Optimal Control Applied to Chemotherapy of Reverse Transcription Inhibitors for HIV

Milestone #2

MATH 325

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1 Introduction

Human immunodeficiency virus (HIV) is a virus that attacks the immune system and affects nearly 40 million people globally. Though the infection is lifelong, modern treatments such as chemotherapy can significantly improve life expectancy and reduce transmission risk for those living with HIV. This paper considers the chemotherapy of reverse transcription inhibitors, which interrupt key mechanisms of the HIV infection process.

The pathogenesis of HIV is characterized by the infection of CD4+ T-cells, integration of viral RNA into host cell DNA, production of new free virus particles, and subsequent cell death, releasing these particles into the bloodstream. This is particularly dangerous because of the essential role that CD4+ T-cells, a type of white blood cell, have in defending the body against infections.

Chemotherapy treatment can increase the concentration of CD4+ T-cells in the blood, leading to improved patient outcomes; however, higher strength chemotherapy treatment is toxic and drug resistance can render the treatment ineffective after a certain period of time. We aim to apply an optimal control model to chemotherapy of HIV to maximize the number of healthy CD4+ T-cells while minimizing the cost of treatment to the body, that is, dangerous side effects. This approach allows us to develop an optimal treatment regimen over a fixed period of time, avoiding the issue of drug resistance. We begin by defining the compartmental infection model and associated optimal control problem, continue by deriving necessary conditions, and conclude by testing the model for different parameter values with a Runge-Kutta 4 approximation in MATLAB.

2 Model Development

2.1 Assumptions

We use a compartmental model (see Figure 1) to best describe the interaction between the immune system and HIV. We let $T(t)$ and $T_i(t)$ be the concentration of uninfected and infected CD4+T cells at time t, respectively, while $V(t)$ represents the concentration of free virus particles. Though the virus particles $V(t)$ and white blood cells $T(t)$ and $T_i(t)$ are separate populations, they are directly related; as infected CD4+T-cells die, they release HIV virions into the body. Note that blood concentration here is measured by population count per unit volume.

We want our differential equation $T'(t)$ to look something like $T'(t) =$ new cell generation + cell growth − cell infections − cell deaths, so we continue by defining the necessary parameters. We assume that healthy CD4+ T-cells are generated in the body at a rate of $\frac{s}{1+V(t)}$ and have a natural death rate of m_1. White blood cell growth can be modeled logistically, with a growth rate parameter of r and a maximum total

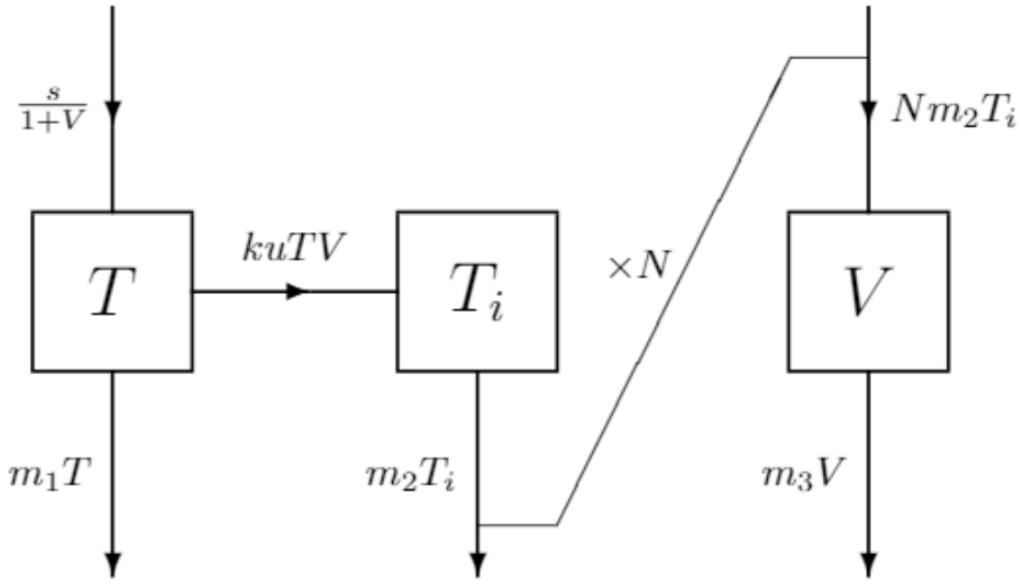

Figure 1: The compartmental model describing interactions between the immune system and HIV. [1]

white blood cell count of T_{max}, which includes both healthy and infected cells. So far, this means $T'(t) = \frac{s}{1+V(t)} + rT(t)[1 - \frac{T(t)+T_i(t)}{T_{max}}] - m_1T(t)$. As CD4+ T-cells are infected, they move from the healthy (T) compartment to the infected (T_i) compartment with a speed that we call the infection rate. To determine what this rate is, we define a parameter k that specifies how often virion-T-cell reactions result in infections. Higher concentrations of virion particles and of uninfected CD4+ T-cells increase the likelihood of these interactions, so we take their product into the differential equation. We can then represent the infection rate as $kT(t)V(t)$. Then, the equation for the concentration of healthy CD4+ T-cells $T'(t)$ is

$$T'(t) = \frac{s}{1+V(t)} + rT(t)[1 - \frac{T(t)+T_i(t)}{T_{max}}] - kT(t)V(t) - m_1T(t).$$

We assume that infected T-cells do not grow since they use their energy to produce new virion particles until cell death. Since CD4+ T-cells can only become infected through the previously explained mechanism, we only need to account for their infection rate $kT(t)V(t)$ and their natural death rate m_2, yielding the following differential equation:

$$T_i'(t) = kT(t)V(t) - m_2T_i(t).$$

Because virion production is directly related to infected cell death, if we assume that an average of N virus particles are produced in each host cell, then virions are created at a rate of $Nm_2T_i(t)$. With a natural death rate of m_3, we have that

$$V'(t) = Nm_2T_i(t) - m_3V(t).$$

Note that all parameters specified above are non-negative. We also assume all initial conditions are positive since it is nonsensical to have a negative concentration of cells or virions. With our system of ordinary differential equations well-defined, we can develop the associated optimal control problem.

2.2 Optimal Control Model

Recall that our goal for the optimal control problem is to maximize the concentration of healthy CD4+T-cells, $T(t)$, while minimizing the toxicity of chemotherapy to the body. We incorporate a weight parameter $A > 0$ to account for the importance we assign to maximizing CD4+ count versus minimizing harmful side effects.

The control $u(t)$ will represent the strength of the chemotherapy treatment, with $u(t) = 0$ being maximum therapy and $u(t) = 1$ being no therapy. Though it is unrealistic to achieve maximum therapy $u(t) = 0$ in practice, selecting this as our lower bound for the control provides a simpler mathematical problem. Modeling the toxicity of chemotherapy to the body requires a term that equals zero when $u(t) = 1$ and becomes large as $u(t)$ approaches zero. This cost term could be $1 - u(t)$, but to make the cost term larger as stronger treatment is used, we square it. Since we are minimizing the cost term, we subtract this from the objective functional.

Optimizing over a fixed time interval allows us to account for drug resistance over time. We assume that treatment will reduce the infectivity of the virus over a finite time horizon until drug resistance occurs. We let t_{final} be the number of days before chemotherapy treatment loses its efficacy, which will vary depending on drug selection.

