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SEEKING BANG-BANG SOLUTIONS OF MIXED IMMUNO-CHEMOTHERAPY OF TUMORS

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Abstract. It is known that a beneficial cancer treatment approach for a single patient often involves the administration of more than one type of therapy. The question of how best to combine multiple cancer therapies, however, is still open. In this study, we investigate the theoretical interaction of three treatment types (two biological therapies and one chemotherapy) with a growing cancer, and present an analysis of an optimal control strategy for administering all three therapies in combination. In the situations with controls introduced linearly, we find that there are conditions on which the controls exist singularly. Although bang-bang controls (on-off) reflect the drug treatment approach that is often implemented clinically, we have demonstrated, in the context of our mathematical model, that there can exist regions on which this may not be the best strategy for minimizing a tumor burden. We characterize the controls in singular regions by taking time derivatives of the switching functions. We will examine these representations and the conditions necessary for the controls to be minimizing in the singular region. We begin by assuming only one of the controls is singular on a given interval. Then we analyze the conditions on which a pair and then all three controls are singular.

1. Introduction

The goal of applying optimal control theory to mathematical models representing the interaction between tumor, immune system, and chemotherapy is to determine the ideal mix of treatments that minimizes both tumor mass and negative effects upon the health of the patient. Recent research into the mixture of chemo- and immunotherapy regimens shows a great deal of potential for the success of such treatment schedules, c.f. [13], [32], [34], [22], [25], [26], [35], [15].

The logic behind the development of a combination chemo-immunotherapy strategy is intuitive - use as little chemotherapy drug as possible to effectively kill tumor cells while utilizing immunotherapy to bolster the patient's immune system, thus strengthening the body's natural defenses against both the tumor cells and the dangerous side effects of the chemotherapy.

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The application of optimal control theory to mathematical models incorporating the interaction between tumors and treatments has provided valuable information in the past. Works by Kim *et al.* [18], Swan and Vincent [37], and Murray [30] have successfully utilized control theory to maximize the effectiveness of chemotherapy against tumor cells and minimize the toxic effects of such treatments. Optimal control has also been effectively applied to immunotherapy models; for example, Swan [36], Kuznetsov and Knott [24], and Kirschner *et al.* [20] have contributed research on applications to immunotherapy strategies for cancer and HIV. The more recent approach of combining chemo- and immunotherapy is being explored by several researchers; Kirschner and Panetta [21] present a model detailing tumor-immune interaction with chemotherapy, while Burden *et al.* [2] apply quadratic control to that model. In addition, in the works by de Pillis and Radunskaya [5], [6], and de Pillis *et al.* [7], [4] the authors explore various approaches to combining chemo- and immunotherapies through numerical simulation and the implementation of numerical linear controls.

The model presented in this paper is an expansion of the model presented by de Pillis *et al.* [4]. The modifications are introduced in response to newer research on the kinetics of IL-2 and immune cell populations. Another alteration to this model is the inclusion of constraints to limit both the tumor mass after treatment and the total concentration of lymphocytes during treatment. These additional constraints introduce a slight variation on the typical optimal control problem and must be dealt with by other means than the standard application of Pontryagin's Maximum/Minimum Principle [31]. We turn to works by Kirk [19], Hartl *et al.* [14], and Kamien and Schwartz [17] for the methods necessary to incorporate these constraints.

The interest in applying control in a linear fashion to this model is somewhat pragmatic, given standard chemotherapy treatments. A widely used approach to cancer treatment is to give a maximum dosage of chemotherapy drug for some period of time, followed by a period of recuperation in which no drug is given. This type of treatment correlates theoretically with bang-bang control. However, when dealing with linear controls, we investigate the possibility of singular arcs and which conditions are necessary for those arcs to be optimal. In this paper, we use the Generalized Legendre-Clebsch conditions - as given by Krener [23] - to generate the higher order necessary conditions for the optimality of the singular arcs. A more detailed discussion of this is given in Section 3.

The outline of the paper is as follows. In Section 2, we present the model and discuss the model's components. Section 3 deals with the application of optimal control to the model, beginning with the description of the objective functional. The section continues with the proof of existence of an optimal control in this context and concludes with the conditions under which singular controls are optimal. Section 4 summarizes the conclusions reached from analysis of the data. In the appendices we provide full statements of certain theorems and detailed equations used to develop the work in this paper.

2. Three-Cell Three-Chemical Model

2.1. **Model Development and Cellular Dynamics.** Medical advances have given doctors more options in cancer treatment. Traditional chemotherapy schedules may now be supplemented with various forms of immunotherapy. The existence

of more options, however, can make it more challenging to find the best treatment. A mathematical model of all the processes involved can help to reveal improved treatment strategies. In this paper we analyze a model exploring the possible dynamics that can occur in different regions of parameter space. The hope is that the analysis will provide intuition into the interactions of the tumor, chemotherapy, and immunotherapy.

The model tracks 6 quantities

- Tumor Cells, $T(t)$ (Units: Number of Cells)
- Natural Killer Cells, $N(t)$ (Units: Number of Cells per Liter)
- Circulating Lymphocytes, $C(t)$ (Units: Number of Cells per Liter)
- Tumor Specific $CD8^+$ T-Lymphocytes, $L(t)$ (Units: Number of Cells per Liter)
- Interleukin 2, $I(t)$ (Units: International Units (IUs) per Liter)
- Medicine, $M(t)$ (Units: Milligrams per Liter)

The circulating lymphocyte population represents all B and T lymphocytes in the bloodstream. Natural killer cells, which are also lymphocytes, are tracked as a separate population. The quantity L represents the concentration of cells that have been activated by a tumor related antigen.

2.2. **Tumor Equation (T).** Simple logistic growth of the tumor cell population, in the absence of medicine and immune interactions, is used. Death of tumor cells due to natural killer cells is given by a mass action term cNT, whereas death due to CTLs is given by a ratio dependent term, D. Note that unlike other cell populations, T is measured as an absolute number and not a concentration.

2.3. **Natural Killer Cell Equation (N).** A constant source term of Natural Killer cells differentiating from Circulating Lymphocytes and a linear death term are both assumed. We also assume that natural killer cells die when they have interacted with a tumor cell; so we include a mass action death term identical to that in the T equation. For N, L, and C the quantity given is cells per liter of blood.

2.4. **Circulating Lymphocyte Equation.** This population has the simplest dynamics: a constant source term and a linear death rate.

2.5. **Tumor Specific T Cell (CD8+T CTL) Equation.** We assume that these cells have a linear death rate, $-mL$, as well as a quadratic death rate, $-uL^2C$. The latter term represents the activity of regulatory T-cells, which are a subset of circulating lymphocytes. The CTLs may also die through interaction with the tumor and this is represented by a mass action term,$-qLT$. Interactions of the tumor with the larger lymphocyte populations, N and C, stimulate CTL production. These stimulatory terms are represented by the two positive mass action terms. Additionally, tumor-related antigens stimulate the proliferation of CTLs through $j\frac{TL}{k+T}$.

2.6. **Dynamics and Effects of Medicine.** Once injected, medicine (chemotherapy) is assumed to have a linear decay rate. The medicine interacts with each of the four cell populations, T, N, L and C through a term of the form $K_X(1-e^{(-\delta_X M)})X$, [12]. For each cell population, this term represents cell death due to the medicine.

2.7. **Dynamics and Effects of IL-2.** Although naturally produced, the cytokine IL-2 is often used to treat cancer. This model assumes a linear decay rate and a constant source from circulating lymphocytes. Additionally, when a T-cell is stimulated by IL-2, the T-cell will secrete more IL-2 as represented by $\omega\frac{LI}{g_I+L}$.

IL-2 also stimulates the proliferation of Natural Killer cells and CTLs. This stimulation is represented by the Michaelis-Menten terms, $p\frac{XI}{g+X}$, in each equation. Also, IL-2 inhibits the linear death term but stimulates the quadratic death term in the CTL equation.

