Optimization of Time Delay for Cancer Cell Drug Response Model

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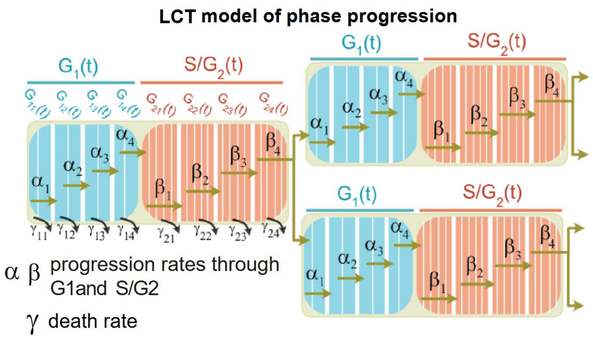
BACKGROUND

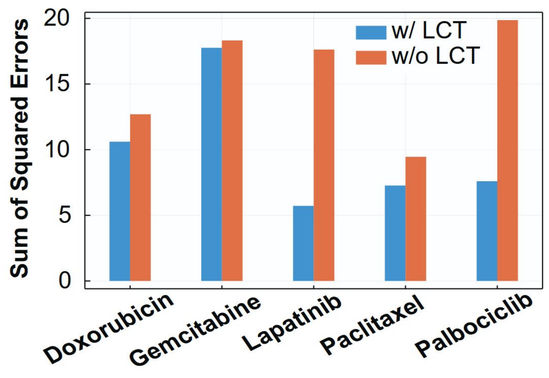
Finding effective drug treatments for cancer can be very effective but also very difficult due to the complexity of cancer cells.

Gross SM et al. (2023) developed a system of ordinary differential equations (ODE) to model cancer cell population responses to give insight into drug effects and aid predictions for treatments.



Linear Chain Trick (LCT): simulating time delay through additional sub-phases within the ODE model

However, this model has difficulty in capturing responses for **doxorubicin** and **gemcitabine**, drugs that affect the S and G2 phases of the cell cycle.



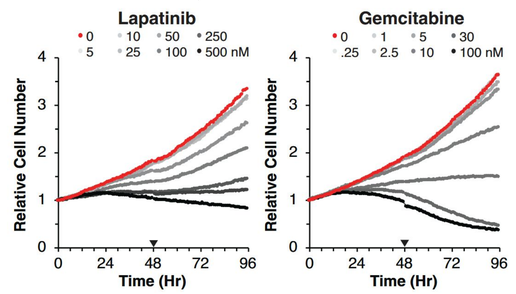
To try to improve the fit to population responses for S-G2 drugs, **time delay was altered by varying and optimizing the number of sub-phases** used by the ODE model.

METHODOLOGY

Materials

Experimental cell data from Gross SM et al. for 3 drugs (Lapatinib, Doxorubicin, Gemcitabine)

- HER2+ AU565 cells, 96 hours and 8 concentrations



Methods

Cost Function: Sum of squared errors between predicted and experimental cell numbers

Parameters: $\alpha, \beta, \gamma_1, \gamma_2, i, j$

1. Using BlackBoxOptim.jl package in Julia, **optimize both parameters and sub-phases** to minimize error
2. **Fix *i* and *j*** to the optimized number of sub-phases and optimize parameters for final predictions
3. Compare **final sum of squared errors** and **qualitative fit** between original and optimized sub-phases

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

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

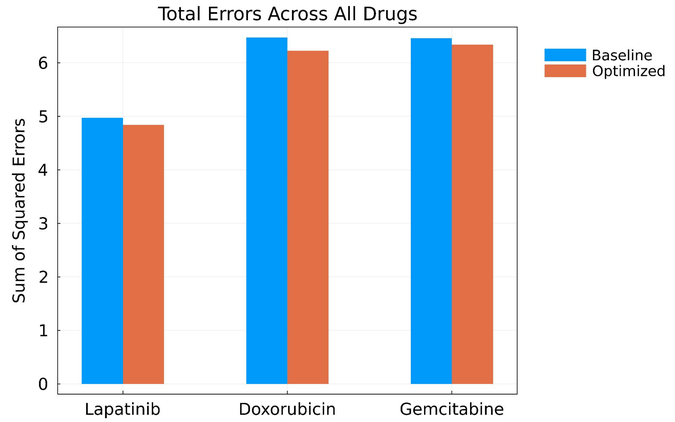
$$1 \le k \le 4, 1 \le i \le ?$$

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

$$\frac{dG_{2k,j}}{dt} = +\beta_k G_{2k,j-1} - (\alpha_j + \gamma_{2,j})G_{2k,j}$$

$$1 \le k \le 4, 1 \le j \le ?$$

RESULTS & DISCUSSION



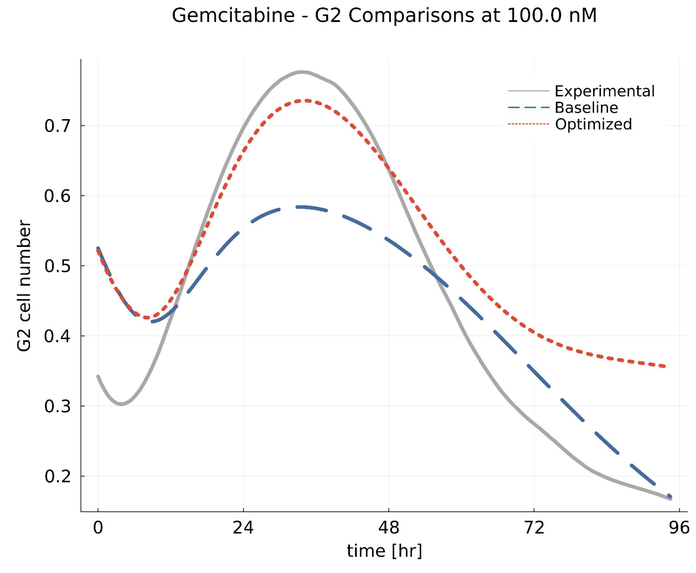


Fig 1. Comparisons of error between original model and optimized model

All optimized models had improvements from the original model.

However, these improvements are all fairly minor as the original model already does a good job with capturing population dynamics.

Lapatinib and doxorubicin both show little improvement in qualitative fit.

Fig 2. Comparison of G2 cell populations in response to highest dosage of gemcitabine

Though lapatinib and doxorubicin show very little qualitative change, gemcitabine shows a big improvement in capturing dynamics.

The oscillatory behavior as the population rises and decreases is much better captured by the optimized model.

These overall results shows promise in the idea that time delay can be altered for better model predictions and could further improve insights and predictions for treatment

CONCLUSION

Although it is a minor improvement, altering time delay through sub-phases is a simple change that improves the model's ability to capture population dynamics.

Further research can look at other bigger changes to time delay within the model, such as the addition of the mitosis phase or separation of S and G2 phases.

REFERENCES

Original model code and data:
Gross SM et al. Analysis and modeling of cancer drug responses using cell cycle phase-specific rate effects. Nature Communications. 2023

https://github.com/meyer-lab/DrugResponseModel.jl