Putting this all together, we can now state the formal optimal control problem

$$\begin{aligned}
&\max_u \int_0^{t_{final}} AT - (1-u(t))^2 dt \\
\text{subject to } &T'(t) = \frac{s}{1+V(t)} + rT(t)[1 - \frac{T(t)+T_i(t)}{T_{max}}] - kT(t)V(t) - m_1 T(t), \\
&T_i'(t) = kT(t)V(t) - m_2 T_i(t), \\
&V'(t) = Nm_2 T_i(t) - m_3 V(t) \\
&0 \le u(t) \le 1 \\
&T(0) = T_0 > 0, T_i(0) = T_{i0} > 0, V(0) = V_0 > 0.
\end{aligned}$$

3 Model Solution

We begin by defining the Hamiltonian. Each of our three states requires an associated adjoint equation, which we call $\lambda_1(t), \lambda_2(t),$ and $\lambda_3(t)$. These adjoints serve to append the differential equations $T(t), T_i(t),$ and $V(t)$ to the objective functional, and here we use them to solve for our optimal control $u^*(t)$. The basic form of the three-state Hamiltonian is $H = f + \lambda_1 T'(t) + \lambda_2 T_i(t) + \lambda_3 V(t)$, where f is the objective functional. Then, our full Hamiltonian is

$$\begin{aligned}
H = AT - (1-u(t))^2 + \lambda_1[\frac{s}{1+V(t)} + rT(t)[1 - \frac{T(t)+T_i(t)}{T_{max}}] - kT(t)V(t) \\
-m_1 T(t)] + \lambda_2[kT(t)V(t) - m_2 T_i(t)] + \lambda_3[Nm_2 T_i(t) - m_3 V(t)].
\end{aligned}$$

The Hamiltonian provides us with the adjoint and optimality conditions, which are essential in the development of our numerical approximation. The adjoint equations $\lambda_1'(t), \lambda_2'(t),$ and $\lambda_3'(t)$ are defined as

$$\lambda_1'(t) = -\frac{\partial H}{\partial T}, \qquad \lambda_2'(t) = -\frac{\partial H}{\partial T_i}, \qquad \lambda_3'(t) = -\frac{\partial H}{\partial V},$$

and from the Hamiltonian, we find that

$$\lambda_1'(t) = \lambda_1 m_1 - A - \lambda_1 r[1 - \frac{T(t)+T_i(t)}{T_{max}}] + \frac{\lambda_1 r T(t)}{T_{max}} + \lambda_1 k u(t) V(t) - \lambda_2 k u(t) V(t)$$
$$\lambda_2'(t) = \frac{\lambda_1 r T(t)}{T_{max}} + \lambda_2 m_2 - \lambda_3 N m_2$$
$$\lambda_3'(t) = \lambda_1 k T(t) u(t) + \frac{\lambda_1 s}{(1+V(t))^2} - \lambda_2 k T(t) u(t) + \lambda_3 m_3.$$

We continue by finding the optimality condition, which describes the ideal chemotherapy treatment. Because our system has a bounded control, it is sufficient to solve $\frac{\partial H}{\partial u} = 0$ in terms of u^* and then incorporate the bounds into the equation for u^*. In our forward-backward sweep, we will set the guess for u^* to be

$$\min(1, \max(0, \frac{\partial H}{\partial u} = 0)$$

which accounts for both endpoints without requiring extra calculus. It can be verified that

$$u^*(t) = 1 - \frac{\lambda_1 k T(t) V(t) + \lambda_2 k T(t) V(t)}{2}.$$

All that is left is to define transversality conditions for the adjoints; as there are no payoff terms or other odd behavior, we simply set $\lambda_1(t_{final}) = \lambda_2(t_{final}) = \lambda_3(t_{final}) = 0$.

Our final system to be solved is

$$T'(t) = \frac{s}{1+V(t)} + rT(t)[1 - \frac{T(t)+T_i(t)}{T_{max}}] - kT(t)V(t) - m_1 T(t),$$
$$T_i'(t) = kT(t)V(t) - m_2 T_i(t),$$
$$V'(t) = Nm_2 T_i(t) - m_3 V(t)$$
$$\lambda_1'(t) = \lambda_1 m_1 - A - \lambda_1 r[1 - \frac{T(t)+T_i(t)}{T_{max}}] + \frac{\lambda_1 r T(t)}{T_{max}} + \lambda_1 k(1 - \frac{\lambda_1 k T(t) V(t) + \lambda_2 k T(t) V(t)}{2}) V(t)$$
$$- \lambda_2 k(1 - \frac{\lambda_1 k T(t) V(t) + \lambda_2 k T(t) V(t)}{2}) V(t)$$
$$\lambda_2'(t) = \frac{\lambda_1 r T(t)}{T_{max}} + \lambda_2 m2 - \lambda_3 N m_3$$
$$\lambda_3'(t) = \lambda_1 k T(t)(1 - \frac{\lambda_1 k T(t) V(t) + \lambda_2 k T(t) V(t)}{2}) + \frac{\lambda_1 s}{(1+V(t))^2} - \lambda_2 k T(t)(1 - \frac{\lambda_1 k T(t) V(t) + \lambda_2 k T(t) V(t)}{2}) + \lambda_3 m_3$$
$$\lambda_1(t_{final}) = \lambda_2(t_{final}) = \lambda_3(t_{final}) = 0$$
$$T(0) = T_0 > 0, T_i(0) = T_{i0} > 0, V(0) = V_0 > 0,$$

Certainly the complexity of this system eliminates the possibility of finding an analytical solution. In the following section, we analyze the results of our Runge-Kutta 4 forward-backward sweep algorithm in MATLAB.

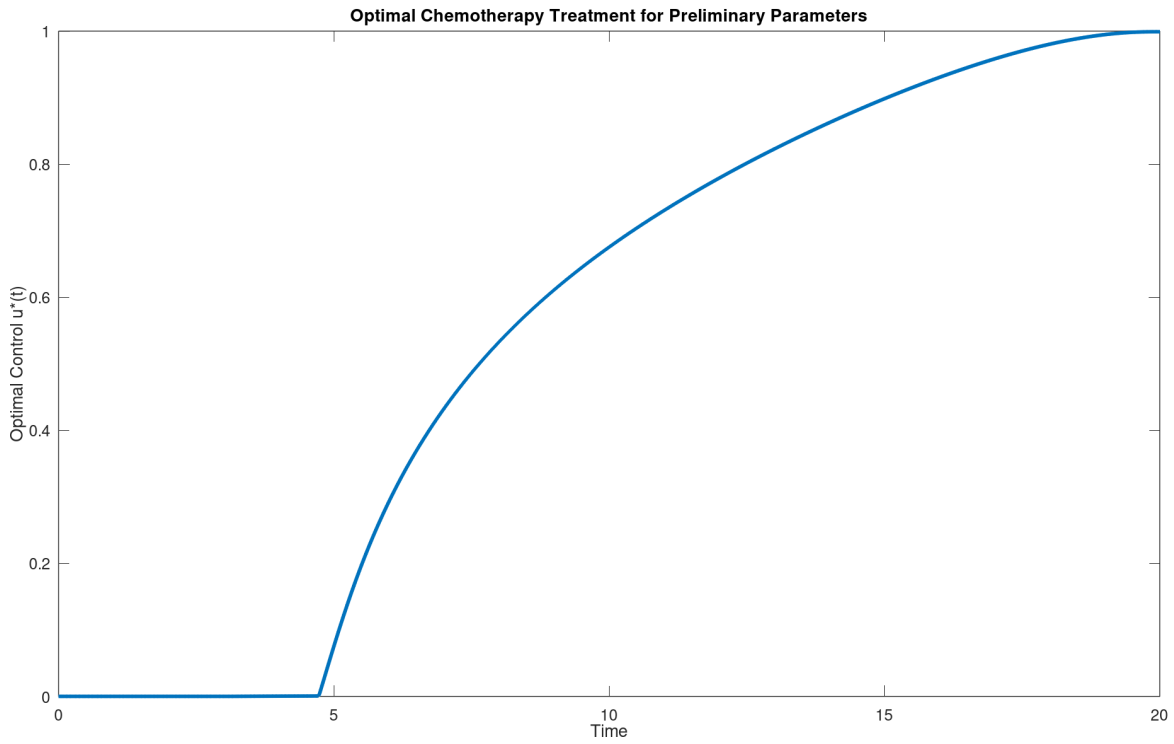

Figure 2: Optimal Chemotherapy Regimen for parameters provided below. Observe that $u^*(t)$ begins with maximal treatment then decreases to no treatment by day 20.

4 Experimentation

4.1 Preliminary Testing

We begin our simulation with the following parameters:

$$s = 10 \quad m_1 = 0.02 \quad m_2 = 0.5 \quad m_3 = 4.4 \quad r = 0.03 \quad T_{max} = 1500 \quad k = 0.000024$$
$$N = 300 \quad T_0 = 800 \quad T_{i0} = 0.04 \quad V_0 = 1.5 \quad A = 0.05 \quad t_{final} = 20.$$

We see from Figure 2 that the optimal chemotherapy regimen begins with the maximum dose $u(t) = 0$ administered for 5 days before steadily decreasing treatment. From Figure 3, we can see that healthy T-cell concentration steadily increases over the course of 20 days. HIV virion and infected T-cell concentrations decrease significantly between $t = 0$ and $t = 18$, then increasing marginally as treatment is halted near the end of the time interval.

