Modeling cross-resistance of 2-drug treatment in cancer

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Abstract

Resistance to targeted therapy is a major obstacle to successfully treating cancer. This paper shows that the resistance to various drugs can be caused by random genetic point mutation by analyzing a linear system of ordinary differential equations(ODEs) by improving the Skipper-Schabel-Wilcox model. The resistance generated before the treatment begins is greater than that generated during the treatment. The concentration of the drug determines the amount of resistance. We also evaluate the effects of different treatment strategies on the mutant cancer cell population. For low-turnover rate cancer, combination therapy is beneficial. However, for cancer with high-turnover rate, it can not significantly reduce the resistance of mutants.

Introduction

In this chapter, we discuss the dynamics of drug resistance with the related issue of cancer stem cells. We use our new mathematical model from *Mathematical modeling of drug resistance and cancer stem cells dynamics*(Tomasetti, 2010) compared with Kangbo Bao's Research article *An elementary mathematical modeling of drug resistance in cancer* (2016). We change the variables D, the natural death rate, and H, the death rate induced by drugs to see how the number of resistance of cells changes. In our model, it is assumed that a stem cell can either renew symmetrically, producing two daughter stem cells or differentiate symmetrically, producing two differentiated (not stem cells) daughters. We also assumed that only point mutations happened and the two anticancer drugs targeted two different carcinogenic sites. Therefore, the mutant cancer cells can obtain resistance to both drugs. Derived from this two-drugs-resistance model, our goal is to clarify the effectiveness of each parameter on the model and gain inspiration in anticancer treatments by analyzing the mutant cell population after introducing drugs.

Problem Description

Cancer is a crucial public health challenge and one of the major causes of death nationwide around the whole world. Reliable clinical methods to treat cancer are always desired, such as targeted therapy, due to its difficulty to be healed. Drug resistance is one of the major obstacles to improving the chances of clinical anticancer treatment success. After a long period of development, it is proved an efficient and standard way for anticancer therapies. However, according to Tomasetti, in the paper *An elementary approach to modeling drug resistance in*

cancer, drug resistance to targeted therapy often "strongly limits the long-term effectiveness of treatment and reduces the survival rates for cancer patients"(Tomasetti, 2010). Therefore, we will focus on whether the future relapse happens depends on the drug resistance in this paper since the efficiency of the treatment of cancer is crucial. It is necessary to verify the validity of the resistance to cancers when introducing multiple drugs in treatment.

Simplification

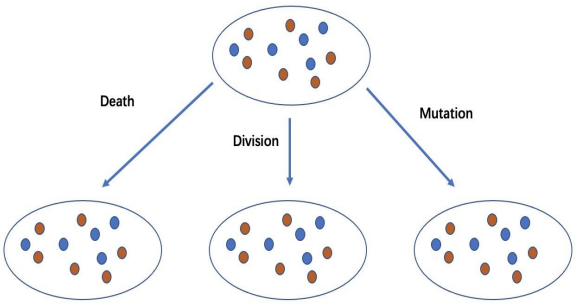


Figure 1. Three basic processes

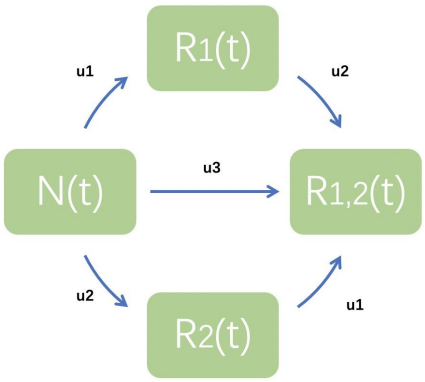


Figure 2. visualization of the mathematical model

According to the diagram, we can add the coefficient of$u_1$or u_2(the mutant rates of the first and second drugs) onto the model of the wildtype group in order to construct the model of the first and second drug mutant by time after treatment, respectively. Alternatively, we can also include the coefficient u_3(the mutant rate of the overlap of the two drugs) to construct the overlap resistance of mutant cancer cell populations after treatment of both drugs. The relationships above build up the systems of the models of the mutant cell population after introducing each drug and both drugs combined as treatment.

Mathematical model

The mathematical model is the new one we built based on the Skipper-Schabel-Wilcox model.

Definition of parameters in the model:

-Let L, D, u, and t denote the birth rates, death rates, mutation rates, and time, respectively. We assume that $0 \leq D < L$ and $0 < u \ll 1$.

