An Analysis on the Intrinsic Resistance to Cancer Treatment Using Chemical Reaction Network

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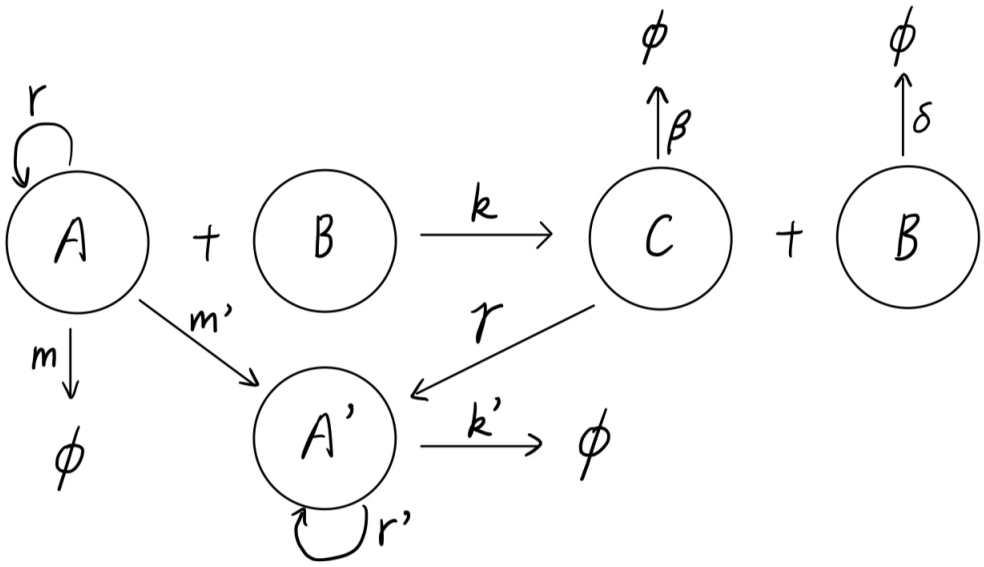
Introduction

Cancer remains one of the most formidable challenges in modern medicine, characterized by its complex nature and the ability of cancer cells to rapidly adapt and develop resistance to treatments. As advancements in biomedical sciences continue to evolve, mathematical modeling has emerged as a powerful tool for understanding the dynamics of cancer growth and the efficacy of treatments. Though the modeled population was bacteria and virus, Luria and Delbrück showed that genetic mutation is independent from environment[2]. Such idea impacted years of research on cancer evolution, giving many mathematical model a stochastic and genetic change flavor when studying the evolution of cancer. Aside from the Darwinian idea, recent research by Angelini, Wang, and etc. has shown therapy can in fact induce drug resistance through phenotypical change[1]. Considering the complexity of cancer as a evolutionary story, we decided to study this biological question through a mathematical lens by incorporating both principles.

Throughout this academic quarter of studying mathematical theory of cellular dynamics, we have learned several key concepts of predict interaction and evolution of cells, as well as population growth and declines. This term paper aims to give the insights from our group and formulate the mathematical model that captures the interaction between sensitive cancer cells and medication, while also accounting for the emergence of drug-resistant cancer cells. In the following sections, we will first describe a deterministic differential equation system formulation of the model, which is built upon the chemical reaction network. Then, examine the assumptions and parameters involved through numerical computation. Lastly, analyze the implications of the results derived from this model. With these steps, we have shown that the most deployed strategy of cancer therapy can only delay the intrinsic return of tumor cells.