We test the efficacy of our model by varying each parameter and evaluating their effects on the chemotherapy treatment $u^*(t)$ and on T-cell and virion concentrations $T(t), T_i(t),$ and $V(t)$.

4.2 Varying A

We begin by testing the effects of varying the weight parameter A, the weight we assign to maximizing $T(t)$. Figure 4 shows the impact of decreasing A by one half. We see that the smaller value of A results in maximum treatment halting a day earlier. Additionally, we observe a marginal decrease in healthy CD4+ concentration, whereas both infected CD4+ cell count and free virus particles are nearly doubled compared to the baseline system. Both systems exhibit the same general behavior.

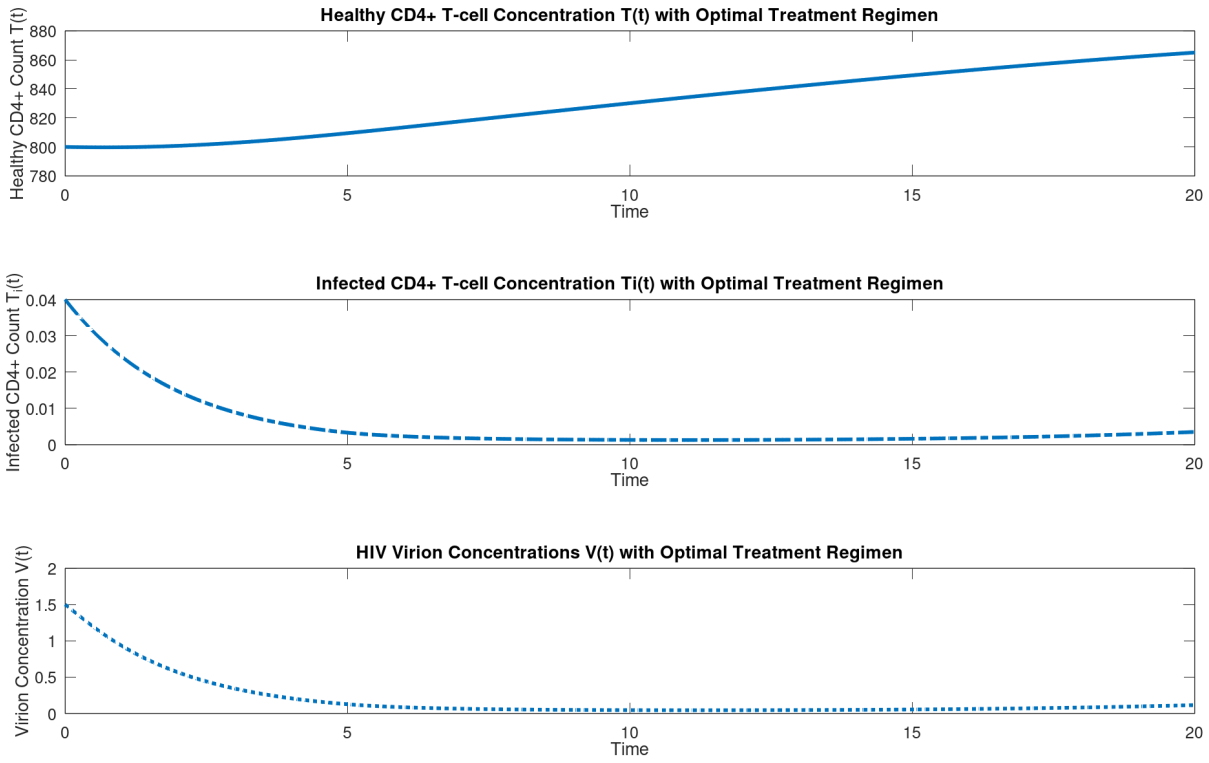

Figure 3: Optimal States for parameters provided for preliminary testing. Notice that due to the chemotherapy treatment, healthy T-cell concentration slowly rises whereas infected T-cell and free virus concentrations quickly drop after about 5 days.

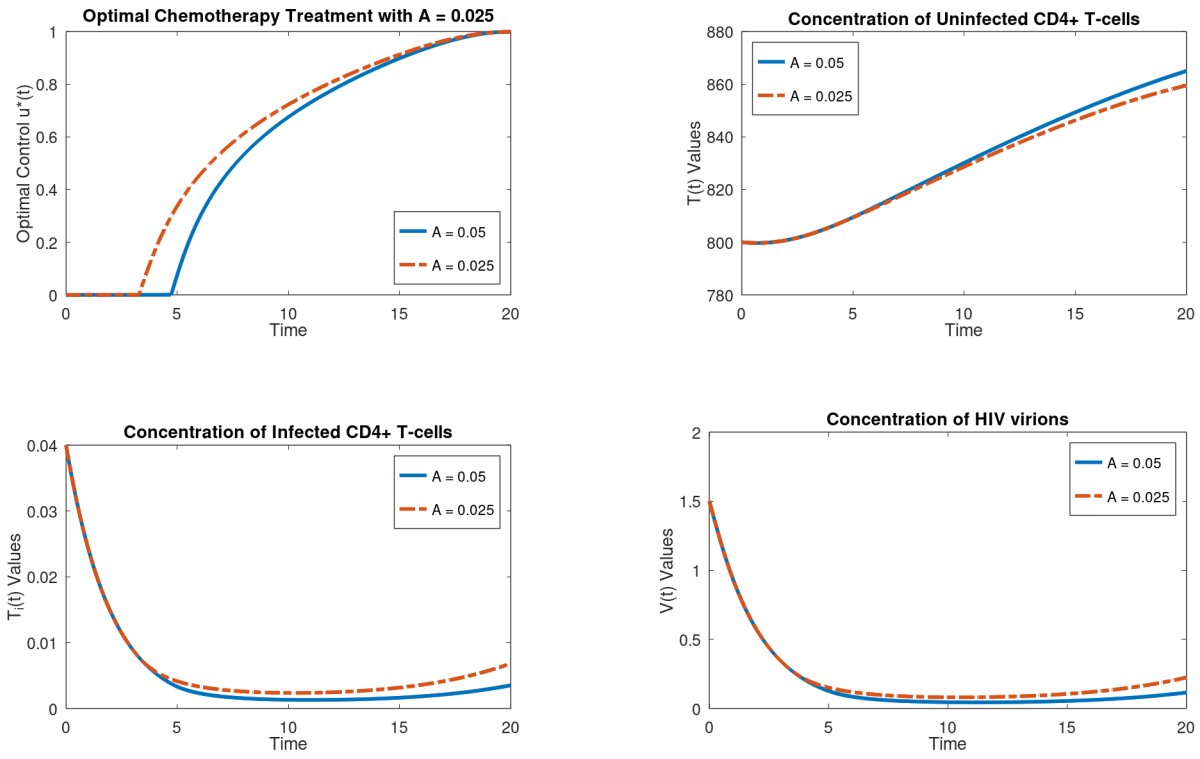

Figure 4: Optimal Chemotherapy Treatment with $A = 0.05$ (blue) and $A = 0.025$ (red). A larger value of A leads to a more aggressive treatment regimen.

4.3 Varying N

We next consider the impact of N on the optimal control, as seen in Figure 5. Decreasing N slightly produces a less aggressive treatment, with maximum strength therapy halted about one day earlier. A dramatic reduction to $N = 50$ results in no maximal strength treatment being used; rather, low-strength therapy is applied until about day 10, when practically no treatment is used.

4.4 Varying r

The growth rate of healthy T-cells, r, is tested in Figure 6. While chemotherapy treatment, concentration of infected T-cells, and virion concentration are nearly identical for the two r values, there is a significant difference by $t = 20$ days for the healthy T-cells, with $T(20) = 950$ when r is larger and $T(20) = 860$ when r is smaller.

4.5 Varying k

Increasing the parameter k by 33% results in a slightly more aggressive treatment regimen, with maximum treatment sustained for an extra day to maintain the same final concentration of healthy CD4+ T-cells. Despite the increase in treatment, this small change in k nearly doubles the final concentrations of infected white blood cells and HIV virus particles by day 20. Compared to the marginal increases we saw in Figure 3, this spike near the end of the time interval is certainly significant.

