Mathematical Modeling of Cancer Treatment and the Development of Resistance

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Introduction

The American Cancer Society projects that in 2025, there will be approximately 2,041,910 new cancer cases and 618,120 cancer deaths in the United States (Siegel., et al 2025). Despite the decrease in mortality rate over recent years, cancer remains the second leading cause of death in the United States, driving the need for improved detection, new therapeutics, and optimized treatment plans. One significant challenge to therapy is the heterogeneity of cancers, which consist of populations with varying degrees of drug-resistance (Gatenby et al., 2009). Additionally, cancers exhibit significantly different properties. Aggressive cancers, which typically have greater dysregulation of cell cycle genes, tend to exhibit higher proliferation rates than their less aggressive counterparts (Zhang et al., 2024). Aggressive types are also known for their ability to inhibit apoptosis. Although counterintuitive, as much as 70% of the cells in glioblastoma, an aggressive cancer, were shown to be apoptotic, possibly due to the inconsistency of regulatory mechanisms in tumor cells (Morana et al., 2022). To explore the dynamics of susceptible and drug-resistant tumor cells in aggressive and slow-growing tumors, a mathematical model of tumor populations is analyzed, and numerical simulations are performed.

Mathematical and Numerical Analysis

Susceptible and Resistant Tumor Model

The model can be described using the following system of equations, where x and y represent the number of susceptible and drug-resistant tumor cells respectively. The constants r_1 and r_2 represent the replication rate of the susceptible and drug-resistant cells. The carrying capacity K defines the equations as a logistic growth model, in which susceptible and drug-resistant populations compete for the same resources.

$$\begin{cases} \dot{x} = r_1 x\left(1 - \dfrac{x+y}{K}\right) - d_1(t)x \\ \dot{y} = r_2 y\left(1 - \dfrac{x+y}{K}\right) - d_2 y \end{cases} \tag{1}$$

$$r_1 > r_2 > 0, \quad d_1(t) \geq d_2 > 0$$

The rate of death $d_1(t)$ is a piecewise function which is equivalent to d_{tr} during on-treatment periods and the constant d_2, which is the rate of death for both populations during off-treatment periods.

$$d_1(t) = \begin{cases} d_{tr}, \ (i-1)(T_0 + T_{tr}) < t < (i-1)(T_0 + T_{tr}) + \ T_{tr} \\ d_2, (i-1)(T_0 + T_{tr}) + T_{tr} < t < i(T_0 + T_{tr}) \end{cases}$$

$$d_{tr} \in (d_2, \ d_{max})$$

The model operates under several assumptions. First, the drug is assumed to be evenly distributed among all cells, such that the rate of death $d_1(t)$ is only affected by the presence of treatment. The model also assumes that no new populations emerge, and that the initial number of susceptible cells x_0 greatly exceeds the number of drug-resistant cells y_0. Finally, the rates of replication and death are set to zero when a population is eliminated; spontaneous reemergence of a population is not possible. To focus on the optimization of treatment schedules, the bounds of the replication rate will be modified to $r_1 > \ r_2 > d_2$, such that neither cell population will be naturally eliminated.

Derivation of Steady States

The steady states can be derived by setting the derivatives of the system to zero.

$$\begin{cases} r_1 x\left(1 - \dfrac{x+y}{K}\right) - d_1(t)x = 0 \\ \ r_2 y\left(1 - \dfrac{x+y}{K}\right) - d_2 y = 0 \end{cases}$$

Upon inspection, the first steady state $(0, 0)$ is observed, which describes the cancer-free state of the patient. Substituting $y = 0$ from the second equation into the first, the steady state describing a susceptible population dominant and drug-resistant population free tumor is derived.

$$x = K\left(1 - \frac{d_1(t)}{r_1}\right)$$

Conversely, substituting x = 0 from the first equation into the second, the steady state describing a drug-resistant population dominant and susceptible population free tumor is derived.

$$y = K\left(1 - \frac{d_2}{r_2}\right)$$

Continuing to isolate x and y,

$$\begin{cases} 1 - \dfrac{x+y}{K} = \dfrac{d_1(t)}{r_1} \\ \ 1 - \dfrac{x+y}{K} = \dfrac{d_2}{r_2} \end{cases}$$

Since $d_1(t)$ is a function of time defined by two constants, d_{max} and d_2, the stability of the system must be analyzed separately for on-treatment and off-treatment periods to analyze the coexistence states. During on-treatment, the following coexistence steady state is observed. Coexistence during off-treatment is not possible because $r_1 \neq r_2$.