2.8. **The Equations.** The system of differential equations describing the growth, death, and interactions of these populations with a chemotherapy treatment is given by

$$\frac{dT}{dt} = aT(1-bT) - cNT - DT - K_T(1-e^{-\delta_T M})T \tag{2.1}$$

$$\frac{dN}{dt} = f\big(\frac{e}{f}C - N\big) - pNT + \frac{p_N NI}{g_N+I} - K_N(1-e^{-\delta_N M})N \tag{2.2}$$

$$\begin{aligned}\frac{dL}{dt} &= -\frac{\theta mL}{\theta+I} - qLT + r_1NT + r_2CT + \frac{p_I LI}{g_I+I} - \frac{u_0L^2CI}{\kappa+I} \\ &\quad + \frac{jTL}{k+T} - K_L(1-e^{-\delta_L M})L + \eta_1 v_L(t)\end{aligned} \tag{2.3}$$

$$\frac{dC}{dt} = \beta\big(\frac{\alpha}{\beta} - C\big) - K_C(1-e^{-\delta_C M})C \tag{2.4}$$

$$\frac{dM}{dt} = -\gamma M + \eta_2 v_M(t) \tag{2.5}$$

$$\frac{dI}{dt} = -\mu_I I + \phi C + \frac{\omega LI}{\zeta+I} + \eta_3 v_I(t) \tag{2.6}$$

where $D = d\frac{(L/T)^\ell}{s/n^\ell+(L/T)^\ell}$, $T(0)=T_0$, $N(0)=N_0$, $L(0)=L_0$, $I(0)=I_0$, $C(0)=C_0$, and $M(0)=M_0$.

In Table 1, we have provided a summary of equation term descriptions, and in Table 2 we have a list of parameters with their units and biological interpretation.

Table 1: Equation Descriptions

Eq.	Term	Description
$\frac{dT}{dt}$	$aT(1-bT)$	Logistic tumor growth
	$-cNT$	NK-induced tumor death
	$-DT$	CD8+ T cell-induced tumor death
	$-K_T(1-e^{-\delta_T M})T$	Chemotherapy-induced tumor death
$\frac{dN}{dt}$	eC	Production of NK cells from circulating lymphocytes
	$-fN$	Natural killer breakdown
	$-pNT$	Natural killer death by exhaustion of tumor-killing resources
	$\frac{p_N NI}{g_N+I}$	Stimulatory effect of IL-2 on NK cells
	$-K_N(1-e^{\delta_N M})N$	Death of NK cells due to medicine toxicity
	$-\frac{m\theta L}{\theta+I}$	CD8+T cell breakdown

$\frac{dL}{dt}$	$-qLT$	CD8+T cell death by exhaustion of tumor-killing resources
	r_1NT	CD8+ T cell stimulation by NK-lysed tumor cell debris
	r_2CT	Activation of naive CD8+T cells in the general lymphocyte population
	$\frac{p_I LI}{g_I+I}$	Stimulatory effect of IL-2 on CD8+T cells
	$-\frac{u_0 L^2 CI}{\kappa+I}$	Breakdown of surplus CD8+T cells in the presence of IL-2
	$\frac{jTL}{k+T}$	CD8+ T cell stimulation by CD8+ T cell-lysed tumor cell debris
	$-K_L(1-e^{-\delta_L M})L$	Death of CD8+ T cells due to medicine toxicity
	$\eta_1 v_L(t)$	External TIL therapy, controllable
$\frac{dC}{dt}$	α	Lymphocyte synthesis in bone marrow
	$-\beta C$	Lymphocyte breakdown
	$-K_C(1-e^{-\delta_C M})C$	Death of lymphocytes due to medicine toxicity
$\frac{dM}{dt}$	$-\gamma M$	Excretion and breakdown of medicine
	$\eta_2 v_M(t)$	External chemotherapy, controllable
$\frac{dI}{dt}$	$-\mu_I I$	IL-2 breakdown
	ϕC	Production of IL-2 due to naive CD8+T cells and CD4+T cells
	$\frac{\omega LI}{\zeta+I}$	Production of IL-2 from activated CD8+T cells
	$\eta_3 v_I(t)$	External IL-2, controllable

Table 2: Parameter Descriptions

Eq.	Param.	Description	Units
$\frac{dT}{dt}$	a	Growth rate of tumor	1/day
	b	Inverse of carrying capacity	1/cells
	c	Rate of NK-induced tumor death	liter/(cells·day)
	K_T	Rate of chemotherapy-induced tumor death	1/day
	δ_T	Medicine efficacy coefficient	liter/mg
$\frac{dN}{dt}$	e/f	Ratio of rate of NK cell creation with rate of cell death	unitless
	f	Rate of NK cell death	1/day
	p	Rate of NK cell death due to tumor interaction	1/(cells·day)
	p_N	Rate of IL-2 induced NK cell genesis	1/day
	g_N	Concentration of IL-2 for half-maximal NK cell genesis	IU/liter
	K_N	Rate of NK depletion from medicine toxicity	1/day
	δ_N	Medicine toxicity coefficient	liter/mg
	m	Natural decay rate of CD8+T cells	1/day
	θ	Concentration of IL-2 to halve effectiveness of CD8+T self-regulation	IU/liter

$\frac{dL}{dt}$	q	Rate of CD8+T cell death due to tumor interaction	1/(cells·day)
	r_1	Rate of NK-lysed tumor cell debris activation of CD8+T cells	1/(cells·day)
	r_2	Rate of CD8+T cell production from circulating lymphocytes	1/(cells·day)
	p_I	Rate of IL-2 induced CD8+T cell activation	1/day
	g_I	Concentration of IL-2 for half-maximal CD8+T cell activation	IU/liter
	u_0	CD8 self-limitation feedback coefficient	$\text{liter}^2/(\text{cells}^2\cdot\text{day})$
	κ	Concentration of IL-2 for half-maximal IL-2-dependent CD8+T self-regulation	IU/liter
	j	Rate of CD8+T-lysed tumor cell debris activation of CD8+T cells	1/day
	k	Tumor size for half-maximal CD8+T-lysed debris CD8+T activation	cells
	K_L	Rate of CD8+T depletion from medicine toxicity	1/day
	δ_L	Medicine toxicity coefficient	liter/mg
	η_1	TIL therapy administration rate	1/day
	$v_L(t)$	Externally administered TIL CD8+T therapy concentration	cells/liter
$\frac{dC}{dt}$	α/β	Ratio of rate of circulating lymphocyte production to death rate	cells/liter
	β	Rate of decay of circulating lymphocytes	1/day
	K_C	Circulating lymphocyte-toxicity of medicine	1/day
	δ_C	Medicine toxicity coefficient	liter/mg
$\frac{dM}{dt}$	γ	Rate of decay of medicine	1/day
	η_2	Chemotherapy administration rate	1/day
	$v_M(t)$	Externally administered chemotherapy concentration	mg/liter
$\frac{dI}{dt}$	μ_I	Rate of decay of IL-2	1/day
	ϕ	Rate of IL-2 production from circulating lymphocytes	IU/(cells·day)
	ω	Rate of IL-2 production from CD8+T cells	IU/(cells·day)
	ζ	Concentration of IL-2 for half-maximal CD8+T IL-2 production	IU/liter
	η_3	Exogenous IL-2 administration rate	1/day
	v_I	Externally administered IL-2 conentration	IU/liter
D	d	Immune system strength coefficient	liter/day
	l	Immune strength scaling coefficient	unitless
	s	Concentration of CD8+T cells in tumor for half-maximal tumor death	cells/liter
	n	Number of CD8+T cells that infiltrate tumor	cells

In addition to the system of differential equations, there are two constraints associated with this model. The first is a terminal condition in which the tumor

population is required to be limited by an upper bound,

$$T(t_f) \leq \Omega_T, \tag{2.7}$$

where Ω_T is constant.