4.6 Varying s

While infected T-cell and free virus particle concentrations are near-identical for different values of s, there is a significant difference in the final number of healthy CD4+ T-cells for each value of s (top right) which

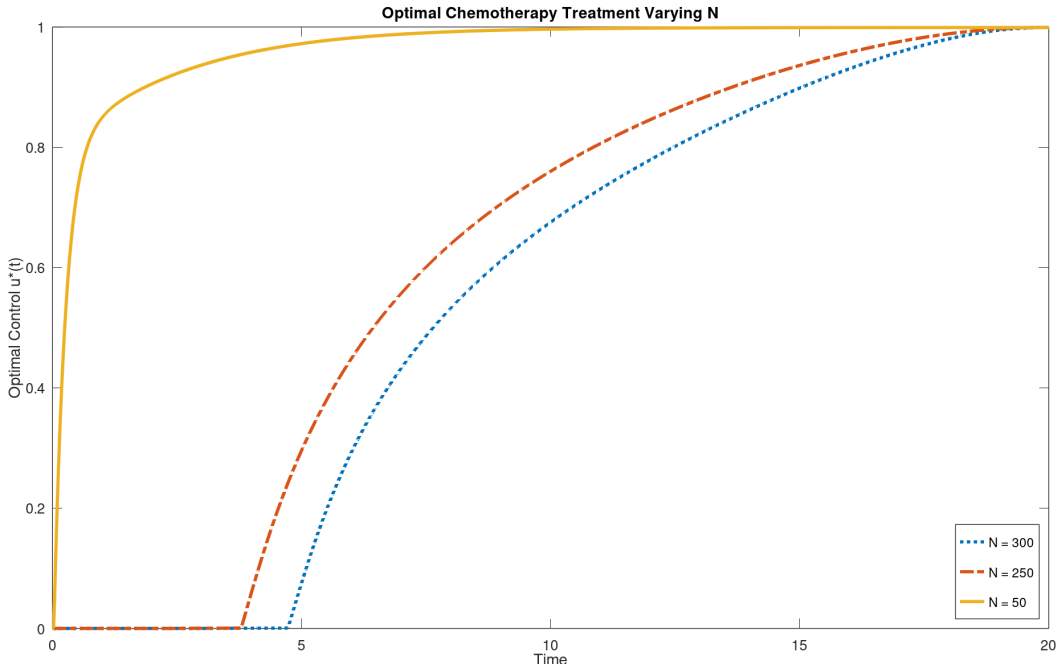

Figure 5: Optimal Chemotherapy Treatment Regimen Varying N, the number of free virions produced from each infected cell.

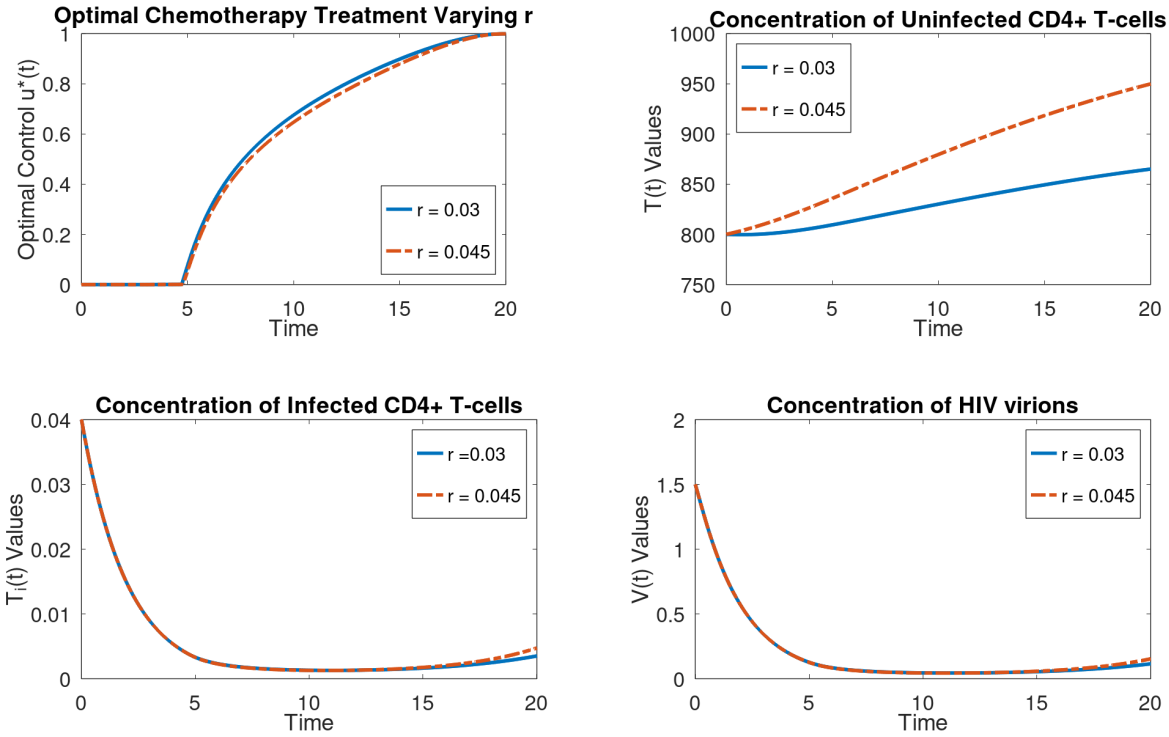

Figure 6: Plot of Optimal States and Control with $r = 0.03$ (blue) and $r = 0.045$ (orange).

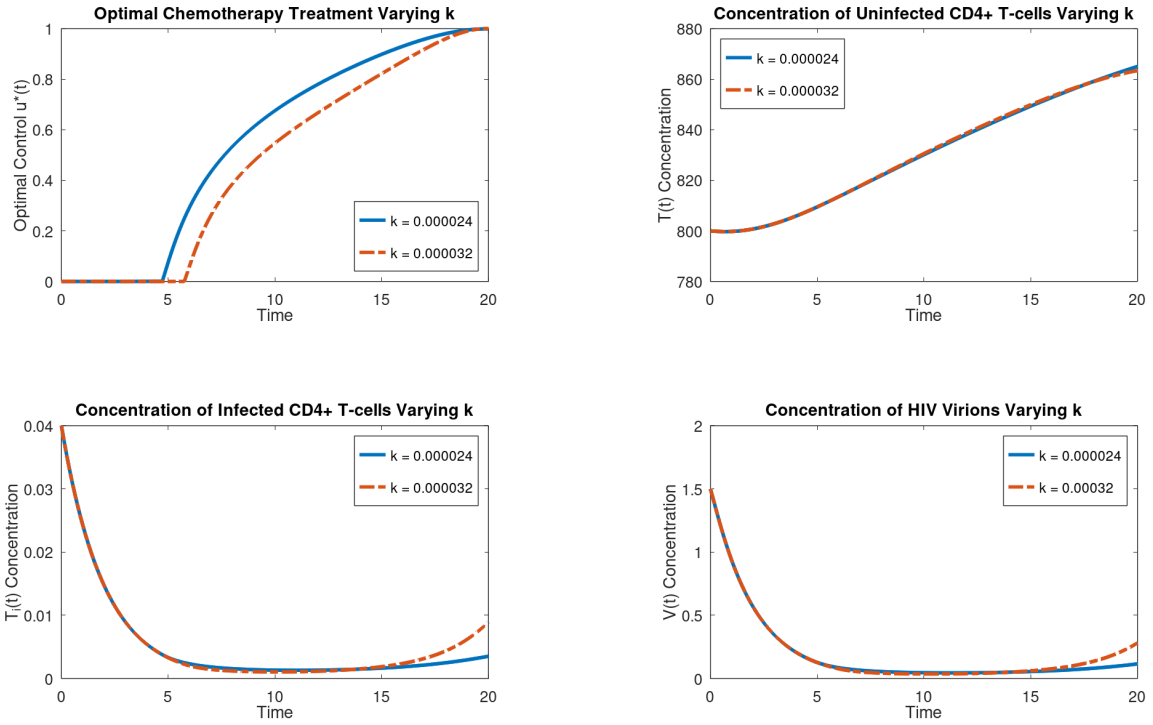

Figure 7: Optimal Chemotherapy Treatment, CD4+ T-cell concentration, Infected CD4+ T-cell Concentration, and free virion concentration with $k = 0.000024$ (blue) and $k = 0.000032$ (orange).