-$N(t)$: The first group, composed of wild-type cancer cells（are sensitive to the drugs), at time t

-$N'(t)$: rate of change of the number of wild-type cancer with respect to time t

-$R_1(t)$, $R_2(t)$, $R_{12}(t)$: the resistance of mutant cancer cell populations that mutated by time t for the first drug, second drug, and the overlap of both drugs

-$R_1'(t)$, $R_2'(t)$, $R_{12}'(t)$: the rate of the resistance of mutant cancer cell populations that mutated by time t only for the first drug, the second drug, and the overlap of both drugs.

-u_1, u_2,u_3: the mutation rate for the first, second, and both drug

-D, D_1, D_2, D_3: the death rate of the wild-type cancer cell, the death rate of the mutated cells by the first, second drug, and both drug

-t^* : we assume the therapy starts at t* (time treatment starts)

-H, H_1, H_2: the drug-induced death rate of wild-type cancer cells (N), and the drug-induced death rate of mutated cells by the first drug (R1), and the second drug (R2) that appears after t*

M: the total number of cancer cells at time t

The drug model before treatment (t < t*):

$$N'(t) = (L - D)N(t)$$

$$R_1'(t) = (L - D)R_1(t) + u_1 N(t)$$

$$R_2'(t) = (L - D)R_2(t) + u_2 N(t)$$

One drug model after treatment (t < t* or t = t*):

We introduce the first drug in this case to show the model after treatment by only one type of drug. Below are the coefficients we will be using:

$$c_2 = \frac{Mu_1}{D - D1 + H - H_1 + u_1 + u_3}$$
$$c_4 = L - D_1 - H_1 - u_2$$
$$c_6 = L - D - H - u_1 - u_2 - u_3$$

The following system of models to demonstrate the one drug model after treatment:

$$N(t) = Me^{c_6 t}$$

$$R_1(t) = c_2 e^{c_4 t} - c_2 e^{c_6 * t}$$

Two-drug model after treatment (t >t*):

Below are the coefficients we will be using:

$$
\begin{aligned}
c_1 &= \frac{u_2 c_2}{c_7 - c_4} - \frac{u_2 c_2 + u_1 c_3 - c_4}{c_7 - c_6} + \frac{u_1 c_3}{c_7 - c_5} \\
c_2 &= \frac{M u_1}{D - D1 + H - H_1 + u_1 + u_3} \\
c_3 &= \frac{u2 * M}{D - D_2 + H - H_2 + u_2 + u_3} \\
c_4 &= L - D_1 - H_1 - u_2 \\
c_5 &= L - D_2 - H_2 - u_1 \\
c_6 &= L - D - H - u_1 - u_2 - u_3 \\
c_7 &= L - D_3
\end{aligned}
$$

The system of models to demonstrate the one drug model after treatment:

$$N'(t) = (L - D - H)N(t) - u_1 N(t) - u_2 N(t) - u_3 N(t) \quad (1)$$

$$R_1'(t) = (L - D_1 - H_1)R_1(t) + u_1 N(t) - u_2 R_1(t) \quad (2)$$

$$R_2'(t) = (L - D_2 - H_2)R_2(t) + u_2 N(t) - u_1 R_2(t) \quad (3)$$

$$R_{12}'(t) = (L - D_3)R_{12}(t) + u_2 R_1(t) + u_1 R_2(t) + u_3 N(t) \quad (4)$$

$$N(t) = M e^{c_6 t} \quad (5)$$

$$R_1(t) = c_2 e^{c_4 t} - c_2 e^{c_6 * t} \quad (6)$$

$$R_2(t) = c_3 e^{c_5 t} - c_3 e^{c_6 t} \quad (7)$$

$$R_{12}(t) = c_1 e^{c_7 t} - \left(\frac{u_2 c_2}{c_7 - c_4}\right) e^{c_4 t} + \left(\frac{u_2 c_2 + u_1 * c_3 - c_4}{c_7 - c_6}\right) e^{c_6 t} - \left(\frac{u_1 c_3}{c_7 - c_5}\right) e^{c_5 t} \quad (8)$$

The improvements from the original model is that we divide parameters to individual ones described as above, so that we are able to discover more relationships between parameters and the solution equations.We also change the definition of the R_1 and R_2, they are the population of resistance of mutant cancer cells only for the first drug or second drug. If they are mutated from both drugs then, they belong to R_{12} instead of R_1 or R_2.