The second constraint is a condition on the control v_M in which the total drug administered is limited by a constant. The constant is divided by 2 for mathematical convenience.

$$\frac{\tau}{2} - \int_0^{t_f} v_M(t) \geq 0, \tag{2.8}$$

where τ is constant.

3. Linear Control

The goal of implementing linear control on the model described in Section 2 is to determine theoretically the optimal treatment schedule for a cancer patient. We prove the existence of such a control using the Filippov-Cesari Theorem, as stated in Hartl, Sethi, and Vickson [14]. Constraints (2.7) and (2.8) prevent the direct application of Pontryagin's Minimum Principle to find the first order necessary conditions for the control to be optimal. We therefore use conditions given by Kamien and Schwartz [17] and Hartl et al. [14] to deal with the terminal inequality conditions generated by constraint (2.7). Constraint (2.8) is incorporated into the state system using a method detailed by Kirk [19].

When implementing linear control, we must investigate the possibility of singular arcs. A singular arc is one for which one or more of the control variables v_α satisfies

$$\frac{\partial H}{\partial v_\alpha} = 0,$$

where H is the Hamiltonian. In this situation, first order necessary conditions are inadequate; therefore, we use the generalized Legendre-Clebsch conditions (see Appendix A, (4.3)) as given by Krener [23] to generate these higher order necessary conditions for optimality.

3.1. Objective Functional.

Now, seeking a bang-bang solution, we wish to minimize the objective functional

$$J(v_L, v_M, v_I) = \int_0^{t_f} \left(T(t) + \epsilon_L v_L(t) + \epsilon_M v_M(t) + \epsilon_I v_I(t)\right) dt, \tag{3.1}$$

which is linear in the three controls and where ϵ_L, ϵ_M and ϵ_I are weight factors.

3.2. Existence.

We first establish the existence of an optimal control building on the existence theorem of Filippov-Cesari, the full statement of which is provided in Appendix A, Theorem (4.1).

Theorem 3.1 (Existence of a Linear Optimal Control)**.** *Given the objective functional* (3.1)*, subject to system* (2.1)-(2.6) *with* $T(0) = T_0$*,* $N(0) = N_0$*,* $L(0) = L_0$*,* $C(0) = C_0$*,* $M(0) = M_0$*,* $I(0) = I_0$*,* $T(t_f) \leq \Omega_T$*, and* $\frac{\tau}{2} - \int_0^{t_f} v_M dt \geq 0$*, and the control set*

$$U = \{v_L(t), v_M(t), v_I(t) \text{ piecewise cont. } : 0 \leq v_L(t), v_M(t), v_I(t) \leq 1, \forall t \in [0, t_f]\},$$

the conditions (1) − (4) *of Theorem* (4.1) *are met, and therefore there exists an optimal control* $\vec{V}^*(t) = (v_L^*(t), v_M^*(t), v_I^*(t))$ *such that*

$$\min_{\vec{V}\in[0,1]} J(V) = J(V^*).$$

Applying the notation of Theorem 4.1 to the optimal control problem (2.1)-(2.6), (3.1), we have

$$\mathbf{x} = \begin{pmatrix} T \\ N \\ L \\ C \\ M \\ I \end{pmatrix}$$

$$N(\mathbf{x},t) = \begin{pmatrix} T(t) + \epsilon_L v_L(t) + \epsilon_M v_M(t) + \epsilon_I v_I(t) \\ aT(1-bT) - cNT - DT - K_T(1-e^{-\delta_T M})T \\ f\left(\frac{e}{f}C - N\right) - pNT + \frac{p_N NI}{g_N+I} - K_N(1-e^{-\delta_N M})N \\ -\frac{\theta mL}{\theta+I} - qLT + r_1 NT + r_2 CT + \frac{p_I LI}{g_I+I} - \frac{u_0 L^2 CI}{\kappa+I} + \frac{jTL}{k+T} - K_L(1-e^{-\delta_L M})L + \eta_1 v_L(t) \\ \beta\left(\frac{\alpha}{\beta} - C\right) - K_C(1-e^{-\delta_C M})C \\ -\gamma M + \eta_2 v_M(t) \\ -\mu_I I + \phi C + \frac{\omega LI}{\zeta+I} + \eta_3 v_I(t) \end{pmatrix}$$

where $\tilde{\gamma} \le 0$, and $v_L, v_M, v_I \in \Omega(x,t)$.

Proof. We know there exists an admissible solution pair for the state and controls as seen in previous work, [8]. For the second condition, we define $w_1 =$

$$\begin{pmatrix} T(t) + \epsilon_L v_{L_1}(t) + \epsilon_M v_{M_1}(t) + \epsilon_I v_{I_1}(t) \\ aT(1-bT) - cNT - DT - K_T(1-e^{-\delta_T M})T \\ f\left(\frac{e}{f}C - N\right) - pNT + \frac{p_N NI}{g_N+I} - K_N(1-e^{-\delta_N M})N \\ -\frac{\theta mL}{\theta+I} - qLT + r_1 NT + r_2 CT + \frac{p_I LI}{g_I+I} - \frac{u_0 L^2 CI}{\kappa+I} + \frac{jTL}{k+T} - K_L(1-e^{-\delta_L M})L + \eta_1 v_{L_1}(t) \\ \beta\left(\frac{\alpha}{\beta} - C\right) - K_C(1-e^{-\delta_C M})C \\ -\gamma M + \eta_2 v_{M_1}(t) \\ -\mu_I I + \phi C + \frac{\omega LI}{\zeta+I} + \eta_3 v_{I_1}(t) \end{pmatrix},$$

and $w_2 =$

$$\begin{pmatrix} T(t) + \epsilon_L v_{L_2}(t) + \epsilon_M v_{M_2}(t) + \epsilon_I v_{I_2}(t) \\ aT(1-bT) - cNT - DT - K_T(1-e^{-\delta_T M})T \\ f\left(\frac{e}{f}C - N\right) - pNT + \frac{p_N NI}{g_N+I} - K_N(1-e^{-\delta_N M})N \\ -\frac{\theta mL}{\theta+I} - qLT + r_1 NT + r_2 CT + \frac{p_I LI}{g_I+I} - \frac{u_0 L^2 CI}{\kappa+I} + \frac{jTL}{k+T} - K_L(1-e^{-\delta_L M})L + \eta_1 v_{L_2}(t) \\ \beta\left(\frac{\alpha}{\beta} - C\right) - K_C(1-e^{-\delta_C M})C \\ -\gamma M + \eta_2 v_{M_2}(t) \\ -\mu_I I + \phi C + \frac{\omega LI}{\zeta+I} + \eta_3 v_{I_2}(t) \end{pmatrix}$$

for some $\tilde{\gamma_1}, \tilde{\gamma_2} \le 0$, and $v_{L_j}, v_{M_j}, v_{I_j} \in \Omega(x,t)$, with $j = 1, 2$.

We then let $w_3 = \lambda w_1 + (1-\lambda)w_2$ for $\lambda \in [0,1]$. To prove that $N(\mathbf{x},t)$is convex, we need to show that $w_3 \in N(\mathbf{x},t)$ However, since the controls appear linearly, we note that this occurs naturally.

For the third condition we need to show that there exists a number δ such that $\|x\| \le \delta$, $\forall t \in [0, t_f]$ and all admissible pairs $(\vec{\mathbf{x}}, \vec{\mathbf{V}})$. We need to determine an upper

bound on the right hand sides of the differential equations (2.1)-(2.6). To do this, we first consider the right hand side of (2.1), the tumor cell population. With $T_{\max}$ as an upper bound solution associated with T and $T(t) \geq 0$, then $T_{\max} = T_0 e^{at_f}$.