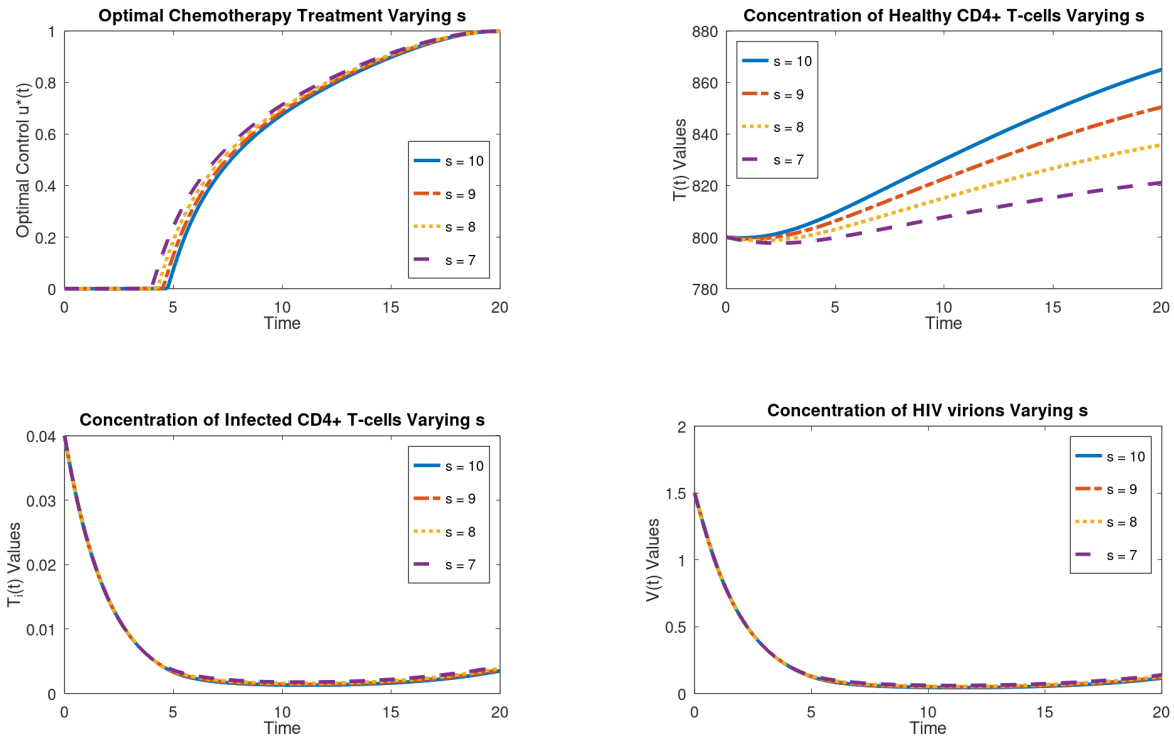

Figure 8: Varying s, the generation rate of new T-cells from the thymus.

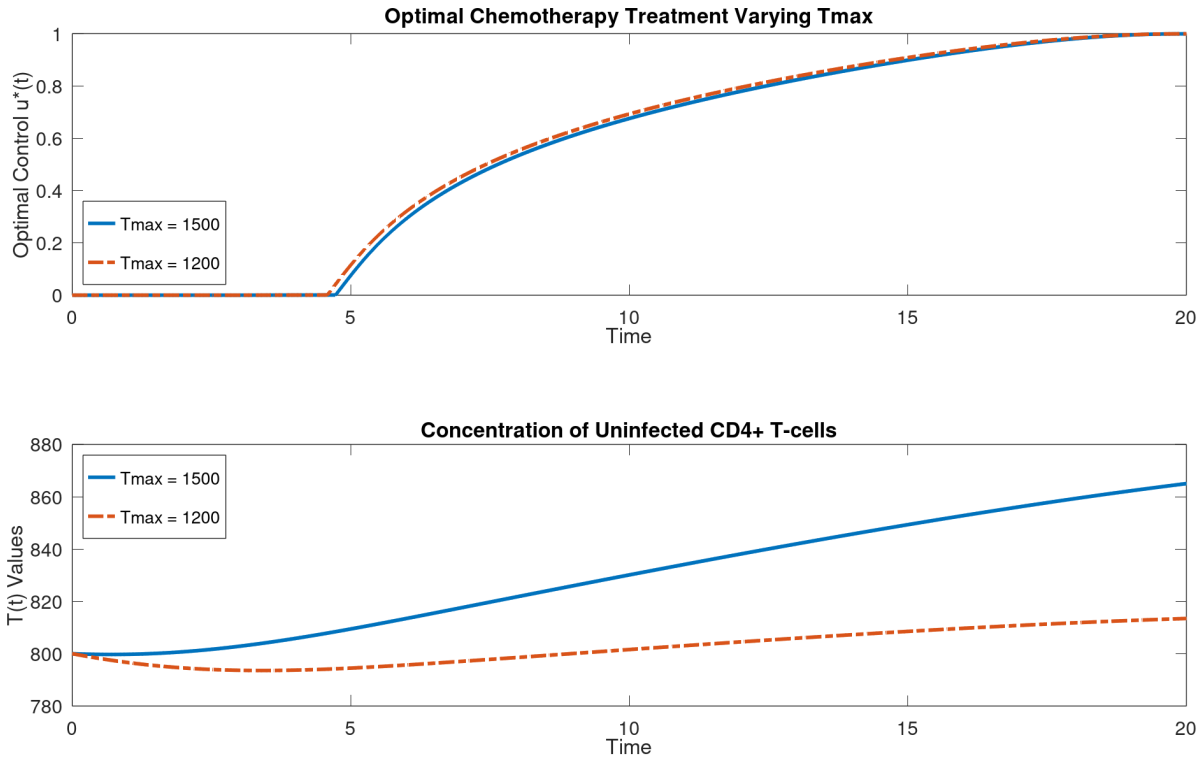

Figure 9: Varying T_{max}, the carrying capacity of white blood cells in the body. Plots of $T_i(t)$ and $V(t)$ not pictured due to their significant similarities when $T_{max} = 1500$ and $T_{max} = 1200$.

correspond to slightly different treatment regimens (top left). Generally, we see shorter intervals of maximum level treatment with smaller values of s. As expected, different T-cell growth rates with the same initial T-cell concentration result in vastly different final cell counts, with lower values of s leading to lower CD4+ T-cell concentrations.

4.7 Varying T_{max}

The slight decrease in this parameter (shown in Figure 9) results in a near-identical treatment regimen with radically different healthy CD4+ T-cell concentrations. In the second system $T_{max} = 1200$, we see that despite $T(t)$ initially decreasing, the final healthy T-cell concentration is only slightly above the initial T-cell concentration. By contrast, the first system $T_{max} = 1500$ increases steadily after the first two days, leading to a difference of about 70 cells/unit volume between the two simulations by $t = 20$.

4.8 Varying t_{final}

As expected, when $t_{final} = 10$ (red plot in Figure 10), we see maximum treatment applied for shorter periods of time, steadily decreasing to no treatment by the end of the time interval. This leads to less drug administered overall, which is apparent in Figure 11; by $t = 10$, we see a much larger concentration of infected CD4+ T-cells and free virus particles compared to the original 20-day treatment. More side effects will naturally arise in a 20-day treatment compared to a 10-day treatment, so we also consider the optimal treatment regimen for a smaller time interval $t_{final} = 10$ and a smaller weight parameter $A = 0.1$. This simulates allowing the same overall amount of side effects in both treatments. Observe that this small modification results in an extra day of maximum-strength treatment while halving the number of infected CD4+ T-cells and the virion concentration compared to when we set $t_{final} = 10$ with no adjustment to A.

