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Analysis of the CD3_CD123 and THP1x Bispecific Antibody Model

Introduction

The purpose of this project is to study how the parameters of the CD3_CD123 and THP1x models effect the outputs of the model. Analysis of the similarities and differences between the two models will be done. Another goal of this project was to create a model that displays the statistics of the both models graphically. This project started with familiarizing myself with the CD3_CD123 model through both RuleBender and MatLab before I could begin building. I studied the different parameters (inputs) the model takes in and what the model does with them to return the observables (outputs). In short, the CD3_CD123 model analyzes the way in which a bispecific antibody which is the drug in the model binds to both a T Cell receptor and a cancer cell to stimulate cell death. After studying the model in RuleBender I began to run parameter scans that allowed me to change different parameters and see its impact on the observables. This was all in an effort to have a better understanding of why the model worked the way that it did. After intensive studying of the model in RuleBender, I used to MatLab to start the creation of my descriptive model. After building the CD3_CD123 model I began developing the THP1x model. For this model I took many similar steps to learn about the trends of the parameters in the model and how the parameters effect the model before building the model. The differences in the two models lies in the complexity of the model. In the CD3-CD123 model cell death is stimulated by the biding of the the cancer cell and the t cell to the drug (bi specific antibody). The THP1x model has additional factors that stimulate cell death. Some of these factors are bridge formation, the number of bridges to form a synapse, and T cell activation. A deeper look into my research process and results will be shown in the upcoming sections.

Materials and Methods

RuleBender

RuleBender is a biological modeling software that allows you to create rule-based models, simulations, and visualizations. The original CD3_CD123 and THP1x model is written in BioNetGen's source code. RuleBender is a graphical interface for BioNetGen. My main use of RuleBender was to better understand how both models work and the effects that parameters have on their outputs.

RuleBender Parameter Scan

This is a function in RuleBender that was very helpful in learning how the model works. It allows you to change any one of the parameters and see how the outputs are affected by this.

MatLab

"MATLAB® is a programming platform designed specifically for engineers and scientists. The heart of MATLAB is the MATLAB language, a matrix-based language allowing the most natural expression of computational mathematics." The use of MatLab in my project was to study the CD3_CD123 which is also written MatLab and to write my own model.

Objectives, Results and Interpretations

The main parameters I analyzed are APM which is the amount of drug given in picomolar. The amount of acute myeloid leukemia cancer cells and receptors which in both models is referred to with a 123 extension. The amounts or cells and receptors was studied in the CD3_CD123 model. While the effects of the on and off rates of cancer cell receptors was one of the main studies in both models. The amount of T cells and T cell receptors was also studied for the CD3_CD123 model and is commonly referred to with a 3 extension. The second main study of my research was to find the impact that the T cell on and off rates have on cancer cell death. The initial focus was on how a multitude of parameters effect the CD3_CD123 model and specifically the amount of cancer cell death. Simple analysis of parameters can be run through

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RuleBender parameter scans. From this I progressed to my first objective which was to write a script in MatLab that would take in the original model and loop through a set of apm values, this was done on a log scale. The output showed how the amount of dead aml changed in response to changes in apm.