By using the bound $T_{\max}$, we can form a set of supersolutions for system (2.1)-(2.6). This set of supersolutions $\bar{T}$, $\bar{N}$, $\bar{L}$, $\bar{C}$, $\bar{M}$, $\bar{I}$ of

$$\begin{aligned}
\frac{d\overline{T}}{dt} &= a\overline{T} \\
\frac{d\overline{N}}{dt} &= p_N\overline{N} + e\overline{C} \\
\frac{d\overline{L}}{dt} &= r_1\overline{N}T_{\max} + (p_I + j)\overline{L} + r_2\overline{C}T_{\max} + \eta_1 v_L \\
\frac{d\overline{C}}{dt} &= \alpha \\
\frac{d\overline{M}}{dt} &= \eta_2 v_M \\
\frac{d\overline{I}}{dt} &= \omega\overline{L} + \phi\overline{C} + \eta_3 v_I
\end{aligned}$$

is bounded on a finite time interval. We see that system (2.1)-(2.6) can be written as

$$\begin{pmatrix} \bar{T} \\ \bar{N} \\ \bar{L} \\ \bar{C} \\ \bar{M} \\ \bar{I} \end{pmatrix}' = \begin{pmatrix} a & 0 & 0 & 0 & 0 & 0 \\ 0 & p_N & 0 & e & 0 & 0 \\ 0 & r_1 T_{\max} & p_I + j & r_2 T_{\max} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \omega & \phi & 0 & 0 \end{pmatrix} \begin{pmatrix} \bar{T} \\ \bar{N} \\ \bar{L} \\ \bar{C} \\ \bar{M} \\ \bar{I} \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ \eta_1 v_L \\ \alpha \\ \eta_2 v_M \\ \eta_3 v_I \end{pmatrix}$$

Since this supersolution system involves only constants then it has a finite upper bound. Letting this upper bound be δ satisfies the third condition.

The fourth condition is satisfied by definition, since $0 < v_\alpha < 1$, for all controls v_α. □

3.3. **Characterization of the Optimal Control.** We now develop the representations of the optimal control, using Pontraygin's Maximum/Minimum Principle (see Appendix A, (4.2)), conditions from Kamien and Schwarz[17], and the generalized Legendre-Clebsch conditions (see Appendix A, (4.3)).

Before proceeding with the characterization of the optimal control, we must consider the constraints that accompany the model. The terminal constraint (2.7) generates additional transversality conditions which are included in the following theorem. However, the treatment of the integral control constraint (2.8) requires some explanation, so we will show the method used to deal with it before stating the representation of the optimal control.

By introducing a state variable A, we can express constraint (2.8) equivalently as

$$\frac{dA}{dt} = v_M(t), \tag{3.2}$$

with boundary conditions $A(0) = 0$ and $A(t_f) \leq \frac{\tau}{2}$. Note that this modification produces a second terminal inequality condition, which will be dealt with in the same manner as (2.7).

We will now treat equation (3.2) as an additional state equation, adding it to system (2.1)-(2.6) along with the conditions $T(t_f) \leq \Omega_T$, $A(0) = 0$, and $A(t_f) \leq \frac{\tau}{2}$. With these modifications, we state the representation of the optimal control.

Theorem 3.2 (Characterization of the Optimal Control)**.** *Given an optimal control triple, $\vec{V} = ({v_L}^*(t), {v_M}^*(t), {v_I}^*(t))$, and solutions of the corresponding state system, there exist adjoint variables λ_i for $i = 1, 2, \ldots, 7$ satisfying the following:*

$$\frac{d\lambda_1}{dt} = -1 - \lambda_1\Big(a - 2abT - cN - D + \frac{\frac{s}{n^\ell} d\ell \big(\frac{L}{T}\big)^\ell}{\big[\frac{s}{n^\ell} + \big(\frac{L}{T}\big)^\ell\big]^2} - K_T(1 - e^{-\delta_T M})\Big) + \lambda_2 pN - \lambda_3\left(-qL + r_1 N + r_2 C + \frac{jkL}{(k+T)^2}\right) \tag{3.3}$$

$$\frac{d\lambda_2}{dt} = \lambda_1 cT + \lambda_2\left(f + pT - \frac{p_N I}{g_N + I} + K_N(1 - e^{-\delta_N M})\right) - \lambda_3 r_1 T \tag{3.4}$$

$$\frac{d\lambda_3}{dt} = \lambda_1\Big(\frac{\frac{s}{n^\ell} d\ell \big(\frac{L}{T}\big)^{\ell-1}}{\big[\frac{s}{n^\ell} + \big(\frac{L}{T}\big)^\ell\big]^2}\Big) - \lambda_6\left(\frac{\omega I}{\zeta + I}\right) + \lambda_3\left(\frac{\theta m}{\theta + I} + qT - \frac{p_I I}{g_I + I} + \frac{2u_0 LCI}{\kappa + I} - \frac{jT}{k+T} + K_L(1 - e^{-\delta_L M})\right) \tag{3.5}$$

$$\frac{d\lambda_4}{dt} = -\lambda_2 e - \lambda_3\left(r_2 T - \frac{u_0 L^2 I}{\kappa + I}\right) + \lambda_4(\beta + K_C(1 - e^{-\delta_C M})) - \lambda_6\phi \tag{3.6}$$

$$\frac{d\lambda_5}{dt} = \lambda_1\delta_T K_T T e^{-\delta_T M} + \lambda_2\delta_N K_N N e^{-\delta_N M} + \lambda_3\delta_L K_L L e^{-\delta_L M} + \lambda_4\delta_C K_C C e^{-\delta_C M} + \gamma\lambda_5 \tag{3.7}$$

$$\frac{d\lambda_6}{dt} = -\lambda_2\left(\frac{p_N g_N N}{(g_N + I)^2}\right) - \lambda_3\left(\frac{\theta m L}{(\theta + I)^2} + \frac{p_I g_I L}{(g_I + I)^2} - \frac{u_0 \kappa L^2 C}{(\kappa + I)^2}\right) + \lambda_6\left(\mu_I - \frac{\omega\zeta L}{(\zeta + I)^2}\right) \tag{3.8}$$

$$\frac{d\lambda_7}{dt} = 0 \tag{3.9}$$

where $\lambda_i(t_f) = 0$ for $i = 2, 3, \ldots, 6$. In addition, there are transversality conditions imposed from the constraints:

$$\lambda_1(t_f) = -\rho_1$$
$$\lambda_7(t_f) = -\rho_2,$$

where $\rho_1, \rho_2 \leq 0$, and

$$\rho_1 K_1 = 0$$
$$\rho_2 K_2 = 0,$$

where $K_1 = \Omega_T - T(t_f)$, $K_2 = \frac{\tau}{2} - A(t_f)$, and $K_i \geq 0$ for $i = 1, 2$.
Furthermore, the representations of the controls are determined by the switching functions

$$\Phi_L = \epsilon_L + \lambda_3\eta_1,$$
$$\Phi_M = \epsilon_M + \lambda_5\eta_2 + \lambda_7, \text{ and}$$
$$\Phi_I = \epsilon_I + \lambda_6\eta_3.$$

The representations of the optimal controls are then given by

$$v_L(t) = \begin{cases} 0 & \text{if } \Phi_L > 0 \\ 1 & \text{if } \Phi_L < 0 \\ \text{singular} & \text{if } \Phi_L = 0, \end{cases} \tag{3.10}$$

$$v_M(t) = \begin{cases} 0 & \text{if } \Phi_M > 0 \\ 1 & \text{if } \Phi_M < 0 \\ \text{singular} & \text{if } \Phi_M = 0, \end{cases} \tag{3.11}$$

$$v_I(t) = \begin{cases} 0 & \text{if } \Phi_I > 0 \\ 1 & \text{if } \Phi_I < 0 \\ \text{singular} & \text{if } \Phi_I = 0. \end{cases} \tag{3.12}$$