Modeling and Formulation

The model integrates key components of cancer treatment, including the population of sensitive cancer cells (A), the impact of medication (B), the development of mutant cancer cells (A'), and the sensitive cells that have interacted with the medication which we will name as post-interaction cells (C). Here, we are considering A' as all cells that have gained resistance to treatment B in all possible ways, including phenotypical change and genetic mutation. Further, we use the assumption from Luria & Delbruck that the probability of A' mutating back to A is negligible[2]. Their reaction network is illustrated in the cartoon below. In our hypothesized reaction network, individual sensitive cell reproduces at rate r, degrade at rate m, and undergo genetic mutation to become resistant cell at rate m'. Sensitive cell population A interacts with treatment B to produce C and B, who acts as a catalyst, at rate k. At rate δ, individual treatment molecule degrades. For individual post-treatment cell, it can either degrade at rate $\beta > m$ or experience phenotypical change at rate γ to become resistant cell. Lastly, each resistant cell degrade at rate $k' < m$ and reproduce at rate $r' > r$.



Throughout this paper, we will use volume mm^3 to measure the population of all cells and treatment to ensure the continuous property. By constructing a set of differential equations, this model seeks to describe the growth and reduction of cancer cells under the influence of medication, the conversion of cancer cells into resistant mutants, and the subsequent impact on the overall cell population.

Cancer cells are characterized by their uncontrolled growth and ability to evade normal regulatory mechanisms of cell division. We introduced the variable A to represent the population of cancer cells at each time step of the computation. This variable involves changes respect to time t. The growth rate of cancer cells, denoted as rA, describe the population changing rate of the cancer cells under cell division and cell death by its own gene. Under medication, a given partition of the existing cancer cell will die under chemical reaction, hence we introduce parameter kAB, which denotes the rate of cancer cell reduction under medication given. However, the medication cannot kill all the cancer cells at once, and they may affect some cancer cells but mutate the cell instead of killing, hence become more drug-resistant. Although cancer cells do not die like normal cells, we still include a parameter for the degradation rate for it, denote as mA. The cancer cell may mutate before treatment, which denotes as $m'A$. Combining all the above, we could form a differential equation about the change of population of cancer cell respect to t:

$$\frac{dA}{dt} = rA - kAB - mA - m'A.$$

Medication are meant to use chemical reaction to the cancer cell to restrict its action, ultimately eliminate active cancer cells from the body and cure the cancer. Since we are assuming it to act like a catalyst to stimulate the sensitive cell death, the only factor that reduces the volume of B would be the metabolism of the patient. Therefore the medication process is fairly simple, and we could introduce a reduction parameter δ:

$$\frac{dB}{dt} = -\delta B.$$

The goal of medication is to cure the cancer, hence the population of the post-interaction cells are essential part of the result from this reaction. From the treatment to cancer cells, we

may have the post-interaction cells from the parameter kAB. The post-interaction cell may die under treatment, so we introduce another parameter β for the death rate of cancer cells after treatment. Just like cancer cells, the post-interaction cells may gain phenotypical advantage under medication in some cases, so we could denote as γ for mutate rate from cancer cell to resistant cell after treatment. We could write the differential equation as:

$$\frac{dC}{dt} = kAB - \beta C - \gamma C.$$

Due to the limit of modern medication, it is very difficult to have all cancer cells been killed at once with one medication. Hence the cancer cells that overcomes the treatment may mutate into a more drug-resisted variant, denoted as A'. It shares a similar composition to the original form of the cancer cell, but may have a different growth rate and reduction rate. Then we cam write a similar differential equation for A':

$$\frac{dA'}{dt} = m'A + r'A' - k'A' + \gamma C.$$

Since there are four key variables to consider, we need to construct four differential equations:

$$\frac{dA}{dt} = rA - kAB - mA - m'A \tag{1}$$
$$\frac{dB}{dt} = -\delta B \tag{2}$$
$$\frac{dC}{dt} = kAB - \beta C - \gamma C \tag{3}$$
$$\frac{dA'}{dt} = m'A + r'A' - k'A' + \gamma C \tag{4}$$

where the description of each parameter are listed below:

- rA: Growth rate of sensitive cancer cells.
- kAB: Rate at which sensitive cancer cells interact with treatment.
- mA: Degradation rate of sensitive cancer cells
- $m'A$: Mutation rate of sensitive cancer cells turning into mutant cells.
- δB: Decrease in medication over time due to consumption and metabolism.
- βC: Death rate of sensitive cancer cells after treatment.
- γC: Mutation rate of sensitive cancer cells into mutant cells after treatment.
- $r'A'$: Growth rate of resistant cells.
- $k'A'$: Degradation rate of resistant cells.

