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Assignment #5 - Final Report

Abstract: Since the mean-field ODE model developed by the Meyer lab to predict anti-cancer drug behavior is presented with a predetermined number of subphases for the G_1 and S-G_2 phases, it is imperative that these values are validated as the most optimal subphase values to ensure minimal error in the output. In order to check the optimality of the subphase values for G_1 and S-G_2 and to search for better alternatives, our group tested different combinations of the number of subphases for G_1 and S-G_2 across three different drugs (doxorubicin, gemcitabine, lapatinib) that were tested in the paper. The resulting models were compared to each other by plotting the predicted number of cells in G_1 and S-G_2 over time. The model was also compared to the original data through the calculation of the sum of squared errors for the model and the original data. Our group found that the mean-field ODE model works best when using subphase values of (8, 20) for doxorubicin, (8, 32) for gemcitabine, and (8, 24) for lapatinib where the first value in the combination represents the number of subphases in G_1 and the second value represents the number of subphases in G_2. By using these optimal values, the error rate of the model is lowered. Thus the increased efficacy and generalization of the model will allow for safer suggestions of anti-cancer drug combinations and sequencing.

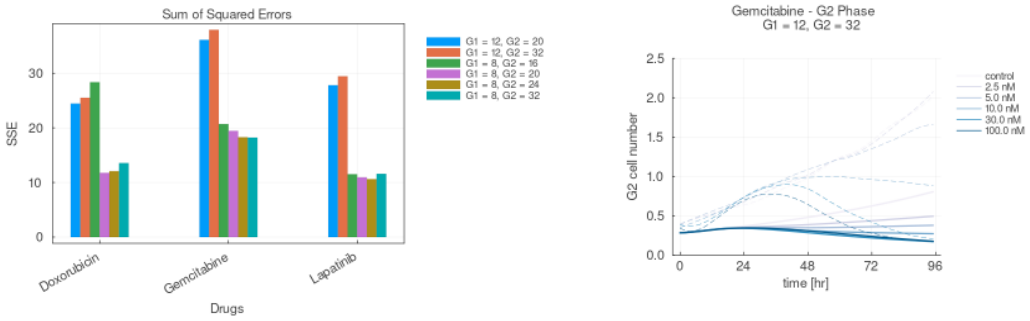
Introduction: Recently, the Meyer lab successfully developed a mean-field ordinary differential equations model to predict the effectiveness of anti-cancer drug combinations by accounting for the dynamic responses of breast cancer cells at each cell cycle phase. The model's success can be attributed to the implementation of a Linear Chain Trick (LCT) technique whose purpose derives from the need to model with consideration to the gamma-distributed dwell times of cells in each cell cycle phase. In order to study the responses of the cells at each phase, this model in particular partitions the cell cycle into two phases, G_1 and S-G_2, while further dividing each phase into subphases of 8 and 20 respectively. The choice to utilize these subphase values in the model is based on the estimation of shape parameters obtained from the gamma distribution measurements of the untreated control cells. As a fundamentally set value in the model, the choice of subphase values is of interest for our study as it is imperative to use the most optimal subphase values to obtain the most accurate representation of combined anti-cancer drug effectiveness. Thus we ask the question: what are the optimal G_1 and S-G_2 sub-phases that should be used to lower the model's error rate?

Methods: In order to predict the number of cells in the G_1 and G_2 phases of the cell cycle, researchers at the Meyer Lab used an ODE model. Thus, we mainly focused on the 'ODEmodel' file. In this file, it is defined that the number of subphases in G_1 is 8 and the number of subphases in S-G_2 is 20 and a transition matrix is created using these dimensions. To look for the number of optimal subphases for G_1 and S-G_2, we tested many values in place of these originally set values to optimize the model. We tested out five combinations of subphases across three of the drugs used in the original paper. The combinations of G_1 and S-G_2 subphases used were (12, 20), (12, 32), (8, 16), (8,24), and (8, 32). The three drugs that we tested the model with are doxorubicin, gemcitabine, and lapatinib.

Using these combinations, we edited the transition matrix to contain different dimensions to correspond with the changed number of subphases. We then used the existing functions with edits to incorporate this new matrix to create parameters by fitting to the data and predicted the cell numbers with those parameters. This process was done for all five new values of subphases across three different drugs as well as the original values.