Proof. The Lagrangian associated with this problem is

$$\begin{aligned} \mathcal{L} = H &- W_1(t)v_L(t) - W_2(t)(1 - v_L(t)) - W_3(t)v_M(t) - W_4(t)(1 - v_M(t)) \\ &- W_5(t)v_I(t) - W_6(t)(1 - v_I(t)), \end{aligned}$$

where H is the Hamiltonian given by

$$\begin{aligned} H &= T(t) + \epsilon_L v_L(t) + \epsilon_M v_M(t) + \epsilon_I v_I(t) \\ &+ \lambda_1(aT(1 - bT) - cNT - DT - K_T(1 - e^{-\delta_T M})T) \\ &+ \lambda_2(f\big(\frac{e}{f}C - N\big) - pNT + \frac{p_N NI}{g_N + I} - K_N(1 - e^{-\delta_N M})N) \\ &+ \lambda_3(-\frac{\theta mL}{\theta + I} - qLT + r_1 NT + r_2 CT + \frac{p_I LI}{g_I + I} - \frac{u_0 L^2 CI}{\kappa + I} + \frac{jT}{k + T}L \\ &- K_L(1 - e^{-\delta_L M})L + \eta_1 v_L(t)) \\ &+ \lambda_4(\beta\big(\frac{\alpha}{\beta} - C\big) - K_C(1 - e^{-\delta_C M})C) + \lambda_5(-\gamma M + \eta_2 v_M(t)) \\ &+ \lambda_6(-\mu_I I + \phi C + \frac{\omega LI}{\zeta + I} + \eta_3 v_I(t)) + \lambda_7 v_M(t) \end{aligned}$$

The adjoint equations are formed from differentiating the Hamiltonian with respect to the corresponding state variables as $\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial T}$.

Since system (3.3)-(3.9) has bounded coefficients and the solutions are bounded on the finite time interval, we know that adjoint variables satisfying (3.3)-(3.9) exist from Lukes [29], p.182. Also, the final conditions are free for all variables with the exception of $T(t)$ and $A(t)$; thus we have that $\lambda_i(t_f) = 0$, for $i = 2, \ldots, 6$. The additional conditions imposed by the terminal inequality constraints are taken from Kamien and Schwarz [17].

We find the representations of (3.10)-(3.12) of the optimal controls by looking at the coefficients of the controls in H; i.e. we consider the sign of $\Phi_L = \frac{\partial H}{\partial v_L}$ to determine the values of v_L. □

The characterization of the controls in singular regions is determined by taking time derivatives of the switching functions. We will examine these representations and the conditions necessary for the controls to be minimizing in the singular region provided that the representations of the singular controls satisfy the control bounds. Note that each interval of singularity is a subinterval of $[0, t_f]$. We will begin by

assuming only one of the controls is singular on a given interval in each of Theorems 3.3-3.5.

Theorem 3.3. *If v_L is singular on the interval (s_L, t_L), the singularity is of degree two and the representation of the control is given by*

$$v_L = -\frac{P_L}{Q_L}, \quad Q_L \neq 0,$$

where Q_L is given by

$$Q_L = \eta_1 \big[\lambda_1 T \frac{\partial^2 D}{\partial L^2} - 2u_0 C \frac{\epsilon_L}{\eta_1}\big(\frac{I}{\kappa + I}\big)\big] \tag{3.13}$$

and P_L is given in Appendix B. Furthermore, if v_L is minimizing on this interval, it is necessary that

$$\lambda_1 T \frac{\partial^2 D}{\partial L^2} \leq 2u_0 C \frac{\epsilon_L}{\eta_1} \left(\frac{I}{\kappa + I}\right).$$

Proof. On the interval (s_L, t_L), we know that time derivatives of Φ_L are identically 0; i.e. $\frac{d}{dt}\Phi_L = 0$, $\frac{d^2}{dt^2}\Phi_L = 0$, etc. In addition, we have that $\lambda_3 = -\frac{\epsilon_L}{\eta_1}$ in this region. We use this information to find v_L. To begin, notice that

$$\frac{d}{dt}\Phi_L = \eta_1 \frac{d}{dt}\lambda_3 = 0, \quad \text{or } \frac{d\lambda_3}{dt} = 0.$$

Then, from the corresponding adjoint equation (3.5), we have that

$$\begin{aligned}
\frac{d\lambda_3}{dt} &= \lambda_1 \left(\frac{\frac{s}{n^\ell} d\ell \big(\frac{L}{T}\big)^{\ell-1}}{\big[\frac{s}{n^\ell} + \big(\frac{L}{T}\big)^\ell\big]^2}\right) - \lambda_6 \Big(\frac{\omega I}{\zeta + I}\Big) \\
&\quad + \lambda_3 \left(\frac{\theta m}{\theta + I} + qT - \frac{p_I I}{g_I + I} + \frac{2u_0 LCI}{\kappa + I} - \frac{jT}{k + T} + K_L(1 - e^{-\delta_L M})\right) \\
&= 0
\end{aligned}$$

Note that

$$\frac{\partial D}{\partial L} T = \frac{\frac{s}{n^\ell} d\ell \big(\frac{L}{T}\big)^{\ell-1}}{\big[\frac{s}{n^\ell} + \big(\frac{L}{T}\big)^\ell\big]^2}$$

This will simplify the notation in the following calculation.

Taking a second time derivative yields

$$\begin{aligned}
\frac{d^2\lambda_3}{dt^2} &= \frac{d\lambda_1}{dt}\left(\frac{\partial D}{\partial L} T\right) + \lambda_1 T \left[\frac{\partial^2 D}{\partial L^2}\frac{dL}{dt} + \frac{\partial^2 D}{\partial T \partial L}\frac{dT}{dt}\right] \\
&\quad + \lambda_1 \left(\frac{\partial D}{\partial L}\frac{dT}{dt}\right) - \frac{d\lambda_6}{dt}\left(\frac{\omega I}{\zeta + I}\right) - \lambda_6 \left(\frac{\omega \zeta}{(\zeta + I)^2}\right)\frac{dI}{dt} \\
&\quad + \lambda_3 \Big[- \frac{\theta m}{(\theta + I)^2}\frac{dI}{dt} + q\frac{dT}{dt} - \frac{p_I g_I}{(g_I + I)^2}\frac{dI}{dt} + 2u_0 LC \left(\frac{\kappa}{(\kappa + I)^2}\right)\frac{dI}{dt} \\
&\quad + 2u_0 \left(\frac{I}{\kappa + I}\right)\left[L\frac{dC}{dt} + C\frac{dL}{dt}\right] - \frac{jk}{(k + T)^2}\frac{dT}{dt} + \delta_L K_L e^{-\delta_L M}\frac{dM}{dt}\Big] \\
&= 0.
\end{aligned}$$

Grouping like terms (by state derivative) and substituting equation (2.3) results in

$$\frac{d^2\lambda_3}{dt^2} = \frac{d\lambda_1}{dt}\frac{\partial D}{\partial L} T - \frac{d\lambda_6}{dt}\left(\frac{\omega I}{\zeta + I}\right)$$

$$
\begin{aligned}
&+\left[\lambda_1 T\frac{\partial^2 D}{\partial T\partial L}+\lambda_1\frac{\partial D}{\partial L}+\lambda_3\left(q-\frac{jk}{(k+T)^2}\right)\right]\frac{dT}{dt}\\
&+\left[\lambda_3\left(-\frac{\theta m}{(\theta+I)^2}-\frac{p_I g_I}{(g_I+I)^2}+2u_0LC\frac{\kappa}{(\kappa+I)^2}\right)-\lambda_6\frac{\omega\zeta}{(\zeta+I)^2}\right]\frac{dI}{dt}\\
&+2u_0\lambda_3 L\left(\frac{I}{\kappa+I}\right)\frac{dC}{dt}+\lambda_3\delta_L K_L e^{-\delta_L M}\frac{dM}{dt}\\
&+\left[\lambda_1 T\frac{\partial^2 D}{\partial L^2}+2u_0\lambda_3 C\left(\frac{I}{\kappa+I}\right)\right]\\
&\times\Big[-\frac{\theta mL}{\theta+I}-qLT+r_1NT+r_2CT+\frac{p_I LI}{g_I+I}-\frac{u_0L^2CI}{\kappa+I}\\
&+\frac{jTL}{k+T}-K_L(1-e^{-\delta_L M})L+\eta_1 v_L(t)\Big]\\
&=0.
\end{aligned}
$$