Solution of the mathematical problem

The first value we solved is t*, the time of the beginning of the treatment. We are sharing the same mathematical model before the treatment with the Skipper-Schabel-Wilcox model, so we have the same t* which is the time when the treatment starts. According to Tomasetti's paper, the time of the beginning of the treatment, t *, can be related to the size of the tumor at that time. If we assume that the total number of cancer cells at time t *is M, we can use the exponential growth of cancer and the relatively small mutation rate u to estimate t * (Tomasetti 25) treatment starts.

$$t^* \approx \frac{1}{L-D} \ln \frac{M}{N_0}$$

The model we developed has more detailed information about the individual rate on different cells. Those individual parameters made the solution equations much longer than the original model, but the information it contains and the parameters we can test are also increased by the difficulty of the equations.

In the following discussion, we will mention how we analyze the different parameters, and how it affects the change of rate of every cell.

Linear analysis was used in our way to solve the equations, we used the matrix to outline our ODEs to a linear system.

Then, we use WolframAlpha online solver to solve our derivative to the population equation, and that is included in our mathematical model .(The two-drug model after treatment starts) The function (5), (6), (7), (8) are the solution equations.

By looking at the solution equations, they are dependent on the individual parameter. The mutation rates u1, u2, and u3 are the ones we can see directly connected to the solutions. There is another factor in Tomasetti's paper, the turnover rate D/L was solved and our models are sharing the same turnover rate. Other than that, we also separate other variables like H, so H, H1, and H2 are the ones we are discussing in the following section. A new rate we will mention is H/u, we call it "HU rate", it will affect the two-drug resistance directly (Assuming the turnover rate does not change). In our discussion, we will analyze those parameters we mentioned from the graph instead of looking at the mathematical model.

Results and Discussion

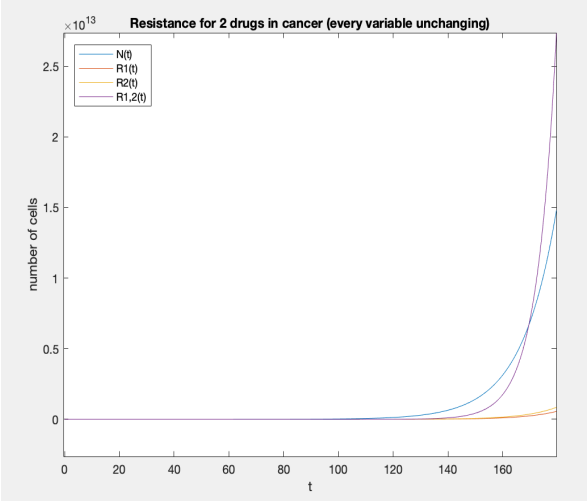
We change the variables in our models to explore if we can find the best condition in extending t#,the time when $R_{1,2}(t)$, cancer cells that gained resistance both to drug 1 and drug 2, become equal to N(t), the drug-susceptible cancer cells. When $R'_{1,2}(t) > N'(t)$, considering the rate of change of $R_{1,2}(t)$, the number of cells with both drug 1 and drug 2 resistance will constantly and exponentially increase to finally become the main type of cancer cells. In this condition, the cancer division will be uncontrollable and irreversible since they reproduce exponentially. Therefore, the accurate estimate of t# is very significant. We can use a new drug to decrease the cells with drug 1 and drug 2 resistance before the t#.

In the following graph analysis, Rd(t) represents the R'(t) , the rate the change of the resistances. (Same with Nd(t)) Under all the cases, we set variables L, D, and H the same to keep the N(t) and N'(t) the same when we are not changing parameters *u a*s (u_1,u_2,u_3).

- Case 1:

L, birth rate; D, death rate; H, drug-induced death rate; and u, natural mutation rate are unchanged.

In the following diagrams, we set $L = 0.2;\ D = 0.06;\ H = 0.06;\ u = 2\times10^{-7}$.



