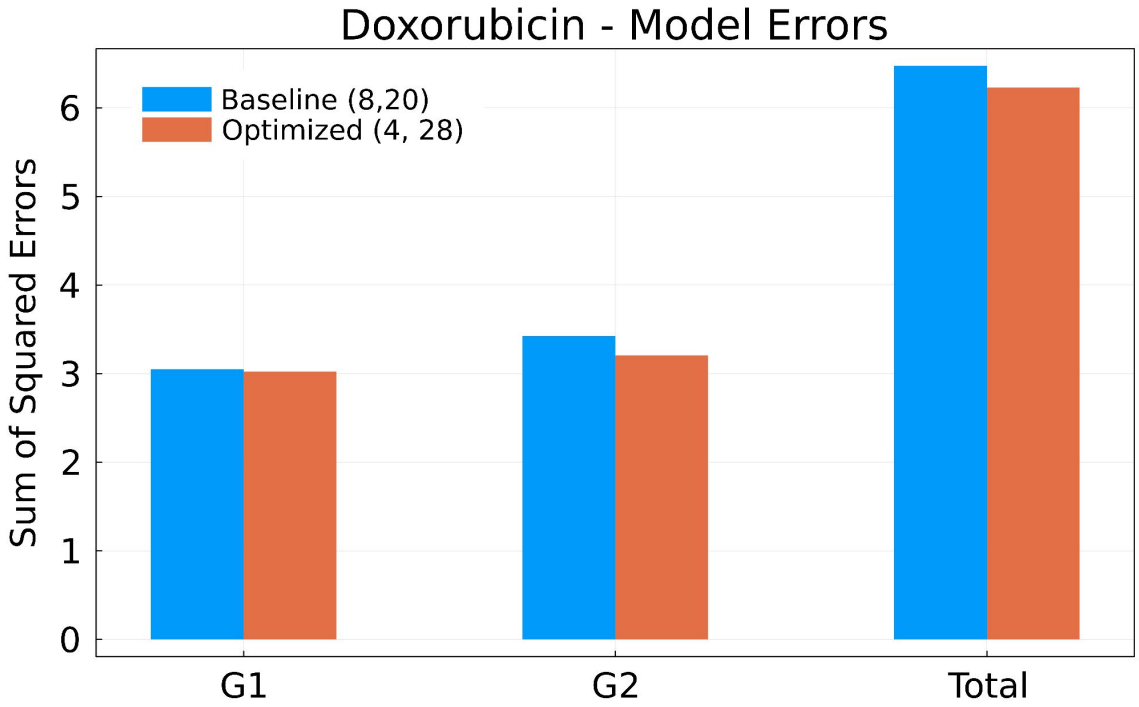
Lapatinib: Error

- **Best model:**
  G1 = 4, G2 = 20
- Original SSE: 4.97
- Best SSE: 4.84
- **Improvement: 2.62%**



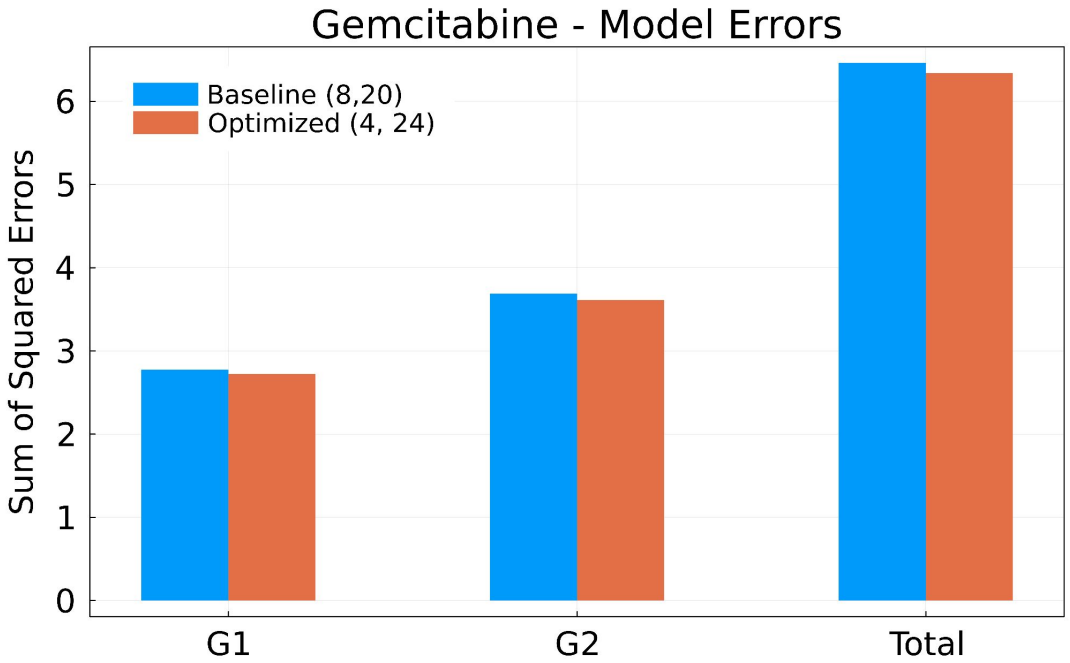
Doxorubicin: Error

- **Best model:**
  G1 = 4, G2 = 28
- Original SSE: 6.47
- Best SSE: 6.23
- **Improvement: 3.80%**



Gemcitabine: Error

- **Best model:**
  G1 = 4, G2 = 24
- Original SSE: 6.46
- Best SSE: 6.34
- **Improvement: 1.90%**



Gemcitabine: G2 predictions