Isolating the v_L term and substituting $\lambda_3=-\frac{\epsilon_L}{\eta_1}$ gives

$$
\begin{aligned}
\frac{d^2\lambda_3}{dt^2}&=\eta_1\left[\lambda_1 T\frac{\partial^2 D}{\partial L^2}-2u_0C\frac{\epsilon_L}{\eta_1}\left(\frac{I}{\kappa+I}\right)\right]v_L\\
&+\frac{d\lambda_1}{dt}\frac{\partial D}{\partial L}T-\frac{d\lambda_6}{dt}\left(\frac{\omega I}{\zeta+I}\right)\\
&+\left[\lambda_1 T\frac{\partial^2 D}{\partial T\partial L}+\lambda_1\frac{\partial D}{\partial L}-\frac{\epsilon_L}{\eta_1}\left(q-\frac{jk}{(k+T)^2}\right)\right]\frac{dT}{dt}\\
&+\left[\frac{\epsilon_L}{\eta_1}\left(\frac{\theta m}{(\theta+I)^2}+\frac{p_I g_I}{(g_I+I)^2}-2u_0LC\frac{\kappa}{(\kappa+I)^2}\right)-\lambda_6\frac{\omega\zeta}{(\zeta+I)^2}\right]\frac{dI}{dt}\\
&-2u_0L\frac{\epsilon_L}{\eta_1}\left(\frac{I}{\kappa+I}\right)\frac{dC}{dt}-\delta_L K_L e^{-\delta_L M}\frac{\epsilon_L}{\eta_1}\frac{dM}{dt}\\
&+\left[\lambda_1 T\frac{\partial^2 D}{\partial L^2}-2u_0C\frac{\epsilon_L}{\eta_1}\left(\frac{I}{\kappa+I}\right)\right]\\
&\times\Big[-\frac{\theta mL}{\theta+I}-qLT+r_1NT+r_2CT+\frac{p_I LI}{g_I+I}-\frac{u_0L^2CI}{\kappa+I}\\
&+\frac{jTL}{k+T}-K_L(1-e^{-\delta_L M})L\Big]\\
&=0.
\end{aligned}
$$

Now, let P_L denote the above sum *excluding* the v_L term. Notice that P_L depends on $\lambda_1,\lambda_2,\lambda_6,T,N,L,C,M,I,v_M,$ and v_I. Next, define Q_L as

$$
Q_L=\eta_1\left[\lambda_1 T\frac{\partial^2 D}{\partial L^2}-2u_0C\frac{\epsilon_L}{\eta_1}\big(\frac{I}{\kappa+I}\big)\right].
$$

Using this condensed notation, we see that

$$
v_L=-\frac{P_L}{Q_L},\quad \text{if } Q_L\neq 0.
$$

Here the degree of the singularity is 2.
Furthermore, *if* v_I and v_M are assumed to be bang-bang on the interval (s_L,t_L),

then the Legendre-Clebsch condition for the control to be minimizing is

$$(-1)\frac{\partial}{\partial v_L}\frac{d^2}{dt^2}\frac{\partial H}{\partial v_L} \geq 0, \quad \text{or} \quad Q_L \leq 0;$$

i.e.

$$\lambda_1 T\frac{\partial^2 D}{\partial L^2} \leq 2u_0 C\frac{\epsilon_L}{\eta_1}\left(\frac{I}{\kappa + I}\right).$$

□

Theorem 3.4. *If v_M is singular on the interval (s_M, t_M), the singularity is of degree two and the representation of the control is given by*

$$v_M = -\frac{P_M}{Q_M}, \quad Q_M \neq 0,$$

where Q_M is given by

$$\begin{aligned} Q_M = -\eta_2\Big[&\delta_T K_T\lambda_1 T(\delta_T e^{-\delta_T M}) + \delta_N K_N\lambda_2 N(-\delta_N e^{\delta_N M}) \\ &+ \delta_L K_L\lambda_3 L(\delta_L e^{-\delta_L M}) + \delta_C K_C\lambda_4 C(-\delta_C e^{\delta_C M})\Big] \end{aligned} \tag{3.14}$$

and P_M is given in Appendix B.
Furthermore, if v_M is minimizing on this interval, it is necessary that

$$\begin{aligned} &\Big[\delta_T K_T\lambda_1 T(\delta_T e^{-\delta_T M}) + \delta_N K_N\lambda_2 N(\delta_N e^{-\delta_N M}) \\ &+ \delta_L K_L\lambda_3 L(\delta_L e^{-\delta_L M}) + \delta_C K_C\lambda_4 C(\delta_C e^{-\delta_C M})\Big] \geq 0. \end{aligned}$$

Proof. If v_M is singular on some interval (s_M, t_M), we know that time derivatives of Φ_M are identically zero in this region; in addition, we have that $\lambda_5 = -\epsilon_M/\eta_2$. As before, note that

$$\frac{d}{dt}\Phi_M = \eta_2\frac{d}{dt}\lambda_5 + \frac{d}{dt}\lambda_7 = 0, \quad \text{or } \frac{d\lambda_5}{dt} = 0,$$

since $\frac{d\lambda_7}{dt} = 0$. Coupling this information with equation (3.7) yields

$$\begin{aligned} \frac{d\lambda_5}{dt} &= \lambda_1\delta_T K_T T e^{-\delta_T M} + \lambda_2\delta_N K_N N e^{-\delta_N M} + \lambda_3\delta_L K_L L e^{-\delta_L M} \\ &\quad + \lambda_4\delta_C K_C C e^{-\delta_C M} + \gamma\lambda_5 \\ &= 0. \end{aligned}$$

Taking a time derivative gives the result

$$\begin{aligned} \frac{d^2\lambda_5}{dt^2} &= \delta_T K_T\left[\lambda_1 T(-\delta_T e^{-\delta_T M})\frac{dM}{dt} + e^{-\delta_T M}\left(\lambda_1\frac{dT}{dt} + T\frac{d\lambda_1}{dt}\right)\right] \\ &\quad + \delta_N K_N\left[\lambda_2 N(-\delta_N e^{-\delta_N M})\frac{dM}{dt} + e^{-\delta_N M}\left(\lambda_2\frac{dN}{dt} + N\frac{d\lambda_2}{dt}\right)\right] \\ &\quad + \delta_L K_L\left[\lambda_3 L(-\delta_L e^{-\delta_L M})\frac{dM}{dt} + e^{-\delta_L M}\left(\lambda_3\frac{dL}{dt} + L\frac{d\lambda_3}{dt}\right)\right] \\ &\quad + \delta_C K_C\left[\lambda_4 C(-\delta_C e^{-\delta_C M})\frac{dM}{dt} + e^{-\delta_C M}\left(\lambda_4\frac{dC}{dt} + C\frac{d\lambda_4}{dt}\right)\right] \\ &\quad + \gamma\frac{d\lambda_5}{dt} \\ &= 0. \end{aligned}$$