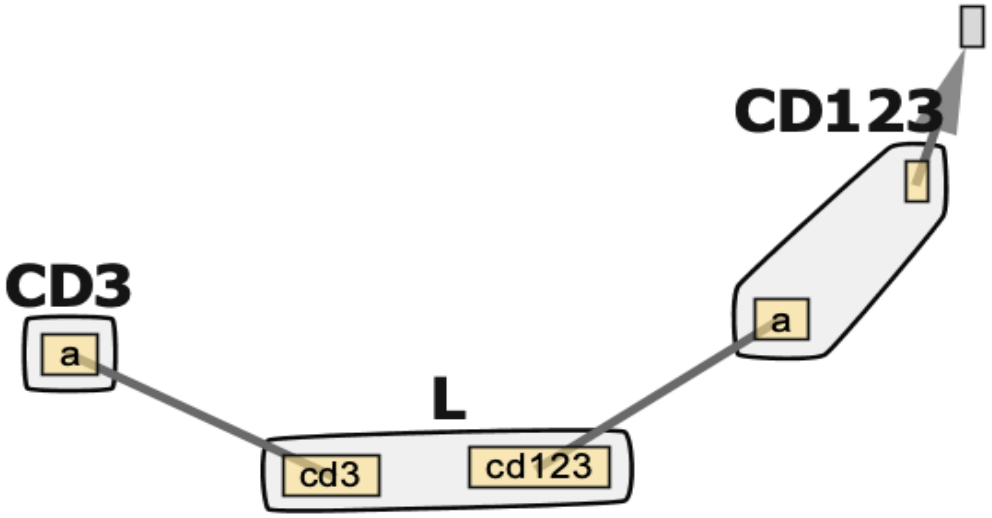

Figure 1: Bispecific antibody binding on CD3 and CD123 causes cancer cell death

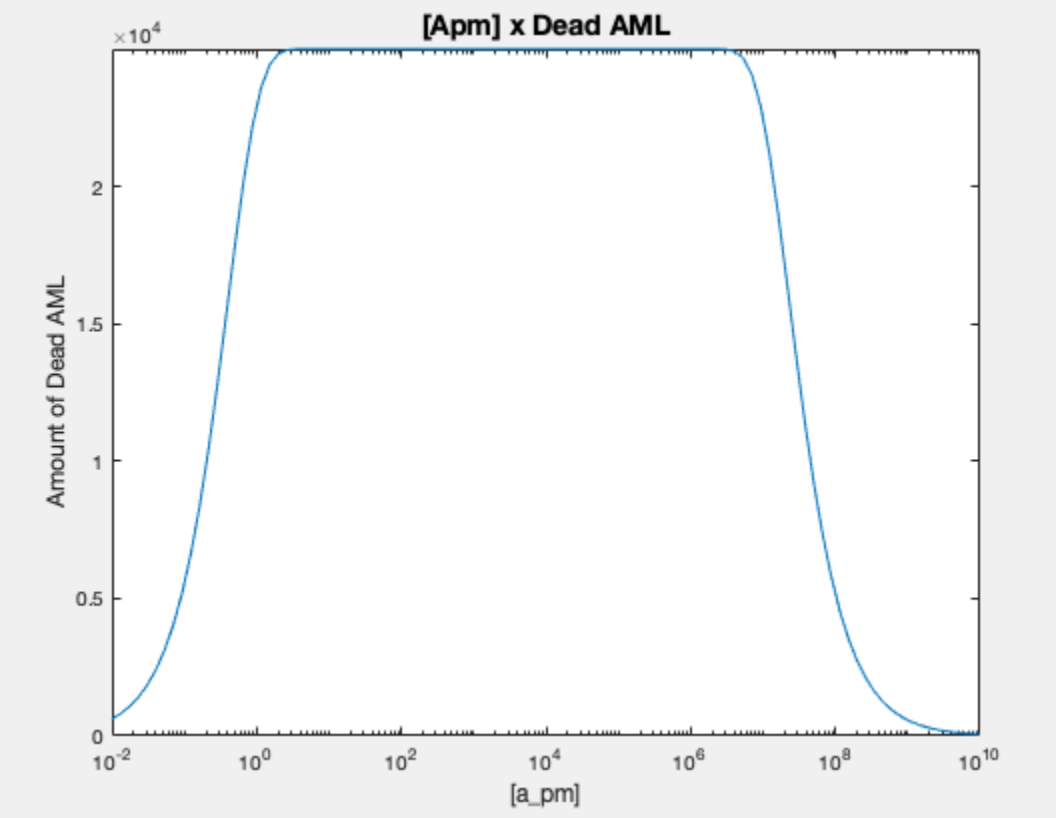

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Figure 2: Graph shows the amount of Dead Aml in response to changes in [Apm] in the CD3_CD123 model