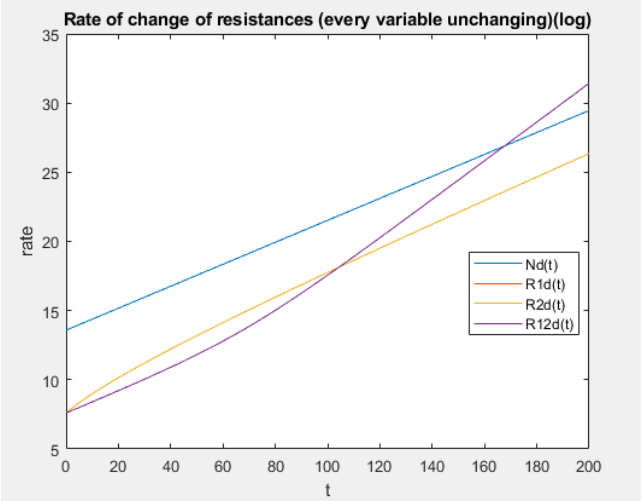


Figure RD$_1$ *Figure RD*$_2$

Figure RD1 and *Figure RD2* in Case 1, we assume the L, D, H, and u are not changing in our models. That means both drug 1 and drug 2 induce the same rate of mutation and same drug-induced death rate in cancer cells but the birth rate and natural death rate of cells are independent.

According to our Figure RD 1 and 2, when all variables are unchanged, we estimate t# = **170** units of time. Our goal is to find the best condition to estimate and extend the t#. It is possible that we could use more new drugs to inhibit drug resistance, but considering the health condition of patients, economic situations, and potential multi-resistance of drugs, we will not use more than 2 drugs in cancer treatment.

-Case 2:

L, birth rate; D, death rate; and H, drug-induced death rate; is unchanged. Since the mutation rate is now affected by two drugs, we seperate the mutation rate into u1, u2, u3.

In the following diagram, we set $L = 0.2;\ D = 0.06;\ H = 0.06;$

$u1 = 2\times10^{-7}\ ;\ u2 = 1.5\times10^{-7}\ ;\ u3 = 0.5\times10^{-7}\ ;$

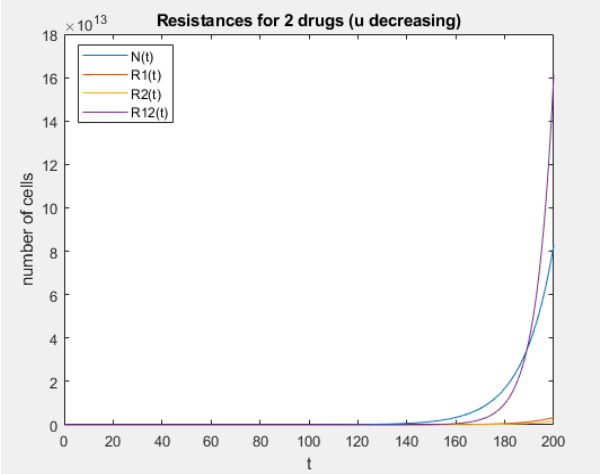


Figure RD_3

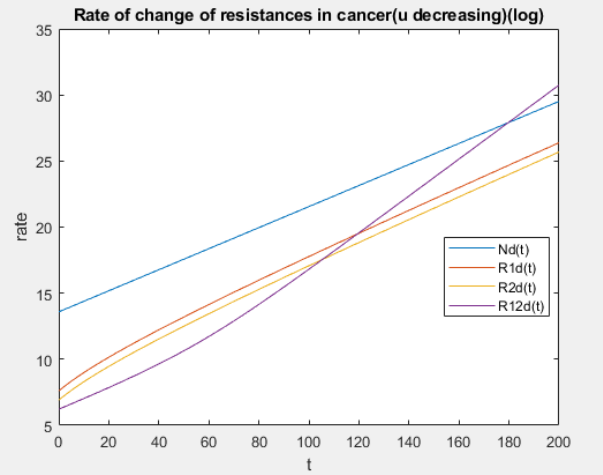
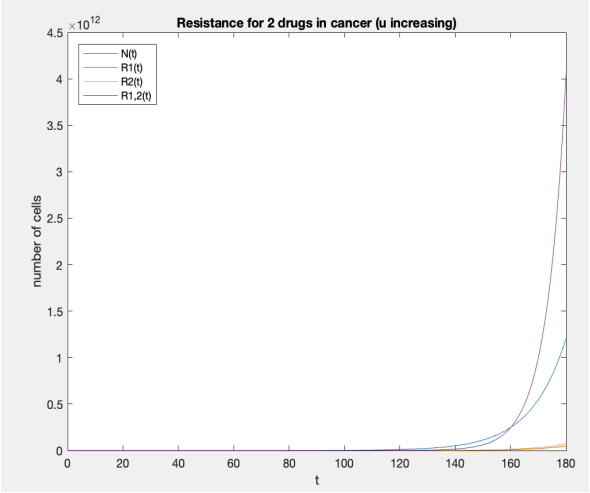