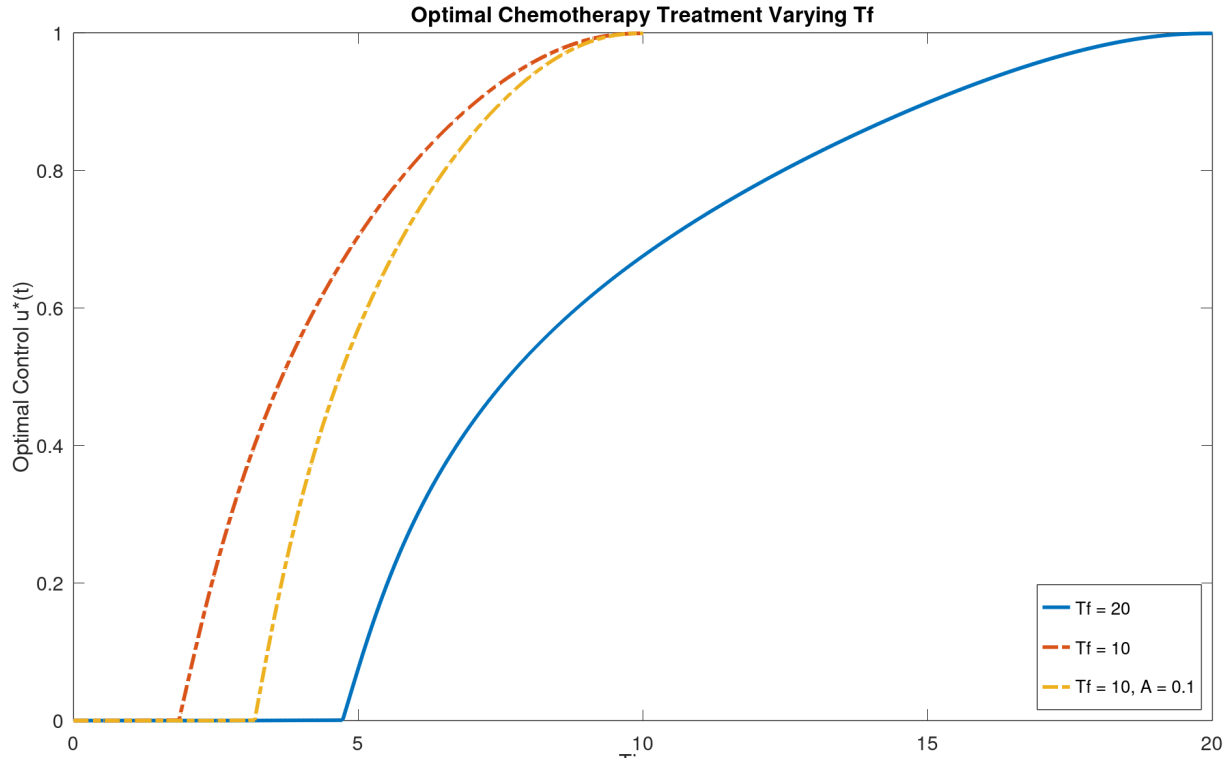

Figure 10: Plots for optimal chemotherapy treatment regimen for different values of t_{final}, the amount of time in days until drug resistance develops. We also include $t_{final} = 10$ plotted with $A = 0.1$ (yellow) to compare ten and twenty day treatment regimens with the same allowance of negative side effects.

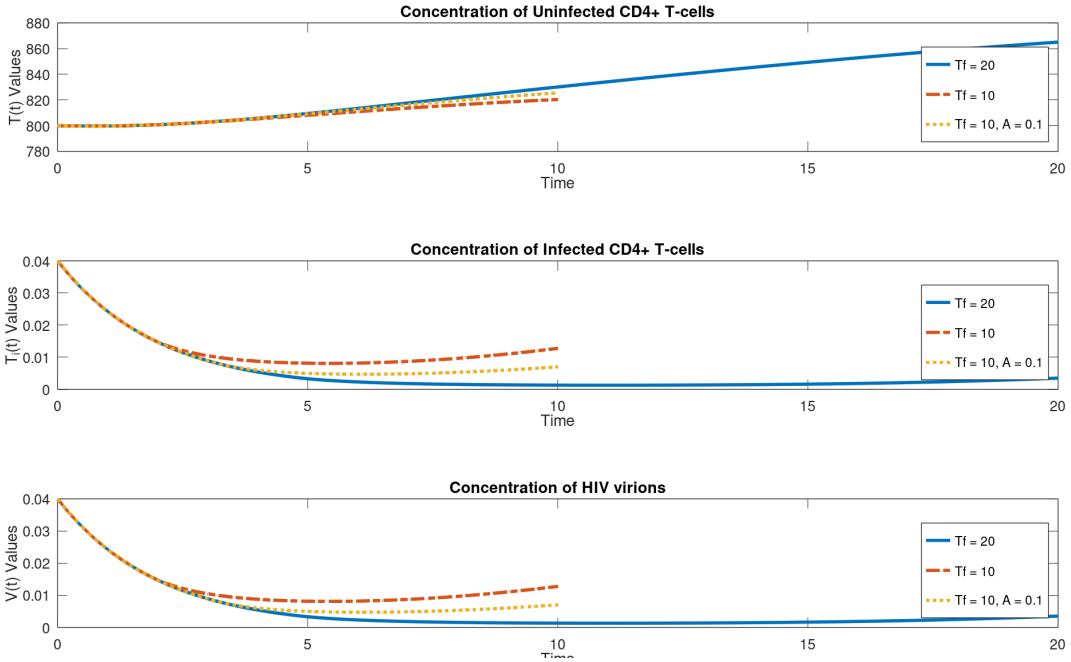

Figure 11: Plots for $T(t)$, $T_i(t)$, and $V(t)$ varying t_{final}, the number of days until drug resistance develops.

4.9 Varying Death Rates $m_1, m_2,$ and m_3

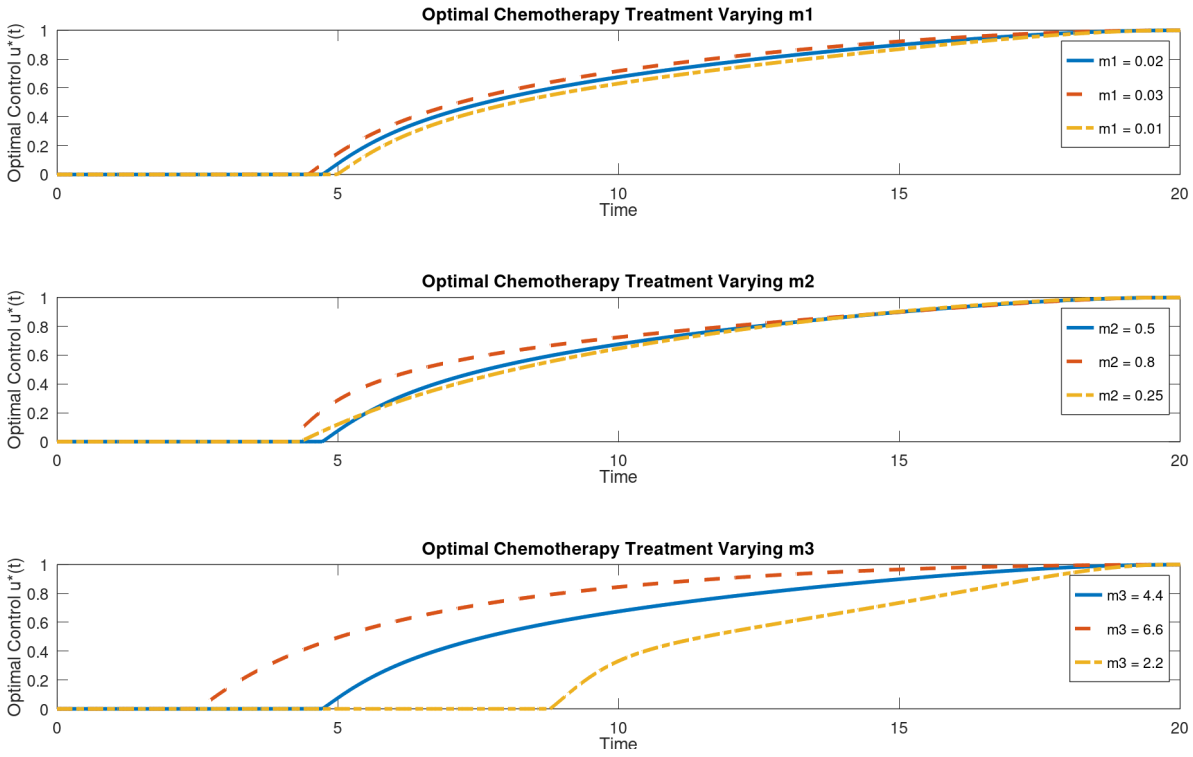

Figure 12: Plots of $u^*(t)$, the optimal treatment regimen, for varying values of m_1, m_2, and m_3, which are the natural death rates of $T(t)$, $T_i(t)$, and $V(t)$, respectively.