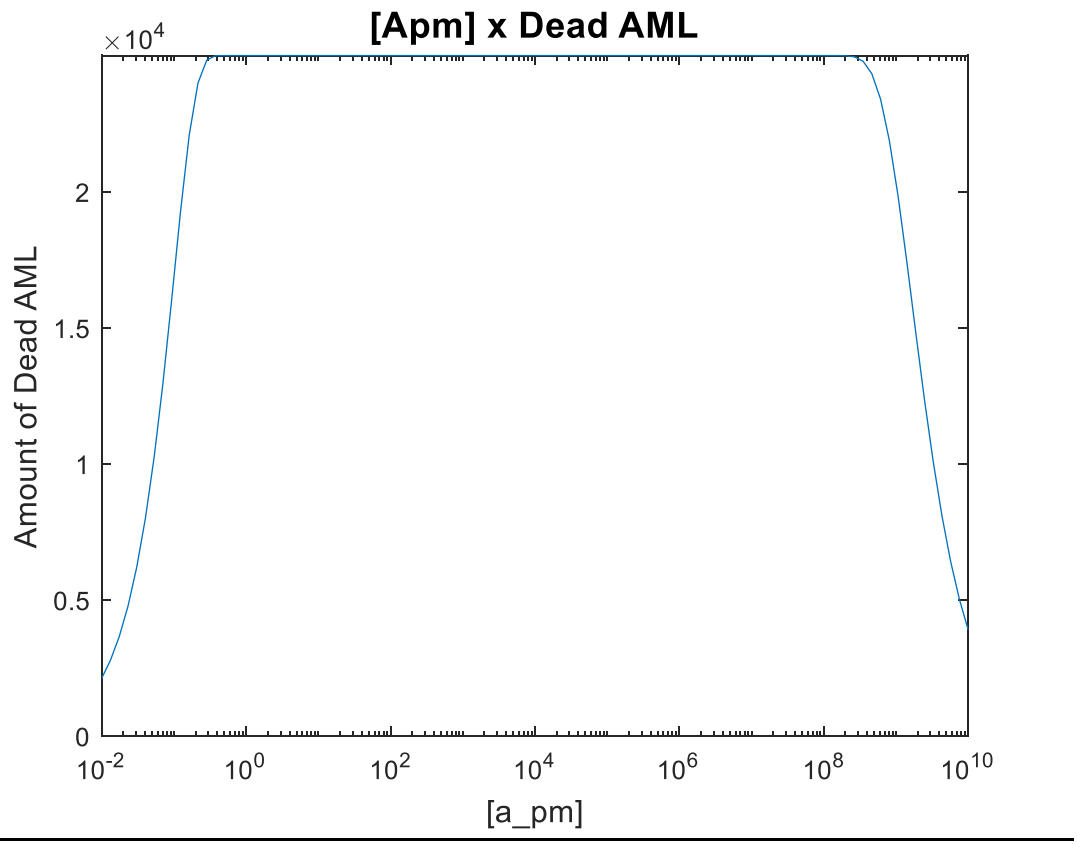

Figure 3: Graph shows the amount of Dead Aml in response to changes in [Apm] in the THP1x model

Figure 2 and 3 shows how with an increase in the amount of drug cancer cell death increases up until a certain point. At this point there is a plateau where the model isn't receptive to a change in drug concentration. Then cancer cell death decreases because the amount of drug in relation to the saturation of Cancer and T cell receptors. At the point where dead aml begins to decrease the concentration of drug was high enough for the drug to begin binding to both receptors independently. As a result, cell death would not be stimulated. Figure 1 shows that to initiate cell death in the CD3_CD123 model the drug must bind to both a cancer cell receptor and a T cell receptor. In the figure the L is the drug. When the concentration of drug is too high what happens is some drug binds to T cell receptors and some binds to cancer cell receptors. Now there are no free cancer or T cells to bind to a drug that has already bound the other receptor to initiate a response and cancer cell death decreases. This process is similar in the THP1x model but you need several of these interactions which are known as bridges in this model to form a synapse. A synapse along with an activated T cell can then stimulate cancer cell death. The differences in the graphs of the two models is very minute here, with the only main observable difference being figure 3 is slightly wider.

My next objective was to go a step beyond the last figures. It was to write a script that would also pass in the original model and loop through a set of apm values but also loop through a set of Kd values for both

the T cell (labeled Kcd3) and the cancer cell (labeled Kcd123). Kd was calculated to be the ratio of the off/on rates for drug binding to both T cell and cancer cell receptors. Once this was completed the model looked at the output of my first objective, the curve of apm vs. dead aml but at varying Kd values. The model looks at the apm vs dead aml at 10000 different combinations of Kd values for T cell and cancer cell receptors. I analyzed the shapes of the individual curves in attempt to characterize the width, the apm value at the maximum amount of dead aml, and the maximum amount of dead aml. In other words, when this script runs to completeness there are 10000 different combinations of Kd values (100 kcd3 values x 100 kcd123 values) that are represented on the heat map below. Each spot represents the model being passed in a specific Kd3 and Kd123 value and showing one of the 3 outputs of the shape data of that individual graph. This was done for both models in an effort to better understand how the models are different and whether the THP1x model gives any insight that the CD3_CD123 model does not. The heat map below shows the 1st of the 3 outputs which is the max amount of dead aml in other words the height of each individual graph.