$$x + y = K\left(1 - \frac{d_{max}}{r_1}\right) = K\left(1 - \frac{d_2}{r_2}\right)$$

$$\frac{d_{max}}{r_1} = \frac{d_2}{r_2}$$

Thus, the following four steady states are obtained.

$$(0, 0)$$

$$(K\left(1 - \frac{d_1(t)}{r_1}\right), 0)$$

$$(0, K\left(1 - \frac{d_2}{r_2}\right))$$

$$(x, y)\ such\ that\ x + y = K\left(1 - \frac{d_{max}}{r_1}\right) = K\left(1 - \frac{d_2}{r_2}\right)$$

Stability Analysis

Stability analysis is performed by calculating the Jacobian of the system

$$J = \begin{bmatrix} r_1\left(1 - \frac{x+y}{K}\right) - \frac{r_1 x}{K} - d_1(t) & -\frac{r_1 x}{K} \\ -\frac{r_2 y}{K} & r_2\left(1 - \frac{x+y}{K}\right) - \frac{r_2 y}{K} - d_2 \end{bmatrix} \quad (2)$$

The Jacobian at $(0, 0)$ for yields the following.

$$J = \begin{bmatrix} r_1 - d_1(t) & 0 \\ 0 & r_2 - d_2 \end{bmatrix}$$

Stability is initially achieved during on-treatment when $d_1(t) = d_{max} > r_1$ and r_2, $d_2 = 0$ of the drug-resistant population. This occurs when the drug-resistant population is eliminated and the treatment d_{max} is sufficiently effective to reduce the susceptible population. The second condition is when both populations have been eliminated, and the rates of death and replication for both populations are zero.

The Jacobian at $(K\left(1 - \frac{d_1(t)}{r_1}\right), 0)$ for the susceptible dominant state yields the following.

$$J = \begin{bmatrix} -r_1 + d_1(t) & -r_1 + d_1 \\ 0 & \frac{r_2 d_1(t)}{r_1} - d_2 \end{bmatrix}$$

For the inequality $\frac{r_2 d_1(t)}{r_1} - d_2 < 0$ in J_{22}, the piecewise function $d_1(t)$ can be broken down to demonstrate that stability is achieved during off-treatment periods since $r_1 > r_2$. For stability during on-treatment periods, $\frac{d_{max}}{r_1} < \frac{d_2}{r_2}$, meaning the drug-resistant cells must be dying at a proportionally higher rate than the susceptible cells.

Inserting $(0, K\left(1 - \frac{d_2}{r_2}\right))$ for the drug-resistant dominant state yields the following.

$$J = \begin{bmatrix} \frac{r_1 d_2}{r_2} - d_1(t) & 0 \\ -r_2 + d_2 & -r_2 + d_2 \end{bmatrix}$$

Stability can only be achieved during on-treatment periods such that $\frac{d_{max}}{r_1} > \frac{d_2}{r_2}$, meaning the drug is sufficiently effective to kill the susceptible cells at a proportionally higher rate than the drug-resistant cells.

Finally, the Jacobian for the coexistence state at $(K\left(1 - \frac{d_{max}}{r_1}\right), K\left(1 - \frac{d_2}{r_2}\right))$ during on-treatment is given by:

$$J = \begin{bmatrix} -2r_1 + d_{max} + \frac{r_1 d_2}{r_2} & -r_1 + d_{max} \\ -r_2 + d_2 & -2r_2 + d_2 + \frac{r_2 d_{max}}{r_1} \end{bmatrix}$$

Stability can be achieved during on-treatment periods when $\frac{d_{max}}{r_1} = \frac{d_2}{r_2}$.

Tumor Treatment from Stability Conditions

Based on the stability analysis, treatment should follow two stages.

The first stage must favor the susceptible dominant steady state during which stability is naturally achieved during off-treatment. If the treatment is sufficiently effective such that $\frac{d_{max}}{r_1} > \frac{d_2}{r_2}$, the on-treatment period should be minimized to carefully control the susceptible population while allowing them to outcompete the drug-resistant population.

Numerical Simulation of Tumor Model

Four fixed doses, maximum, moderate, low, and none were assigned as the following.

$$maximum: d_{max}$$

$$moderate: d_{max}/2$$

$$low: d_{max}/4$$

$$none: 0$$

Additionally, an adaptive treatment solution was implemented using the two-stage strategy described previously. While the resistant population remained above the threshold for elimination, a low dose was applied. After the resistant population was eliminated, a high dose was applied for the remainder of the treatment periods. The following parameters were used for the aggressive and slow-growing cancer alongside their associated properties of cancer.