Figure RD_4

In the following, we change the variables as $u1 = 2\times10^{-7}\ ;\ u2 = 3\times10^{-7}\ ;\ u3 = 4\times10^{-7}\ ;$



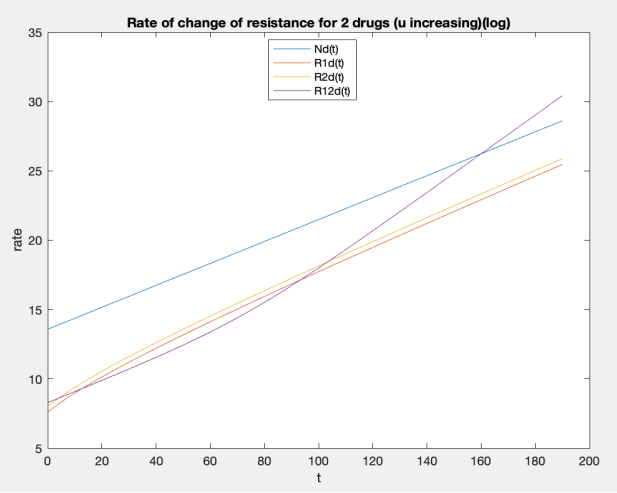


Figure RD_5 *Figure* RD_6

We arrange the drug-induced mutation rate u_1, u_2, and u_3 in decreasing order and increasing order. When mutation rate change in decreasing order, we estimate the t# = **190** units of time. When mutation rate change in increasing order, we estimate the t# = **163** units of time. According to *Figure RD 3, RD 4, RD5, and RD6*, we conclude that when drug-induced mutation rate in cancer cells are different and less than natural death rate u, the t# will be extended; and when drug-induced mutation rate in cancer cells are different and greater than natural death rate u, the t# will be shrinked. In cancer treatment, we expect to have longer t#. Hence, the condition when mutation rate is in decreasing order is the ideal condition we want.

-Case 3:

In the following diagrams, we set $L = 0.2;\ D = 0.06;\ H = 0.06;\ u = 2\times10^{-7}$;