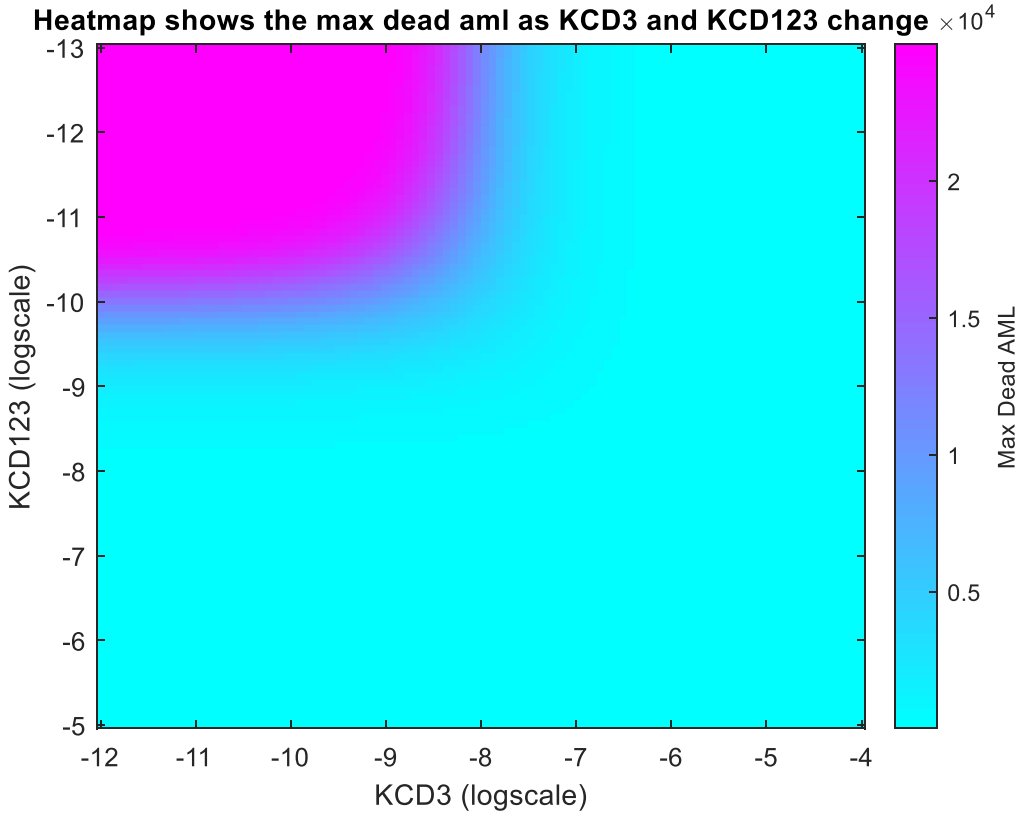

Figure 4: Heat map of Max Dead AML for the CD3_CD123 model

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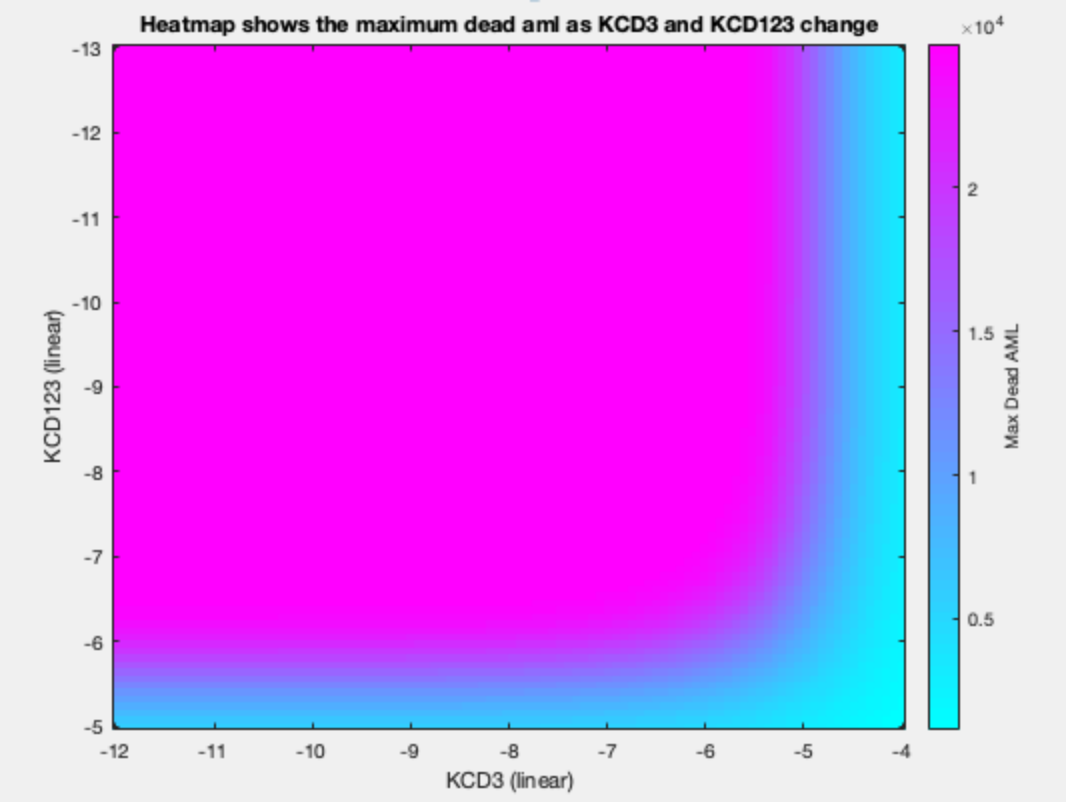

Figure 5: Heat map of Max Dead AML for the Thp1x model

The x axis is the Kcd3 on a log scale. It has 10 ticks but 100 actual data points were taken between 10^-13 and 10^-5. This is the same for the Y axis (Kcd123) spanning between 10^-12 and 10^-4. The top of the parabola is where you would find the max dead aml as seen in figure 1. The colorbar indicates the total amount of dead aml that corresponds with each color. In figure 4 and 