	Parameter	Aggressive	Slow-Growing
Proliferation Rate	r_1, r_2	$r_1 = 1.2, r_2 = 1.0$	$r_1 = 0.6, r_2 = 0.5$
Death Rate	d_2	$d_2 = 0.7$	$d_2 = 0.4$
Angiogenesis	K	$K = 800$	$K = 250$
Drug Effectiveness	d_{max}	$d_{max} = 1.5$	$d_{max} = 2.5$

Table 1: Parameters of aggressive and slow-growing cancers with associated properties of cancer.

All combinations of treatment cycles ranging from an on-treatment time of one to seven days and an off-treatment time of 2-21 days. Optimal parameters for T_{tr} and T_0 were selected based on successful elimination of the resistant tumor cell populations, and degree of clinical feasibility. For the ranges of T_{tr} and T_0 to iterate through, reference values from the 7+3 treatment regimen for AML, in which patients undergo seven days of treatment followed by two to three weeks of rest (Rowe, 2022).

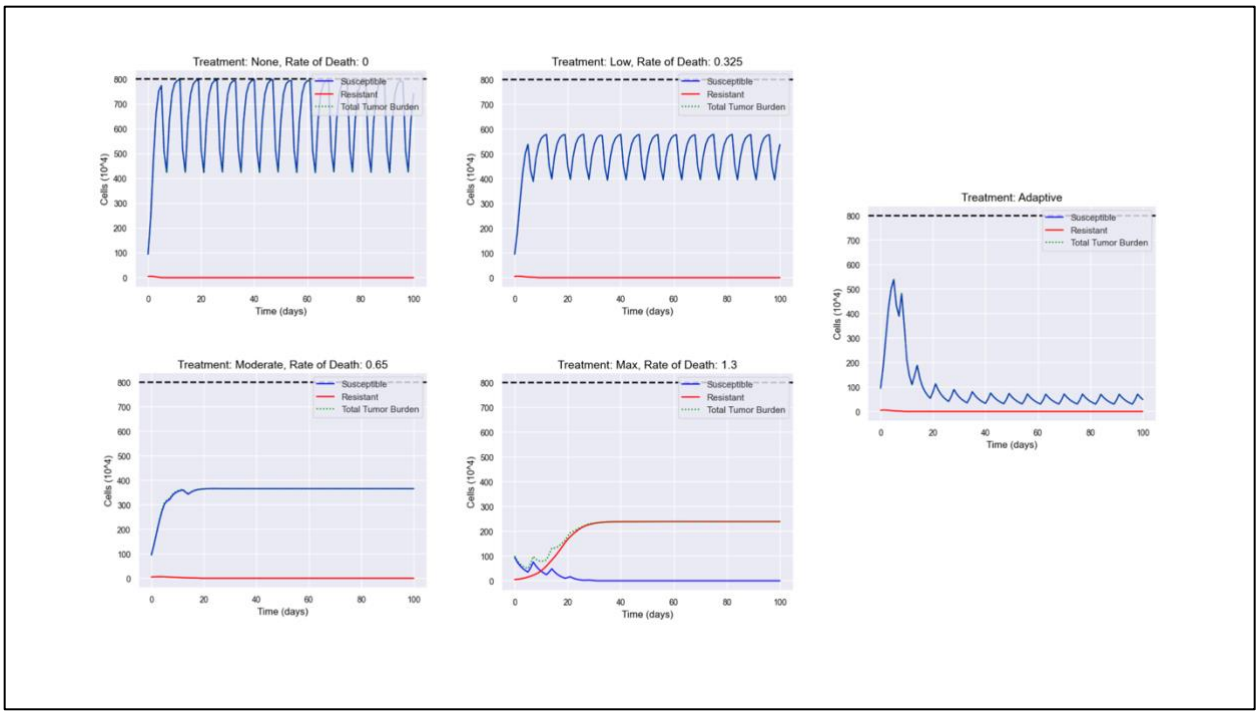

Figure 1: Numerical simulation of aggressive cancer using the parameters described in Table 1. Initial values are $x_0 = 95$ and $y_0 = 5$.