$D1 = 0.05;\ D2 = 0.04;\ D3 = 0.03;$

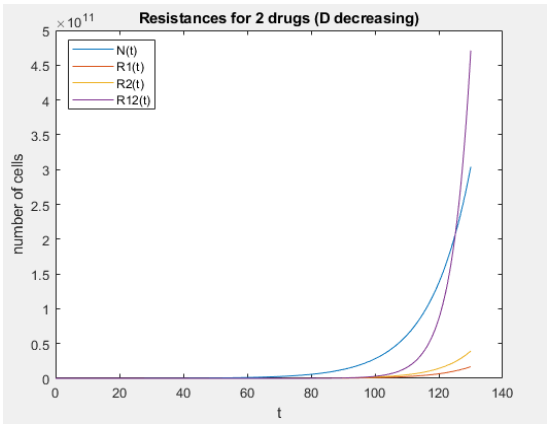


Figure RD$_7$

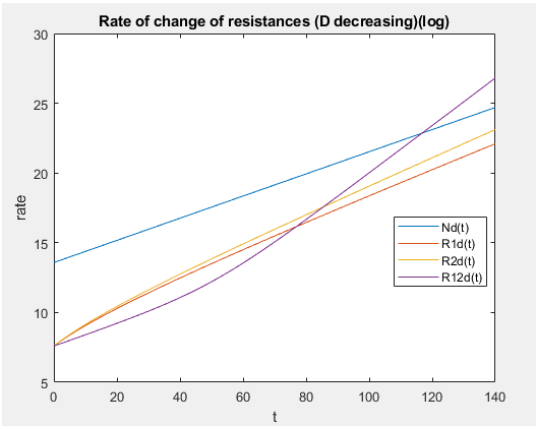


Figure RD$_8$

In the next 2 graphs, we set *D1 = 0.07; D2 = 0.08; D3 = 0.09;*

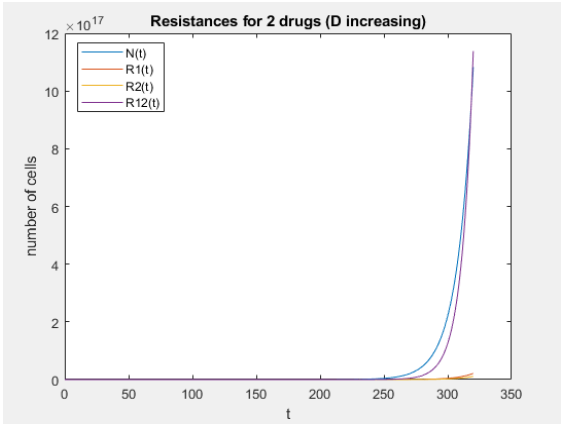


Figure RD$_9$

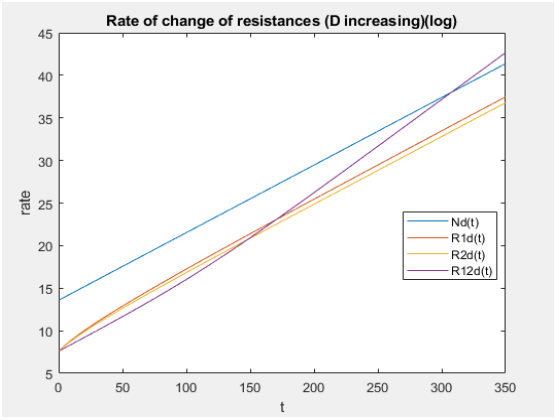


Figure RD$_{10}$

In this case, we are assuming the parameters other than D (natural death of the cells for individual cells) are not changing including L, u, and H. We are assuming D is changing for different cells in both decreasing and increasing order, so that we can compare them to see the

parten. The Figure RD_7, and RD_8 are the graphs for D in decreasing-order ($D_3 < D_2 < D_1 < D$) Then, the graph of increasing-order ($D_3 > D_2 > D_1 > D$) are Figure RD_9,RD_{10}.

The t# we mentioned above for D in decreasing-order is around **125** units of time, and t# for D in increasing-order is around **320** units of time. The difference between them is **195** units of time, and that is a huge difference if we compare it to Case2. The results shows that if D is increasing-order, t# will be extended, and the time-difference is significant compared to Case2. The parameter L is not changing in this case, so the turnover rate (D/L) is getting influenced by the change of D. Then that also means if turnover rate is larger, the t# will be different even if there is a small change to turnover rate. Changing the death rate enables us to testify and analyze the performance by observing the duration of resistance. Although it is doable in the field of mathematics, the death rate is in general uncontrollable or extremely hard to reach in reality. Therefore, we will introduce changing the values of H to accomplish similar results in Case 5.

-Case 4:

In the following diagrams, we set $L = 0.2;\ D = 0.06;\ u = 2\times10^{-7}$;