5 when both the Kcd3 and Kcd123 are at their lowest the amount of dead aml is at its highest. This makes sense because the affinity is the highest at this point so that should lead to the greatest amount of cell death. As the affinity decreases so does the amount of dead aml and that is also shown in the heat map. There is a large difference between figure 4 and figure 5. The Thp1x model is much less dependent upon Kcd3 and Kcd123 in terms of its max dead aml. While CD3_CD123 only peaks at a smaller range of Kcd3 and Kcd123 values.

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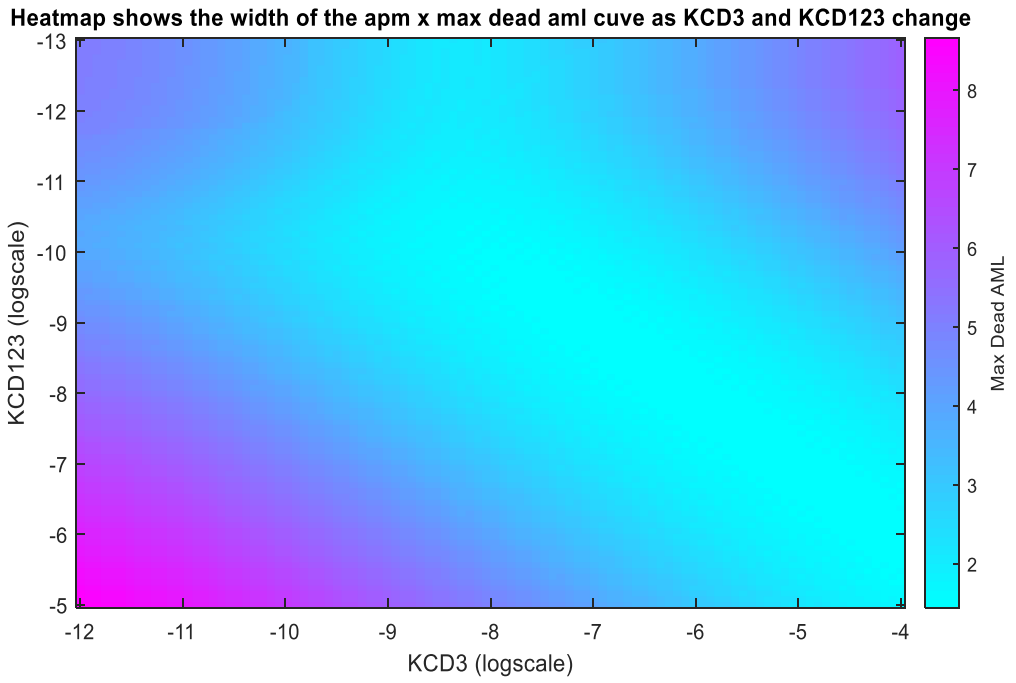