Notice that the last term is zero, since $\frac{d\lambda_5}{dt} = 0$. Grouping the $\frac{dM}{dt}$terms, substituting equation (2.5), and isolating the v_M term in the above equation gives

$$\begin{aligned}
\frac{d^2\lambda_5}{dt^2} &= \eta_2\Big[\delta_T K_T\lambda_1 T(-\delta_T e^{-\delta_T M}) + \delta_N K_N\lambda_2 N(-\delta_N e^{-\delta_N M}) \\
&\quad + \delta_L K_L\lambda_3 L(-\delta_L e^{-\delta_L M}) + \delta_C K_C\lambda_4 C(-\delta_C e^{-\delta_C M})\Big]v_M \\
&\quad + \delta_T K_T e^{-\delta_T M}\left(\lambda_1\frac{dT}{dt} + T\frac{d\lambda_1}{dt}\right) + \delta_N K_N e^{-\delta_N M}\left(\lambda_2\frac{dN}{dt} + N\frac{d\lambda_2}{dt}\right) \\
&\quad + \delta_L K_L e^{-\delta_L M}\left(\lambda_3\frac{dL}{dt} + L\frac{d\lambda_3}{dt}\right) + \delta_C K_C e^{-\delta_C M}\left(\lambda_4\frac{dC}{dt} + C\frac{d\lambda_4}{dt}\right) \\
&\quad - \gamma M\Big[\delta_T K_T\lambda_1 T(-\delta_T e^{-\delta_T M}) + \delta_N K_N\lambda_2 N(-\delta_N e^{-\delta_N M}) \\
&\quad + \delta_L K_L\lambda_3 L(-\delta_L e^{-\delta_L M}) + \delta_C K_C\lambda_4 C(-\delta_C e^{-\delta_C M})\Big] \\
&= 0.
\end{aligned}$$

Now, as before, let P_M denote the above sum, excluding the v_M term. Note that P_M is dependent on all the state and adjoint variables, as well as the control v_L. Define Q_M as

$$\begin{aligned}
Q_M = -\eta_2\Big[&\delta_T K_T\lambda_1 T(\delta_T e^{-\delta_T M}) + \delta_N K_N\lambda_2 N(-\delta_N e^{\delta_N M}) \\
&+ \delta_L K_L\lambda_3 L(\delta_L e^{-\delta_L M}) + \delta_C K_C\lambda_4 C(-\delta_C e^{\delta_C M})\Big].
\end{aligned}$$

Then we have

$$v_M = -\frac{P_M}{Q_M}, \quad \text{if } Q_M \neq 0.$$

Here the degree of the singularity is two.

Furthermore, *if* v_L and v_I are assumed to be bang-bang on the interval (s_M, t_M), then the Legendre-Clebsch condition for the control to be minimizing is

$$(-1)\frac{\partial}{\partial v_M}\frac{d^2}{dt^2}\frac{\partial H}{\partial v_M} \geq 0,$$

or in this situation,

$$Q_M \leq 0.$$

Thus, if v_M is singular on some interval, we have the additional necessary condition

$$\begin{aligned}
&\Big[\delta_T K_T\lambda_1 T(\delta_T e^{-\delta_T M}) + \delta_N K_N\lambda_2 N(\delta_N e^{-\delta_N M}) \\
&+ \delta_L K_L\lambda_3 L(\delta_L e^{-\delta_L M}) + \delta_C K_C\lambda_4 C(\delta_C e^{-\delta_C M})\Big] \geq 0,
\end{aligned}$$

since $\eta_2 \neq 0$, in general. □

Theorem 3.5. *If v_I is singular on the interval (s_I, t_I), the singularity is of degree two and the representation of the control is given by*

$$v_I = -\frac{P_I}{Q_I}, \quad Q_I \neq 0,$$

where Q_I is given by

$$Q_I = \eta_3\left[\frac{2\lambda_2 p_N g_N N}{(g_N + I)^3} + \frac{2\lambda_3\theta m L}{(\theta + I)^3} + \frac{2\lambda_3 p_I g_I L}{(g_I + I)^3} - \frac{2\lambda_3 u_0\kappa L^2 C}{(\kappa + I)^3} - \frac{2\epsilon_I\omega\zeta L}{\eta_3(\zeta + I)^3}\right] \tag{3.15}$$

and P_I is given in Appendix B. Furthermore, if v_I is minimizing on this interval, it is necessary that

$$\frac{\lambda_2 p_N g_N N}{(g_N+I)^3}+\frac{\lambda_3\theta m L}{(\theta+I)^3}+\frac{\lambda_3 p_I g_I L}{(g_I+I)^3}\le\frac{\lambda_3 u_0\kappa L^2 C}{(\kappa+I)^3}+\frac{\epsilon_I\omega\zeta L}{\eta_3(\zeta+I)^3}\ .$$

Proof. Assume v_I is singular on the interval (s_I,t_I); then all derivatives with respect to time of Φ_I are equal to zero and $\lambda_6=-\frac{\epsilon_I}{\eta_3}$. Then

$$\frac{d}{dt}\Phi_I=\eta_3\frac{d}{dt}\lambda_6=0,\quad\text{and so}\quad\frac{d\lambda_6}{dt}=0.$$

Together with equation (3.8), we have

$$\begin{aligned}\frac{d\lambda_6}{dt}&=-\lambda_2\left(\frac{p_N g_N N}{(g_N+I)^2}\right)-\lambda_3\left(\frac{\theta m L}{(\theta+I)^2}+\frac{p_I g_I L}{(g_I+I)^2}-\frac{u_0\kappa L^2 C}{(\kappa+I)^2}\right)\\&\quad+\lambda_6\left(\mu_I-\frac{\omega\zeta L}{(\zeta+I)^2}\right)\\&=0.\end{aligned}$$

Differentiate with respect to t for

$$\begin{aligned}\frac{d^2\lambda_6}{dt^2}&=-\frac{d\lambda_2}{dt}\left(\frac{p_N g_N N}{(g_N+I)^2}\right)-\lambda_2\Big[\frac{(g_N+I)^2 p_N g_N\frac{dN}{dt}-p_N g_N N\cdot 2(g_N+I)\frac{dI}{dt}}{(g_N+I)^4}\Big]\\&\quad-\frac{d\lambda_3}{dt}\left[\frac{\theta m L}{(\theta+I)^2}+\frac{p_I g_I L}{(g_I+I)^2}-\frac{u_0\kappa L^2 C}{(\kappa+I)^2}\right]\\&\quad-\lambda_3\left[\frac{(\theta+I)^2\theta m\frac{dL}{dt}-\theta m L\cdot 2(\theta+I)\frac{dI}{dt}}{(\theta+I)^4}\right.\\&\quad+\frac{(g_I+I)^2 p_I g_I\frac{dL}{dt}-p_I g_I L\cdot 2(g_I+I)\frac{dI}{dt}}{(g_I+I)^4}\\&\quad\left.-\frac{u_0\kappa(\kappa+I)^2\left[L^2\frac{dC}{dt}+2LC\frac{dL}{dt}\right]-u_0\kappa L^2 C\cdot 2(\kappa+I)\frac{dI}{dt}}{(\kappa+I)^4}\right]\\&\quad+\frac{d\lambda_6}{dt}\left[\mu_I-\frac{\omega\zeta L}{(\zeta+I)^2}\right]-\lambda_6\Big[\frac{(\zeta+I)^2\omega\zeta\frac{dL}{dt}-\omega\zeta L\cdot 2(\zeta+I)\frac{dI}{dt}}{(\zeta+I)^4}\Big]\\&=0.\end{aligned}\tag{3.16}$$