$H1 = 0.05;\ H2 = 0.04;$

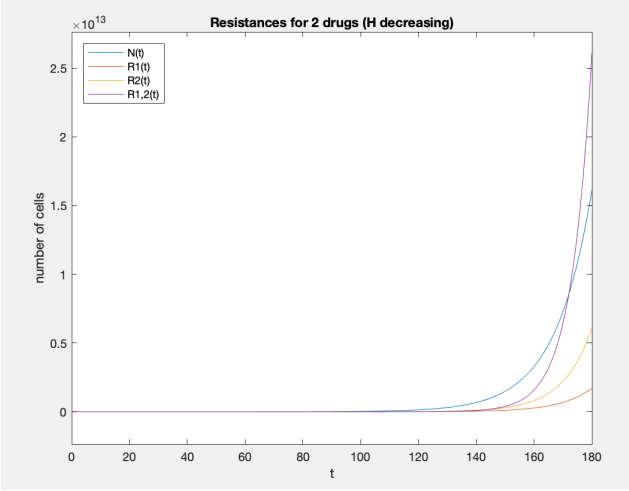


Figure RD_{11}

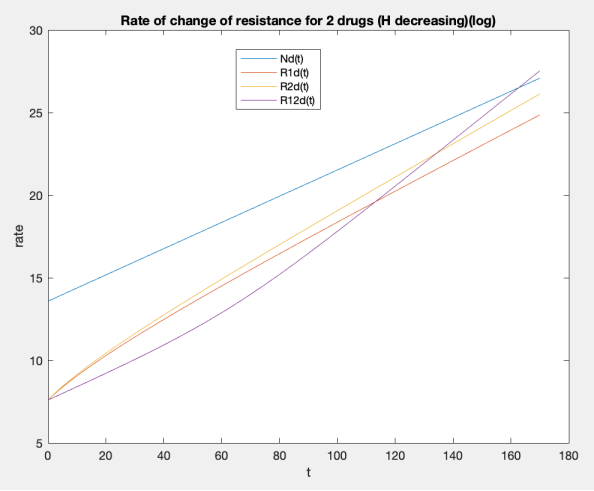


Figure RD_{12}

H1 = 0.07; H2 = 0.08;

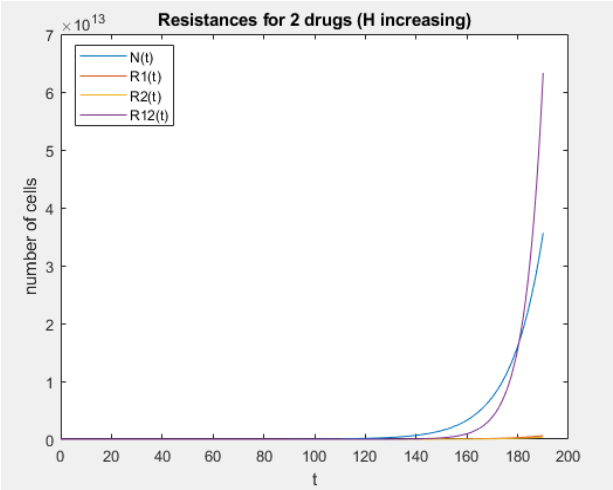


Figure RD_{13}

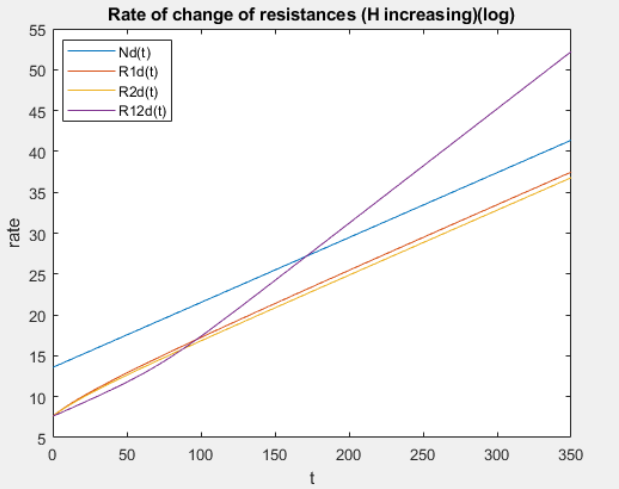


Figure RD_{14}

According to the ending of Case 3, we are changing the parameter H this time. *Figure* RD_{11} and RD_{12} are the ones for H in decreasing-order, and *Figure* RD_{13} and RD_{14} are the ones for H in increasing-order. From the graphs. t# of H in decreasing-order is around **170** units of time (t# = 170). Then, t# of H in increasing-order is around **180** units of time (t# = 180). The difference between those two times are not as impressive as the Case 3, but the changes of H can be easily

controlled by using different drugs on the patient. Parameter H is the one we want to change in our real world case.

-Case 5:

In the following diagrams, we set $L = 0.2;\ D = 0.06;\ u = 2\times10^{-7}$;

$u1 = 2\times10^{-7}$; $u2 = 1.5\times10^{-7}$; $u3 = 0.5\times10^{-7}$;$H1 = 0.07;\ H2 = 0.08;$