Figure 6: Heat map of the width of Apm x Dead Aml curve for the CD3_CD123 model

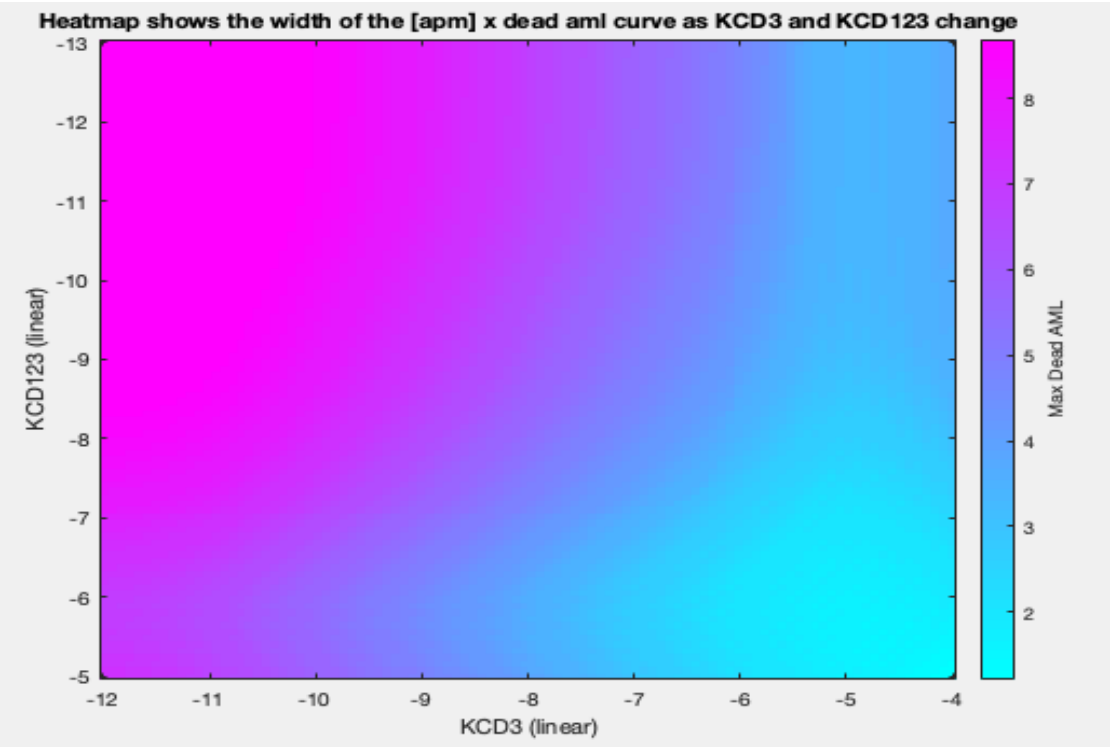

Figure 7: Heat map of the width of Apm x Dead Aml curve for the THP1x model

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The x and y axis where formed the same way as the previous figure. This graph is showing the width of each individual graph as kcd3 and kcd123 varies. The width was calculated as the apm at ½ max on the way up – the apm at ½ max on the way down. It would give us an indication of how sensitive a set of Kcd3 and Kcd123 values are to a change in drug concentration. Figure 6 shows that when one receptor has a low Kd and the other has a high Kd there is a large width. This is a result of one receptor getting saturated first and now only once the receptor for the low affinity receptor gets saturated will the response begin to go down. Along the blue diagonal the receptors have roughly equal affinities so that shrinks the response window. In this case of having one receptor with a higher affinity for the drug and this will decrease the chances of free drug without any bound receptor. Hence the receptor with the higher Kd will find a drug with one of its receptors already bound and stimulate cell death over a larger range of apm values. Figure 7 is very different than figure 6, it appears to have the largest widths when Kcd3 is high and when Kcd123 is above the half way mark. This isn't explained well by affinities but seems to be more of an indication that this model is not as dependent on the change in apm. It naturally plateaus for longer than the CD3_CD123 model.