The aggressive cancer shows successful suppression of the drug-resistant population for the none, low, and moderate treatment conditions, where $\frac{d_{max}}{r_1} < \frac{d_2}{r_2}$ for the none and low conditions. For moderate treatment, the off-treatment period T_0 as well as the replication rate r_1 compared to r_2 were sufficiently large to eliminate the drug-resistant population. For max treatment, $\frac{d_{max}}{r_1} > \frac{d_2}{r_2}$ favored the drug-resistant population. Adaptive treatment depicts successful elimination of the drug-resistant population, and a chronic cancer in which the susceptible population is suppressed, but not eliminated. This occurs when the treatment length T_{tr} is not long enough for the cancer-free steady state $d_{max} > r_1$.

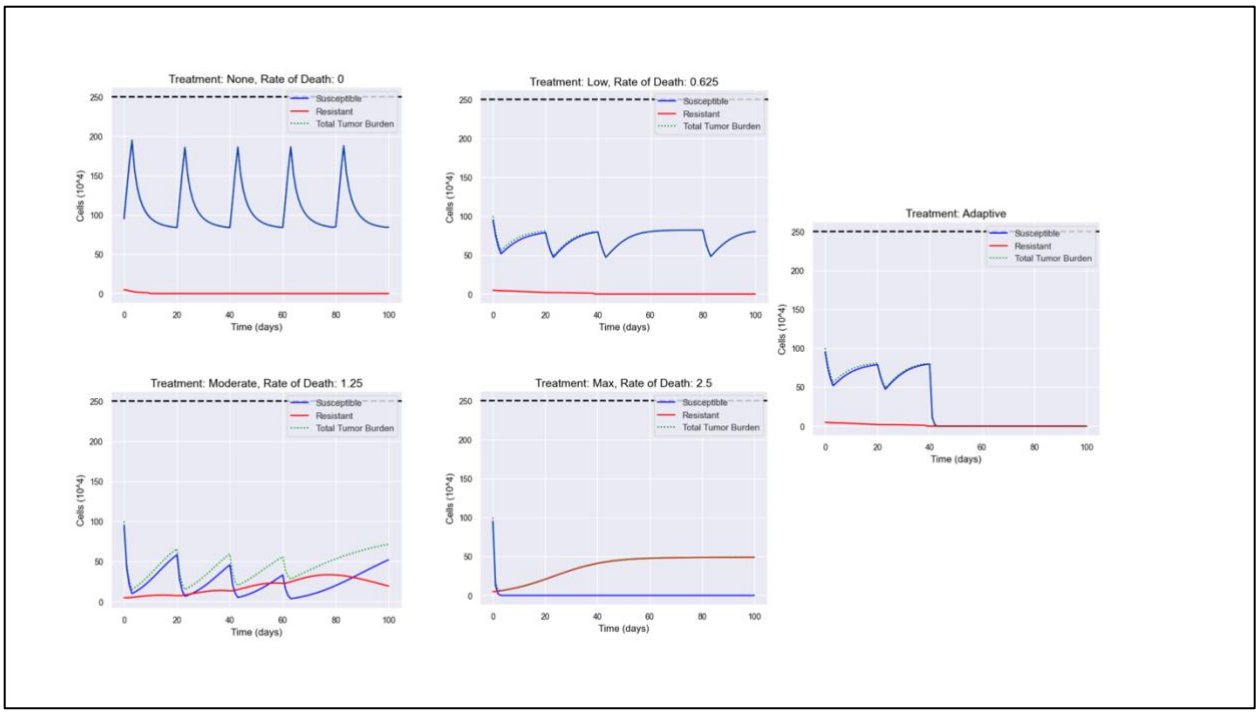

Figure 2: Numerical simulation of slow-growing cancer using the parameters described in Table 1. Initial values are $x_0 = 95$ and $y_0 = 5$.

Similar trends are seen in Fig. 2, in which the none and low treatment conditions favor a susceptible dominant steady state. For the moderate and max treatment conditions, $\frac{d_{max}}{r_1} > \frac{d_2}{r_2}$ favors the drug-resistant population and off-treatment period T_0 is not long enough to allow the susceptible population to regrow. Adaptive treatment shows successful elimination of the cancer. $d_{max} > r_1$ and the on-treatment cycle T_{tr} is long enough.

Conclusion

Adaptive treatment is a promising method of drug delivery which aims to use the susceptible tumor cells to outcompete the drug-resistant tumor cells before delivering a high drug dosage. Fixed treatments, by comparison, result in large susceptible populations for the none and low treatment conditions as well as large drug-resistant populations for the moderate and max treatment conditions.

Code Availability

Analysis code can be found at the following link: https://github.com/aneeshkd/Tumor-Resistance-Modeling

References

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