For equation (2), similarly we could solve for $B(t)$ by:

$$\begin{aligned}
\frac{dB}{dt} &= -\delta B \\
\int \frac{dB}{B} &= \int -\delta \, dt \\
\ln B &= -\delta t + C_2 \\
B(t) &= C_2 e^{-\delta t}
\end{aligned}$$

Clearly, $B(0) = C_2$. For equation (1), we could solve for general solution by separation of variables and use the result of $B(t)$:

$$\begin{aligned}
\frac{dA}{dt} &= rA - kAB - mA - m'A \\
\int \frac{dA}{A} &= \int (r - kC_2 e^{-\delta t} - m - m') \, dt \\
\ln A &= (r - m - m')t + \frac{1}{\delta} k C_2 e^{-\delta t} + C_1 \\
A(t) &= C_1 e^{(r-m-m')t + \frac{kC_2}{\delta} e^{-\delta t}}
\end{aligned}$$

Denote initial value $A(0)$, then we easily get $C_1 = A(0)e^{-\frac{k}{\delta}C_2}$. For equations (3) and (4), they each require their own integration factor $\mu(t)$ to further the analytical solving process. For the sake of readability, let us abbreviate $A(t)$ as A and $B(t)$ as B. First, equation (3):

$$\begin{aligned}
\frac{dC}{dt} &= kAB - \beta C - \gamma C \\
\frac{dC}{dt} + (\beta + \gamma)C &= kAB \\
e^{(\beta+\gamma)t}\frac{dC}{dt} + e^{(\beta+\gamma)t}(\beta + \gamma)C &= kABe^{(\beta+\gamma)t} \\
\frac{d}{dt}(e^{(\beta+\gamma)t}C) &= kABe^{(\beta+\gamma)t} \\
e^{(\beta+\gamma)t}C &= \int kABe^{(\beta+\gamma)t} \, dt + C_3 \\
C(t) &= e^{-(\beta+\gamma)t} \int_0^t kABe^{(\beta+\gamma)u} \, du + C_3 e^{-(\beta+\gamma)t}
\end{aligned}$$

Again, denote initial value $C(0)$ with $t = 0$; which gives us the equivalence of $C(0) = C_3$.

Similarly, we can attempt to solve equation (4) as:

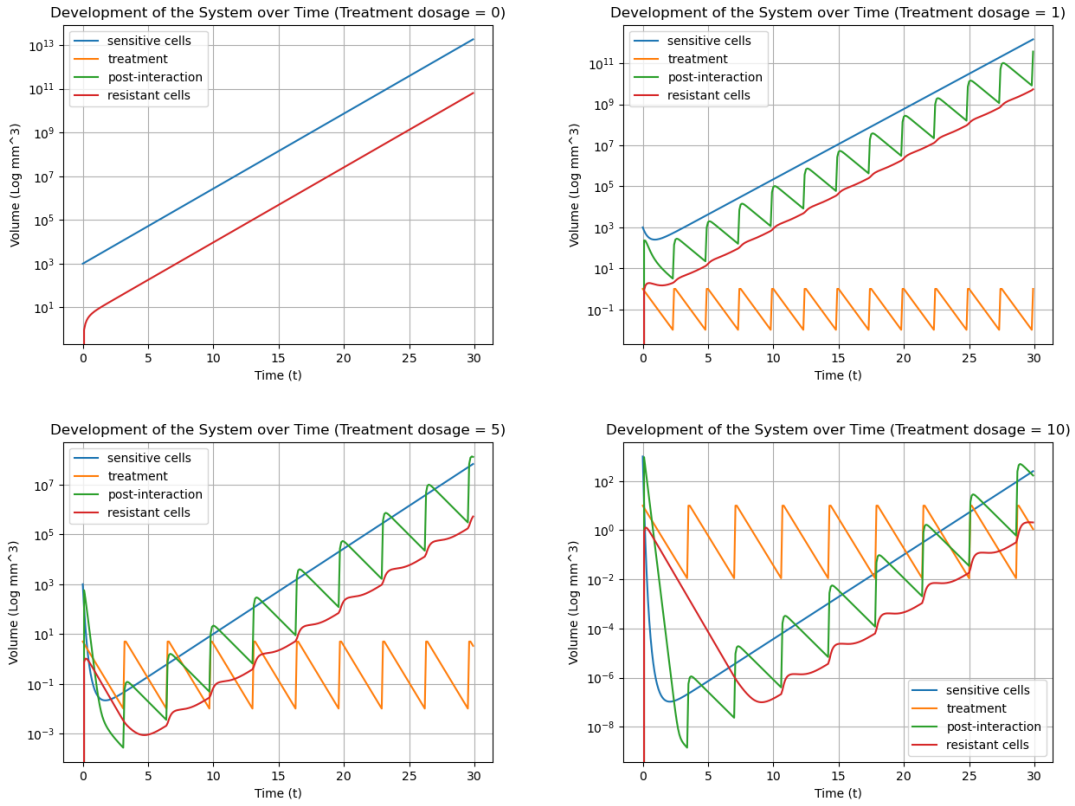
$$\begin{aligned}
\frac{dA'}{dt} &= m'A + r'A' - k'A' + \gamma C \\
\frac{dA'}{dt} + (r'+k')A' &= m'A + \gamma C \\
e^{(r'+k')t}\frac{dA'}{dt} + e^{(r'+k')t}(r'+k')A' &= e^{(r'+k')t}(m'A + \gamma C) \\
\frac{d}{dt}e^{(r'+k')t}A' &= e^{(r'+k')t}(m'A + \gamma C) \\
e^{(r'+k')t}A' &= \int e^{(r'+k')t}(m'A + \gamma C)\, dt + C_4 \\
A'(t) &= e^{-(r'+k')t}\int_0^t e^{(r'+k')u}(m'A + \gamma C)\, du + C_4 e^{-(r'+k')t}
\end{aligned}$$

The strategy to find C_4 is the same as above and we have $A'(0) = C_4$.

As we observe, while $A(t)$ and $B(t)$ can be solved exactly, $C(t)$ and $A'(t)$ fail to produce such clean solutions. It is difficult to study the behavior of our system without proper knowledge from two of the four equations. Hence, we will put our hope in numerical approximation of our system.

Quantitative Approximation

We implemented the above system using Python and plot the reaction trend graph, which are shown below. All of our code is publicly available on github, one may use the link embedded here to see our original code. Let us first examine the system under the following set of rate constants: $r = 1,\ k = 5,\ k' = 0.1,\ m = 0.2,\ m' = 0.01,\ \delta = 2,\ \beta = 10,\ \gamma = 0.01$,. $C_1 = 5,\ C_2 = 1,\ C_3 = -1,\ C_4 = 0$. We will use the trapezoid method to numerically solve for the nested integrals from our model. We have found no significant difference between choosing time advanced steps $h = 0.1$ and $h = 0.01$, so we choose $h = 0.1$ to save some compile time while not lose significant amount of accuracy. The initial conditions are set based on some assumptions: both resistant cells and post-interaction sensitive cells has initial volumes of $C_3 = C_4 = 0$ mm^3, while sensitive cells start at $A(0) = 1000$ mm^3 which gives us $C_1 = 1000e^{-\frac{k}{\delta}C_2}$. We have designed an auto treatment replenishment trigger to simulate the treatment cycles that patients generally undergo. The replenish trigger level is set to 0.01. Once the medication dropped to such level, the booster will automatically apply and refill the overall medication volume back to $B(0) = C_2$. The total time frame for observation is set for 300 unit times. We have set four scenarios: no treatment, continuous treatment with dosages $C_2 = 1$ mm^3, $C_2 = 5$ mm^3, and $C_2 = 10$ mm^3. The plots are shown below with corresponding titles:



Case dosage = 0 **mm**^{3}: In order to observe the behavior of our system better, a 10-based logarithm scale is used for all plots. From the top left plot, we observe exponential growth of both sensitive cells and resistant cells. This is expected based on the form of $A(t)$ and $A'(t)$ and the fact that no treatment intervention is introduced at any time. In this case, all the resistant cells are products of random genetic mutation.

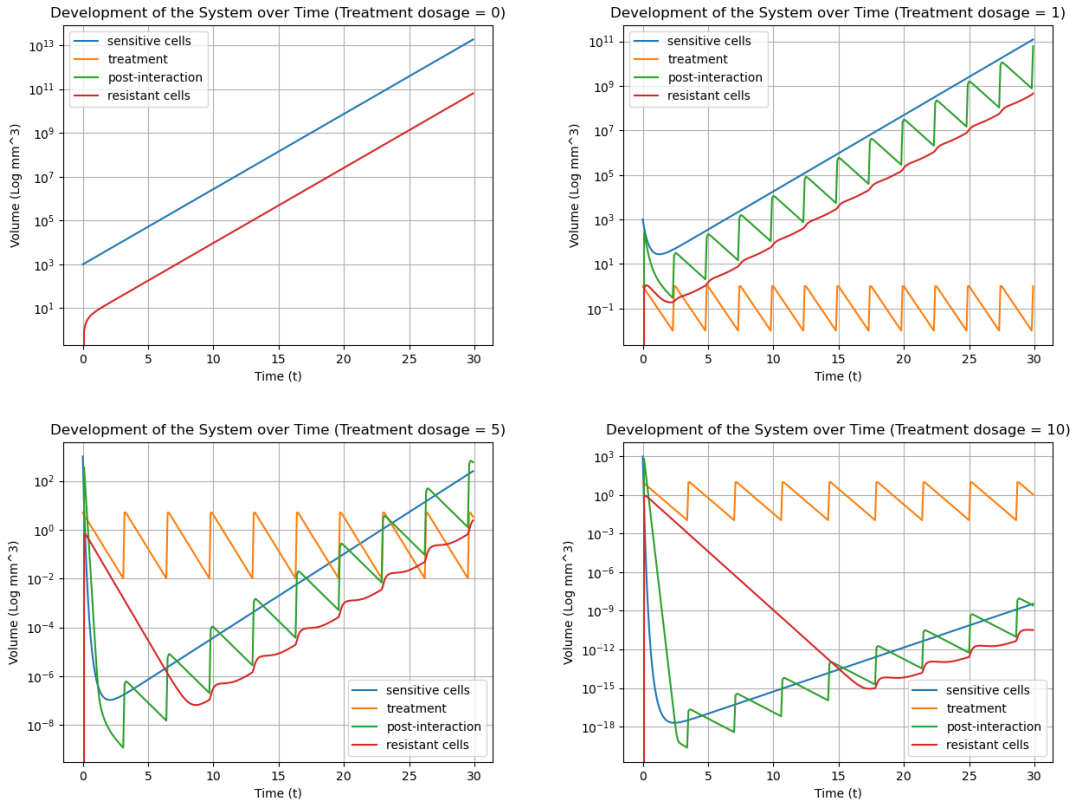
Case dosage = 1 **mm**^{3}: If treatment cycle with low dosage is introduced, we first observe periodic growth of the post-interaction cells that aligns with treatment cycle. This is expected since treatment is the only source of growth for post-interaction cells. With the volume of post-interaction cells being non-zero, resistant cells gain another source of birth from phenotypical change, hence the periodic difference from a pure exponential growth. As for the sensitive cells, the initial treatment gave them a large negative rate of change. However, such decline was quickly recovered and they returned to the exponential growth.