We seek to answer the question: which death rate has the greatest impact on the optimal control? Each subplot in Figure 12 shows three variations of each death rate: the original parameter value from Figure 2, a 50% increase from the original parameter, and a 50% decrease. We see that the variations of m_1 are incredibly close to the original treatment regimen, while changing m_2 results in slightly more pronounced, though still small, differences. The largest changes in treatment are associated with varying m_3, with maximum treatment halted about two days earlier for $m_3 = 6.6$ and four days later when $m_3 = 2.2$ compared to the baseline of $m_3 = 4.4$.

4.10 Varying Initial Conditions $T_0, T_{i0},$ and V_0

We can ask a similar question as the previous case to discern which initial condition, when varied, will produce the most drastic changes in the optimal treatment regimen. In Figure 13, we plot our original simulation along with approximately 50% increases and decreases (not exact due to MATLAB constraints) in each initial condition. Varying T_0 very clearly results in greater changes compared to similar variations in T_{i0} and V_0, with maximum treatment halting three days earlier when $T_0 = 400$ and lasting a day longer when $T_0 = 1000$. We also see that changing T_0 has the most direct impact on $T(t)$, with T-cell counts increasing steadily for $T_0 = 400$ and $T_0 = 800$ but remaining near-constant when $T_0 = 1000$.

Increasing to $T_i(0) = 0.08$ results in slightly longer maximum treatment time, about a day, and decreasing to $T_i(0) = 0.02$ has the opposite effect. Healthy T-cell counts are, as expected, slightly decreased when $T_i(0)$ is increased by 50% and slightly increased when $T_i(0)$ is decreased by 50%. Notably, similar changes in V_0 cause no visible difference in both the optimal treatment regimen or the uninfected T-cell concentrations.

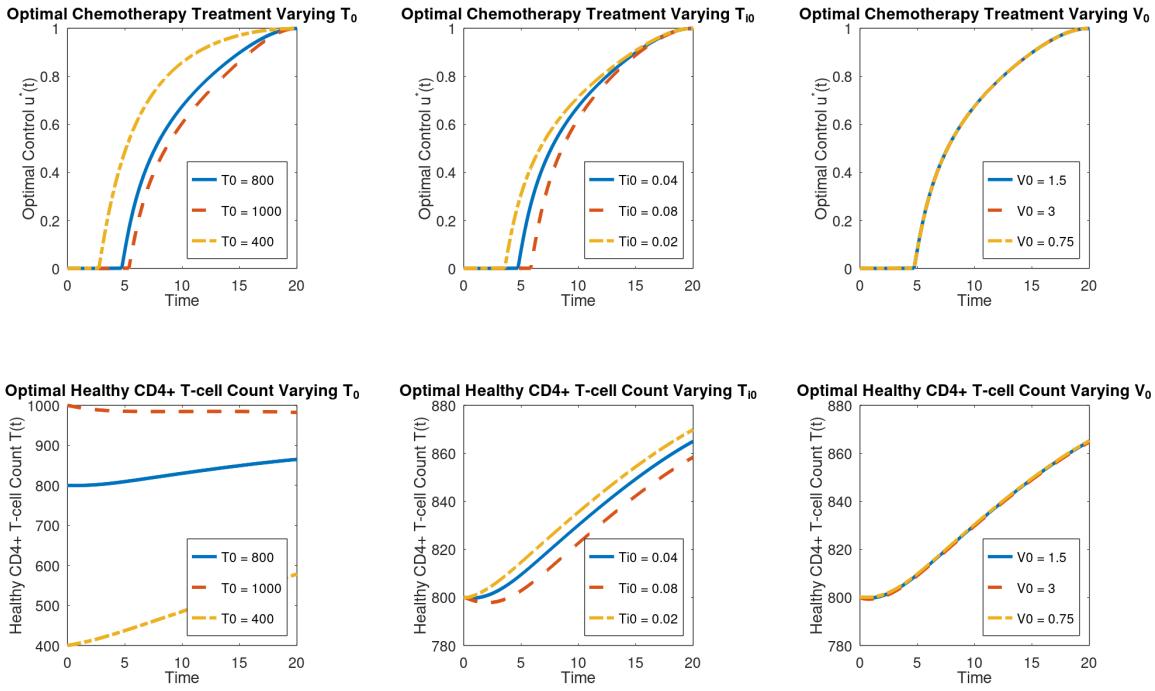

Figure 13: Effects of variations in T_0 (Column 1), T_{i0} (Column 2), and V_0 (Column 3) on the optimal chemotherapy treatment (Row 1) and healthy T-cell concentrations (Row 2).

5 Discussion

From our preliminary parameters, it seems that the chemotherapy regimen is highly effective, nearly eliminating infected CD4+ T-cells and free virus particles from the blood while significantly increasing healthy CD4+ T-cell concentration. A downside of our model is that it only considers single-drug therapies (monotherapy) which require the drug resistance parameter t_{final} to be small. Early drugs such as Zidovudine (AZT) exhibit this behavior. Modern treatments typically administer a combination of anti-retroviral medications to combat drug resistance, meaning patients can receive treatments for longer periods of time.

The marginal increases in $T_i(t)$ and $V(t)$ during the final days of treatment, though expected from the lower therapy strength around $t = 20$, is worrying for patient outcomes. Depending on the infection rate k, it may be possible after treatment that the infection returns, though we are unsure whether that would be at a significant level. We have not tested the efficacy of applying a second treatment if such a scenario occurs, but models currently exist that consider combination chemotherapies, avoiding this issue altogether.

5.1 Weight Parameter A

Larger values of A result in more aggressive treatment regimens, with maximal treatment lasting for longer periods of time. This is easily explained by the structure of our objective functional, since A is directly associated with maximizing the CD4+ T-cell concentration. We should the use smaller values of A for drugs with stronger side effects so that more emphasis is placed on minimizing bodily cost (simulated in Figure 4 with $A = 0.025$). This has the effect of nearly doubling free virion particle and infected T-cell concentrations, a somewhat surprising result as only $T(t)$ was considered in our objective functional. We attribute this behavior to the earlier reduction of treatment when $A = 0.025$; less drug can be administered due to the stronger side effects, leading to higher transmission and greater infection compared to the baseline $A = 0.05$.

5.2 Number of Virions Produced per Infected T-cell N

Figure 5 showed that small changes in N produced small changes in the optimal chemotherapy treatment, with a reduction of 50 virions per infected cell resulting in treatment halting a full day earlier. As discussed in section 1, the infection mechanism of HIV depends on the presence of free virus particles in the body. After initial exposure, new virions can only be produced from infected CD4+ T-cells. We would then expect N, the number of virions produced per infected cell, to significantly impact the amount of chemotherapy required; if infected cells produce fewer free virus particles, then fewer cells will become infected over time, and less drug is required to increase healthy CD4+ concentrations. This aligns with our simulation, since reducing N reduces the amount of time that high doses of chemotherapy are needed at a somewhat proportional level. Notably, treatment ends after only ten days when $N = 50$, likely because the free virus population is brought to such a low level it is unable to self-sustain.

Different strains of HIV may produce different amounts of virions per infected cell, so it is helpful to understand how these changes may affect optimal treatment. Additionally, modern medications such as PrEP (pre-exposure prophylaxis) reduce infectivity by preventing virions from replicating in CD4+ cells, which would have the effect of reducing N.

5.3 T-cell Growth Rate r

The effects of the growth rate r were explored in Figure 6. Though increasing r by 50% did not result in significant changes in optimal treatment, infected CD4+ concentration, or free virus particle count, there was an interesting positive change in the healthy CD4+ concentration. Since r only appeared in the equation for $T'(t)$, this makes sense mathematically. The parameter r governs the logistic growth of the healthy T-cell population, so increasing this growth rate leads to more instances of cell division and a higher final concentration of uninfected CD4+ cells.

Doctors following a mono-therapeutic treatment regimen as described in this model may wish to consider prescribing supplementary medications that increase T-cell growth rates, provided that they do not interfere with the original chemotherapy treatment. This would have the positive result of restoring healthy CD4+ counts while maintaining the same side-effect risk and treatment regimen. A factor not considered in this model is financial cost of the chemotherapy treatment, which in the United States can be significant. If a medication that increases white blood cell growth was cheaper than the original chemotherapy treatment, this could be an added benefit to a dual-therapy regimen.