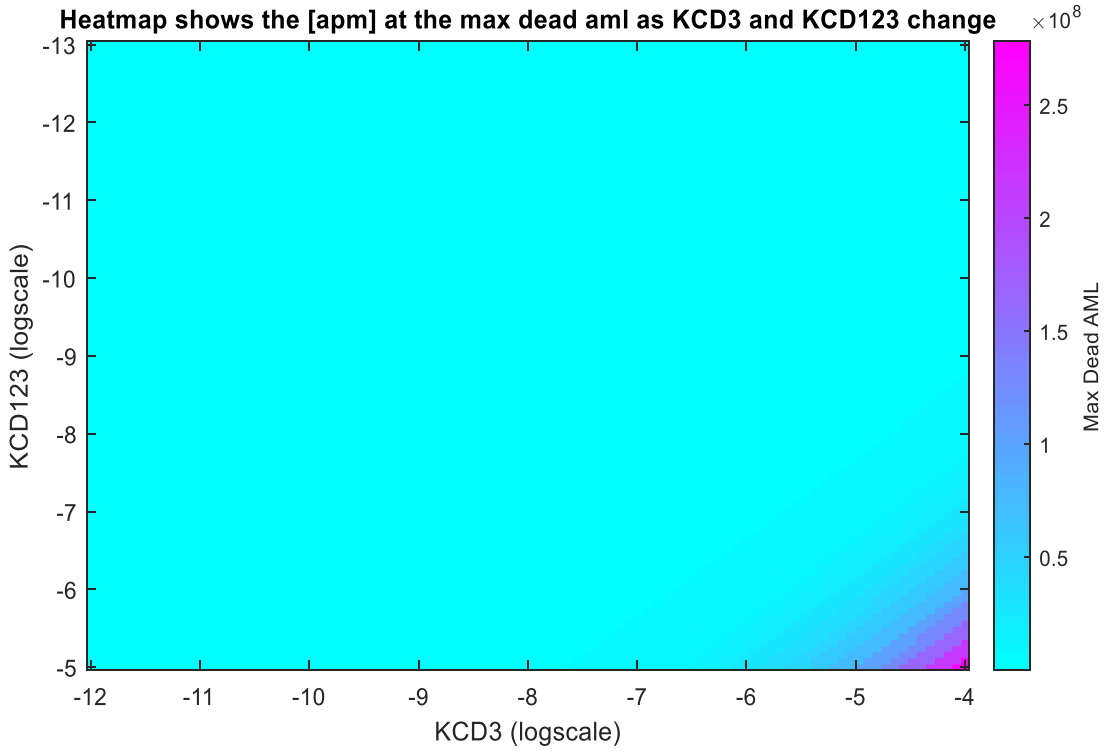

Figure 8: Heat map of the [apm] at the Maximum Dead Aml for the CD3_CD123 model

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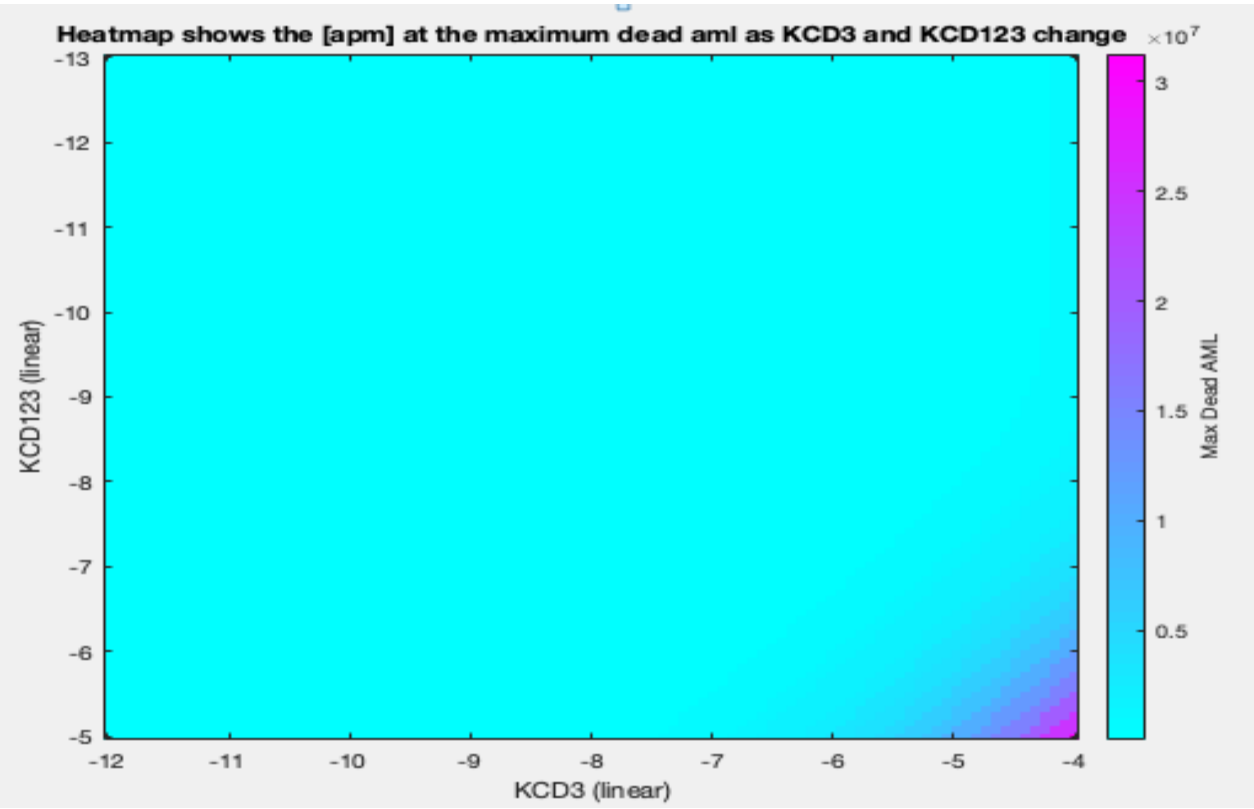

Figure 9: Heat map of the [apm] at the Maximum Dead Aml for the THP1x model

The x and y axis where formed the same way as the previous to figures. This heat map answers the question of what is the apm at the maximum amount of dead aml. It has a real world application in the sense that it tells you the optimal dose to give to cancer patients for the best results. Figure 8 and 9 shows that when the Kd3 and Kd123 are at their highest point the apm at the maximum amount of dead aml is also high. This makes sense because you would expect that when the there is a low affinity you would need a higher amount of drug to reach the maximum amount of cancer cell death. However, even though the results are to be as expected it is interesting how similar figure 8 and 9 are considering the models differences in the other figures.

Discussion

The majority of the results are as expected. The CD3_CD123 model is the more explainable and concrete model. The complexity of the THP1x model goes to explain why the results of the analysis on that model is less clear. There is definitely a difference between the two models and there appears to be some insight that the THP1x model can give that the CD3_Cd123 model does not. Future analysis into the THP1x model is needed in order for a comprehensive understanding.

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Problems and Troubleshooting

With learning any new coding languages and software's there will be always be a degree of problems and troubleshooting. When learning to work with the model, RuleBender, and MatLab I faced difficulties in learning how the software's worked. However, through repetition and continued learning I was able to pick up on the problems I faced and continue to build upon what I've learned to that point. MatLab was probably the most difficult for me to pick up just because it was a completely new language that I was learning on the fly. Nevertheless, at the same time I think that is what made this research fun. When I was writing scripts, I knew what I wanted to do next but I didn't know how to implement it in MatLab. Google as always, was a big help for me and helped me to learn how to implement in MatLab.

Citations

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