Case dosage = 3 **mm**^{3}: If we increase the dose of each treatment cycle to 3 mm^3, a similar long term behavior is observed. Both resistant cells and post-interaction cells grow periodically atop of exponentially, while sensitive cells follow the same growth rate from the previous cases. Though it is worth noting that between time 0 and 5, volume of resistant cells surpasses the volume of sensitive cells before they both pick up the exponential growth.

Case dosage = 5 **mm**^{3}: As we further increase the dose of each treatment cycle to 5 mm^3. We have the exact same trend except the time taken by sensitive cells to regrow to pre-treatment level prolonged drastically.

Empirically speaking, it seems that increasing the dosage does not produce eradication of sensitive and resistant cells in long-term. Instead of continuing with the dosage, let us increase both k and β to $k = 10$ and $\beta = 20$. This is an effort to study the system that undergoes a

treatment that is more efficient at interacting with and killing sensitive cells. Using the same Python implementation, we have the following plots:



We have generate another set of experiment approximation for the same scheme with medication treatment rate increased from 5 to 10 and post-interaction death rate increased from 10 to 20, while other rate constants and initial conditions remain the same. From the four test result plots shown above, we can see that the general trend is very similar, although it is obvious that higher treatment rate efficiency can postpone the exponential growth of cancer cells to a later time frame, but the exponential return of both sensitive and resistant cells is still observable within the 300 unit time limit.

Results and Discussion

The results shown above have proved the exponential growth of cancer cells as well as the mutated cells, both with and without treatment. The treatment can successfully suppress the initial growth of the tumor, but cannot completely cure the cancer once the resistance kicks in. More frequent dosage interval and higher treatment rate can both positively affect the growth suppression of the tumor and increase the survival rate of the patient. Yet, in clinical practice, doctors could not double the dosage blindly as the chemotherapy has toxicity and one patient can only take so much in a certain amount of time. This complexity of treatment can only paint a grimmer outlook.

This model does not include the nutrition factor to the cells. The model we build is a simplified model that only focus on cell interaction with medication, and all other factors are

exempted in our consideration. As a result, we decided to assume the nutrient supply to be infinite, and the tumor will grow indefinitely as the time develops.

In addition, our model only consider single type of chemotherapy medication throughout our model. We does not consider any other treatment types, including immunotherapy, radiation therapy, surgery, etc. Moreover, we limited our model to only let one type of medication in our model to simplify the drug-resistance parameter and interaction factors. The process of drug degeneration over time and interaction rate have been idealized so that the computation would be more direct. The interaction rate is set to a fixed rate instead of a random variable, and the refill time of medication is set to be instant instead of a "smooth" incline.

However, we were able to demonstrate that the simple strategy of killing cancer cells at a higher rate failed containing cancer in long term. Such result agrees with both genetic mutation model[2] and phenotypical mutation model[1]. Therefore, we lay our case that the cure to cancer may not be eradicating cancer's presence, but rather finding a way to co-exist.

References

[1] Erin Angelini et al. "A model for the intrinsic limit of cancer therapy: Duality of treatment-induced cell death and treatment-induced stemness". In: *PLOS Computational Biology* 18.7 (July 2022), pp. 1–17. DOI: 10.1371/journal.pcbi.1010319. URL: https://doi.org/10.1371/journal.pcbi.1010319.

[2] S E Luria and M Delbrück. "MUTATIONS OF BACTERIA FROM VIRUS SENSITIVITY TO VIRUS RESISTANCE". In: *Genetics* 28.6 (Nov. 1943), pp. 491–511. ISSN: 1943-2631. DOI: 10.1093/genetics/28.6.491. eprint: https://academic.oup.com/genetics/article-pdf/28/6/491/34895327/genetics0491.pdf. URL: https://doi.org/10.1093/genetics/28.6.491.