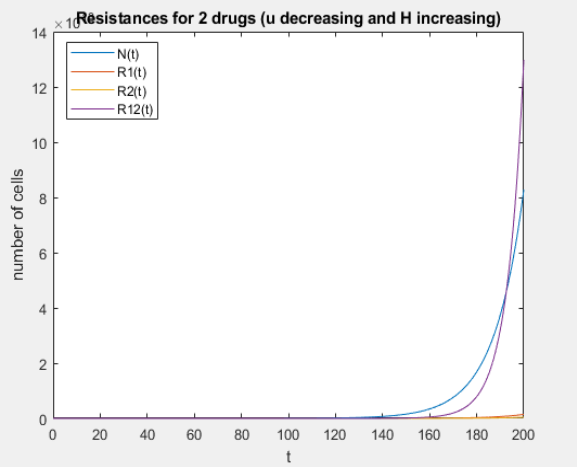


Figure RD$_{15}$

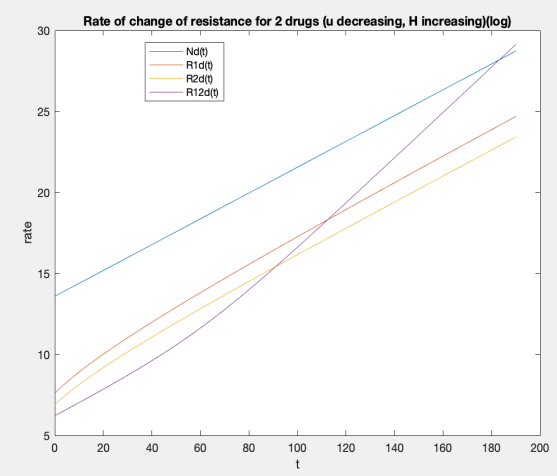


Figure RD$_{16}$

Finally, we combine **Case 2** and **Case 4** to get the most ideal model we want. We change the mutation rate of different cancer cells in decreasing order and drug-induced death rate in increasing order. We then successfully extend time to t# = **196** units of time, which is much longer than the t# = **170** in **Case 1.**

That is the "HU" rate we mentioned above (H/u) in the Solution section. If the "HU" rate gets larger, then t# will be extended for sure. "HU" rate is not like the turnover rate, it could be controlled by the drugs the patient uses. That is more related to reality.

Improvement

In case 3, we introduced the turnover-rate, D/L, to the analysis of our mathematical model. However, the death rate is usually not under control in reality so we introduced an alternative approach by changing H to achieve a similar performance. In other fields, a related derived research could attempt to find factors that can affect the death rate of mutant cells. Any breakthrough on researching death rate would provide more directions for the current research on the resistance time by utilizing both drugs as treatments.

We only introduced the circumstances after one or two types of drugs after treatment. Lacking the cases with treatments by multiple drugs, we cannot assert whether the duration of resistance would increase if we increase the number of drugs as treatment. If we can generate the formula by considering the number of drugs as a variable, considering the side-effects of each drugs(especially when taking multiple drugs at once), we might be able to recommend how many drugs to intake depending on the seriousness of the current condition of cancer in order to avoid the backlash of the combined-side effects after intaking too much drugs. With the established system of models by taking one or two types of drugs for treatment, it's possible to construct formulas that describe the circumstances after intaking three or more types of drugs.

In the constructed system of models utilized above, we assumed L, the birth rate, as a constant. However, this factor should be a parameter that can be possibly changed and can be affected by other variables when taking with other drugs together in reality. If we consider the birthrate of the drugs and wild-type cancer as variables, our current model would be changed significantly. Due to the limited time of the researching period, we could only construct the model by assuming the birth rates are unchanged. Another extended research would be to figure out the model if the birthrate is a variable.

Conclusion

In our paper, we develop the mathematical model about cross-resistance of 2-drug treatment in cancer from Tomasett's paper. We separated the parameter nature death rate(D), the drug-induced death rate(H), and the mutation rates to individual ones for different cells (N, R1, R2, R12). After solving the ODEs to solution equations, we also found the turnover rate (D/L) and the "HU" (H/u) rate could be two of the factors influencing the solution. Then, we decide how those parameters will influence our solution equation by plotting our assumptions.

Case 1 is the case with unchang parameter, and it could give us the image of how it should look like. It also give us the chance to set t#. In **Case 2**, we have changed the mutation rate for each cells, and that gives the results as that t# could be extended by decreasing the mutation rate in order if possible. In Case 3, by plotting changing D in different order, we found that t# will be influenced significantly by change D. t# will be extended in increasing-order, but it is not realistic to change nature's death rate on purpose. Therefore, we plot **Case 5**; changing H will have a similar function. Even though it will not be as impressive as changing D, the change of H could be applied in real life.

After all the four Cases, **Case 5** is the most ideal case we could plot on changing u and H at the same time to extend the t# without changing D which is almost impossible in the real world. Our assumption on "HU" rate is shown on the graph, so that if "HU" could be maximized, the cross-resistance of 2-drug treatment in cancer could be controlled better.

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