Whereas a decrease in N resulted in reductions in treatment to maintain the optimal T-cell count, varying r caused virtually no changes to $u^*(t)$. Presumably, this is a direct result of the objective functional, which only considers the healthy T-cell count and the amount of chemotherapy used. While increasing the growth rate r directly affects $T(t)$, changes in N only indirectly affect T-cells by hindering viral production, changing the overall optimal treatment strategy.

5.4 Infection Rate k

Increasing k by 33% changed the optimal treatment to a more aggressive strategy in order to maintain the same uninfected T-cell concentration. Since k governs the infection mechanism, this is to be expected; higher values of k correspond to a higher proportion of virion-CD4+ cell interactions that cause infections, leading to more infected T-cells, more free virus particles, and fewer healthy T-cells. Notably, the small increases in $T_i(t)$ and $V(t)$ near the end of the time interval we observed with $k = 0.00024$ are much more significant with a larger $k = 0.00032$, nearly double their previous amounts. This is concerning for patient outcomes, particularly if virion and infected cell concentrations continue to grow at this rate once treatment is halted.

5.5 New Cell Generation Rate s

The thymus works to produce white blood cells. By modifying s, we model changes its productivity, with larger values of s corresponding to higher generation rates of new CD4+ T-cells. Figure 8 shows the impact

of reducing s; as expected, we only see major differences in $T(t)$, since this is the only equation in our model containing this parameter. Similar to varying r, even with the same initial condition $T(0)$, we see major differences in healthy T-cell counts by the end of the twenty day period. Since the objective functional depends primarily on $T(t)$, we see changes in treatment strength associated with these variations in s, though small.

Fewer T-cells require less treatment to maintain the same levels of infection. It would then seem that lowering s is beneficial to the patient, as less chemotherapy treatment is needed, reducing potential side effects. However, the goal is still to maximize healthy CD4+ concentration, since these cells are essential for defending against infections. Since there are only small changes in $u^*(t)$ when s is varied, we could consider prescribing medications that increase the generation rate of new CD4+ T-cells alongside the chemotherapy regimen. This would significantly boost healthy T-cell counts while only requiring a slightly more aggressive treatment regimen, effectively increasing $T(t)$ with few side effects. This treatment plan would be less effective than co-prescribing a medication that boosts k, though depending on cost and patient circumstances, it may be a viable option as well.

5.6 Carrying Capacity of CD4+ T-cells T_{max}

White blood cell growth is modelled logistically to account for the carrying capacity, T_{max}, of T-cells in the blood. Since we are maximizing $T(t)$, we may predict that decreasing the maximum number of white blood cells in the body would decrease $T(t)$, and this is the result we observe in Figure 9. Though treatment regimens are near-identical, the smaller carrying capacity allows for decreased concentrations of healthy T-cells, while maintaining similar infected CD4+ cell counts.

Patients who have lower carrying capacities for white blood cells could benefit from a treatment that increases T_{max} in conjunction with chemotherapy, though we are unclear on what such a treatment would look like.

5.7 Days until Drug Resistance Occurs t_{final}

A key element of our model is the finite time horizon, representing time in days until drug resistance develops. For drugs such as AZT, chemotherapy resistance primarily occurs through rapid selection of HIV virions that use different transcription pathways than the one being targeted by treatment [4]. Different medications and the variations in patients' immune systems impact the amount of time that the medication is effective, and such scenarios were simulated in Figures 10 and 11. Halving the treatment time from 20 days to 10 days resulted in maximum treatment administered for only two days compared to the original five, likely because integrating over a smaller time interval produces a smaller maximum.

Doubling the parameter A allowed us to simulate a higher allowance for side effects during the ten-day treatment, resulting in similar toxicity limitations in both the ten-day and twenty-day treatments. Though the more aggressive treatment improved final virion and infected CD4+ concentrations compared to the first ten-day treatment plan, the shorter time horizon could not compare to the original twenty-day treatment plan. We conclude that provided a longer treatment plan and a shorter treatment plan, both with equal risk of side effects, it is better to follow the longer treatment in order to maximize final CD4+ T-cell count. The importance of developing medications that are not at risk of causing resistance cannot be overstated. As previously mentioned, multi-drug therapies address this issue well, though not perfectly. It could also be possible to administer on-and-off treatment, though more research is surely needed.

5.8 Death Rates m_1, m_2, and m_3

It seems that changes to the virion death rate m_3 have greater impact on the optimal treatment regimen than m_1 and m_2. From our model, the results make sense; the parameter m_3 directly influences $V(t)$, the concentration of free virus particles, which in turn has a direct negative impact on $T(t)$. Increasing m_3 then decreases $T(t)$, requiring longer periods of maximum treatment to maintain the baseline concentration of uninfected CD4+ T-cells, which we see in Figure 12. It is slightly surprising that m_2 does not have a greater effect than m_3 on the optimal treatment regimen, since infected cell death releases virions, reducing

$T(t)$ by causing further infections. Additionally, we might ask why similar changes in m_1 does not influence optimal treatment with the same magnitude despite m_1 directly impacting $T'(t)$. Both of these are likely because the estimated value of m_3 was larger than m_1 and m_2 from our initial simulation, so increasing or decreasing its value by 50% results in much larger changes than doing so to m_1 or m_2. However, this method of parameter variation is more practical than changing m_1, m_2, and m_3 uniformly since doing so would result in unrealistic parameter values.

Introducing therapies that directly target free virions would have the effect of decreasing m_3 and reducing the amount of chemotherapy needed. We recognize that this is easier said than done. Further study of physical properties of virion particles could yield treatments that are harmless to bodily cells but neutralize or kill HIV virus.

5.9 Initial Conditions T_0, T_{i0}, $V(0)$

At different stages of HIV infection, patients will have varying concentrations of uninfected and infected CD4+ T-cells and free virion particles. By varying these initial conditions, we can simulate the best time to begin treatment. From Figure 13, we saw that while initial virion concentration did not have any relation to the optimal treatment regimen, both initial infected and uninfected CD4+ T-cell counts did, the latter more so. This should be unsurprising from our objective functional; optimal treatment is considered successful when there is an increase in healthy T-cell concentrations $T(t)$. Therefore, since increasing T_0 directly increases healthy T-cell concentrations, more treatment can be tolerated by the body. Similarly, decreasing T_{i0} reduces the number of infected T-cells, allowing for more healthy T-cells to grow. It is important to consider T_{max}, the carrying capacity of white blood cells in the blood. Larger values of T_0 resulted in lower growth rates of $T(t)$, which we attribute to the population approaching T_{max}. There is then a sweet spot of healthy CD4+ T-cell concentrations at which to begin treatment, though it is unlikely in practice that a patient with HIV would have T-cell counts high enough to cause an issue.

Contrary to our model, most modern HIV treatments are considered effective by their reductions in viral load $V(t)$. This difference in success measures may explain why we saw no difference in optimal treatment from varying initial viral loads. An adjustment to the model may be warranted to account for this. From our results, we find that the best time to start HIV chemotherapy is earlier on in the infection, when healthy CD4+ T-cell counts are higher and infected CD4+ T-cell counts are lower. Treatment can be administered at any viral load.

6 Conclusion

Through the application of an optimal control model, we tested the effect of parameters on the optimal chemotherapy regimen of HIV. We found that while chemotherapy treatment is extremely effective at reducing viral load and increasing uninfected CD4+ T-cell concentrations, multi-therapy regimens may be more effective. Specifically, medications that increase T-cell growth rate k, decrease viral production per cell N, have lower rates of drug resistance A, t_{final}, and increase virion death rates m_3 are ideal. Medications affecting T-cell generation rate s and carrying capacity of T-cells T_{max} may be effective as well, though not to the same degree. We also found that the best time to begin treatment is early in the infection, while infected T-cell counts are lower.

While the model could benefit from incorporation of multi-therapy treatments and a change in success measures, it is rigorous when applied to early HIV treatments. It serves as a baseline for modern models, emphasizing its importance in the growing field of HIV research.

References

[1] Lenhart, S., and Workman, J. T. (2007). Optimal control applied to biological models. Chapman and Hall/CRC.

[2] https://www.cdc.gov/hiv/basics/statistics.html

[3] https://www.niaid.nih.gov/diseases-conditions/hiv-replication-cycle

[4] Kirschner, D.E., Webb, G.F. Understanding drug resistance for monotherapy treatment of HIV infection. Bltn Mathcal Biology 59, 763–785 (1997). https://doi.org/10.1007/BF02458429