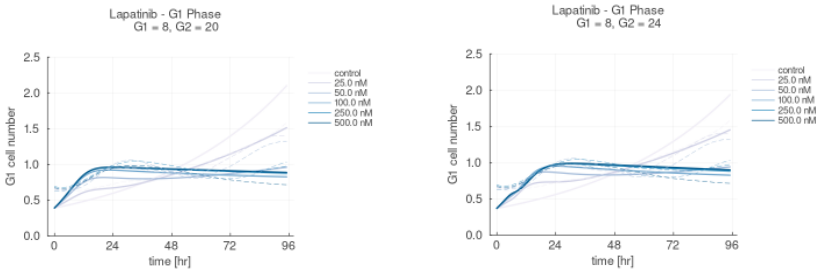
Then, we compared the resulting parameters of the tested values to the original data by plotting the G_1 cells and S-G_2 cells over time. We also compared each of the values by comparing the sum of squared errors of the model to the original data. By visualizing these plots alongside the plots generated with the default values of G_1 and S-G_2 subphases, we were able to compare how well the model behaved with the changed values.

Results:



Looking at the plot of the sum of squared errors, the predictions made when changing the number of G_1 subphases to 12 had high errors across the three drugs. The combination of (12, 32) was the worst across all three. While not shown in the chart, changing the number of G_1 subphases to 4 also had high errors. Looking at the G_2 cell numbers of gemcitabine for the combination (12, 32) shows that this prediction failed to capture the model's behavior as well as failing to capture its final cell numbers.

In comparison, keeping the number of subphases of G_1 to 8 and changing the number of subphases of G_2 resulted in much lower errors. While these four predictions all had similar errors, reducing the number of G_2 subphases to 16 has the highest across all three and is especially high for doxorubicin. The combination with the lowest error, on the other hand, varied across the three drugs. The lowest for doxorubicin was (8, 20) while the lowest for gemcitabine and lapatinib were (8, 32) and (8, 24) respectively.



Looking at the plots for lapatinib in G_1 for (8, 20) and (8, 24), they look very similar with only minor differences between the models that resulted in a slightly lower error for (8, 24).

Discussion: A limitation of trying to change the model was that we had to test combinations in multiples of four since that was how the original matrix was set up and would require too many edits to change that setup. Thus, we were unable to test (6, 22) which was the best fit of the gamma distribution on the original paper. Additionally, running the fitting to get the parameters required a lot of processing time so we were limited in the number of combinations we could test. With more time, we could have been able to test out a wider variety of combinations to find which one might be more optimal. The high errors for $G_1 = 12$ are expected since they greatly differ from the best fit of 6. It is also consistent that $G_2 = 20$ and $G_2 = 24$ had low errors across the three drugs since those numbers are closest to the best fit of 22. However, it is surprising that $G_2 = 32$ had the lowest error for gemcitabine. A possible explanation could be that since gemcitabine affects the G_2 phase, adding more subphases would better reflect that effect, and thus, a higher number of G_2 subphases would result in lower error. These results suggest that changing the number of subphases according to the effect of the drugs could result in more accurate predictions and better modeling. Thus, a future improvement to the model could be to find the best fit of the gamma distribution using the specific drug trial data, rather than using general numbers for all drugs.

Broader Implications: By optimizing the value of the subphases for G_1 and S-G_2, our group was able to lower the error rate of the ODE model created by the Meyer lab. As such, the model's functionality to predict optimal anti-cancer drug combinations and scheduling strategies is now enhanced. Such enhancements provide clinicians with increased clarity and confidence to prescribe cancer patients certain drug combinations that optimize their treatment plans. In addition, the generalizability of such a model that predicts the antagonistic or synergistic relationships between drugs can be used as an experimental platform by researchers to test drug combinations that treat different diseases involving cell proliferation and death. Lastly, the Meyer lab identified that the coupling of the second phase (S-G_2) in their model was a limitation due to the inability of the cell-cycle reporter to distinguish between the S & G_2 phases. Thus, when a more capable cell-cycle reporter is developed, this model can be revamped to accommodate further phase separation thus enhancing the current results.

References

Gross, S. M., Mohammadi, F., Sanchez-Aguila, C., Zhan, P. J., Liby, T. A., Dane, M. A., Meyer, A. S., & Heiser, L. M. (2020). *Analysis and Modeling of Cancer Drug Responses Using Cell Cycle Phase-Specific Rate Effects*. https://doi.org/10.1101/2020.07.24.219907

Appendix:

Changes to the ODEModel.jl and Hill.jl

- Involved changes to functions to make the number of G_1 and G_2 phases editable

CASB 185 - Drug Response Model

- Jupyter Notebook where the model and the new combinations were tested and plotted

CASB 185 Plots

- Folder of all plots and error chart