We substitute $\lambda_6=-\epsilon_I/\eta_3$, and note that the $\frac{d\lambda_6}{dt}$ term equals zero. Then we group terms, substitute equation (2.6), and isolate the v_I term to get

$$\begin{aligned}0&=\frac{d^2\lambda_6}{dt^2}\\&=\eta_3\left[\frac{2\lambda_2 p_N g_N N}{(g_N+I)^3}+\frac{2\lambda_3\theta m L}{(\theta+I)^3}+\frac{2\lambda_3 p_I g_I L}{(g_I+I)^3}-\frac{2\lambda_3 u_0\kappa L^2 C}{(\kappa+I)^3}-\frac{2\epsilon_I\omega\zeta L}{\eta_3(\zeta+I)^3}\right]v_I\\&\quad-\frac{d\lambda_2}{dt}\left(\frac{p_N g_N N}{(g_N+I)^2}\right)\\&\quad-\frac{d\lambda_3}{dt}\left[\frac{\theta m L}{(\theta+I)^2}+\frac{p_I g_I L}{(g_I+I)^2}-\frac{u_0\kappa L^2 C}{(\kappa+I)^2}\right]\\&\quad-\frac{dN}{dt}\left(\frac{\lambda_2 p_N g_N}{(g_N+I)^2}\right)-\frac{dC}{dt}\left(\frac{\lambda_3 u_0\kappa L^2}{(\kappa+I)^2}\right)\end{aligned}$$

$$+\frac{dL}{dt}\left[-\frac{\lambda_3\theta m}{(\theta+I)^2}-\frac{\lambda_3 p_I g_I}{(g_I+I)^2}+\frac{2\lambda_3 u_0\kappa LC}{(\kappa+I)^2}+\frac{\epsilon_I\omega\zeta}{\eta_3(\zeta+I)^2}\right]$$
$$+\left[\frac{2\lambda_2 p_N g_N N}{(g_N+I)^3}+\frac{2\lambda_3\theta mL}{(\theta+I)^3}+\frac{2\lambda_3 p_I g_I L}{(g_I+I)^3}-\frac{2\lambda_3 u_0\kappa L^2 C}{(\kappa+I)^3}-\frac{2\epsilon_I\omega\zeta L}{\eta_3(\zeta+I)^3}\right]$$
$$\times\Big(-\mu_I I+\phi C+\frac{\omega LI}{\zeta+I}\Big).$$

Let P_I denote the above sum excluding the v_I term. Note that P_I depends on all the state and adjoint variables, as well as the control v_L. Let Q_I be defined by

$$Q_I=\eta_3\left[\frac{2\lambda_2 p_N g_N N}{(g_N+I)^3}+\frac{2\lambda_3\theta mL}{(\theta+I)^3}+\frac{2\lambda_3 p_I g_I L}{(g_I+I)^3}-\frac{2\lambda_3 u_0\kappa L^2 C}{(\kappa+I)^3}-\frac{2\epsilon_I\omega\zeta L}{\eta_3(\zeta+I)^3}\right].$$

Then we have

$$v_I=-\frac{P_I}{Q_I},\quad \text{if } Q_I\neq 0.$$

Here the degree of the singularity is 2. Furthermore, *if* v_L and v_M are assumed to be bang-bang on the interval (s_I,t_I), then the Legendre-Clebsch condition for the control to be minimizing is

$$(-1)\frac{\partial}{\partial v_I}\frac{d^2}{dt^2}\frac{\partial H}{\partial v_I}\geq 0,$$

or in this situation, $Q_I\leq 0$. Thus, if v_I is singular on some interval, we have the additional necessary condition

$$\frac{\lambda_2 p_N g_N N}{(g_N+I)^3}+\frac{\lambda_3\theta mL}{(\theta+I)^3}+\frac{\lambda_3 p_I g_I L}{(g_I+I)^3}\leq\frac{\lambda_3 u_0\kappa L^2 C}{(\kappa+I)^3}+\frac{\epsilon_I\omega\zeta L}{\eta_3(\zeta+I)^3},$$

since $\eta_3\neq 0$. □

Having found the representations for each control on a singular interval, we turn our attention to the necessary conditions generated when two of the controls are simultaneously singular on the same interval. Note that the degree of singularity of each control is two; both this fact and the representations found previously will be used to generate the necessary Legendre-Clebsch conditions.

Theorem 3.6. *If v_L and v_M are both singular on some interval (s,t), then the following conditions must hold for v_L and v_M to be minimizing:*

$$Q_L\leq 0,$$
$$Q_L Q_M\geq\eta_1\eta_2(\lambda_3\delta_L K_L e^{-\delta_L M})^2,$$

where Q_L and Q_M are defined as in (3.13) *and* (3.14)*, respectively.*

Proof. Assuming that v_L and v_M are both singular on the interval (s,t), we use the generalized Legendre-Clebsch conditions to form the 2×2 matrix

$$A_{ij}=(-1)^{\frac{h_j+1}{2}}\frac{\partial}{\partial v_i}\frac{d^{(\frac{h_i+h_j}{2}+1)}}{dt^{(\frac{h_i+h_j}{2}+1)}}\frac{\partial H}{\partial v_j}=(-1)\frac{\partial}{\partial v_L}\frac{d^2}{dt^2}\frac{\partial H}{\partial v_M},$$

which is given by

$$A_{v_L,v_M}=\begin{pmatrix}-\eta_1 Q_L & -\eta_1\eta_2\lambda_3\delta_L K_L e^{-\delta_L M}\\ -\eta_1\eta_2\lambda_3\delta_L K_L e^{-\delta_L M} & -\eta_2 Q_M\end{pmatrix},$$

Note that Q_L and Q_M are defined as in (3.13) and (3.14), respectively. This matrix is clearly symmetric. In order for v_L and v_M to be minimizing on the interval (s,t),

the matrix A_{v_L,v_M} must be positive definite. In other words, all upper left minors of A_{v_L,v_M} must be positive; then the conditions

$$Q_L \leq 0,$$
$$Q_L Q_M \geq \eta_1\eta_2(\lambda_3\delta_L K_L e^{-\delta_L M})^2.$$

must hold. □

In a similar fashion, conditions for the pairs v_L, v_I and v_M, v_I to be singular on a given interval are found as noted in the following theorems without proof.

Theorem 3.7. *If v_L and v_I are both singular on some interval (s,t), then the following conditions must hold for v_L and v_I to be minimizing:*

$$Q_L \leq 0,$$
$$Q_L Q_I \geq \eta_1\eta_3(\circledast)^2.$$

where Q_L and Q_I are defined as in (3.13) *and* (3.15)*, respectively, and*

$$\circledast = \left(\frac{\lambda_3\theta m}{(\theta+I)^2} + \frac{\lambda_3 p_I g_I}{(g_I+I)^2} - \frac{2\lambda_3 u_0\kappa LC}{(\kappa+I)^2} + \frac{\lambda_6\omega\zeta}{(\zeta+I)^2}\right). \tag{3.17}$$

Theorem 3.8. *If v_M and v_I are both singular on some interval (s,t), then the following conditions must hold for v_M and v_I to be minimizing:*

$$Q_M \leq 0,$$
$$Q_M Q_I \geq 0.$$

where Q_M and Q_I are defined as in (3.14) *and* (3.15)*, respectively.*

Finally, we will use the Legendre-Clebsch conditions to find the conditions necessary for all three controls to be minimizing on the same interval.

Theorem 3.9. *If v_L, v_M, and v_I are simultaneously singular on some interval (s,t), then the following conditions must hold for these controls to be minimizing:*

$$Q_L \leq 0,$$
$$Q_L Q_M \geq \eta_1\eta_2(\ominus)^2,$$
$$Q_L Q_M Q_I \leq \eta_1\eta_3 Q_M \circledast + \eta_1\eta_2 Q_I \ominus,$$

where Q_L, Q_M, Q_I and $\circledast$ are defined by (3.13), (3.14), (3.15)*, and* (3.17)*, respectively, and*

$$\ominus = -\lambda_3\delta_L K_L e^{-\delta_L M}. \tag{3.18}$$

Proof. Assuming v_L, v_M, and v_I are all singular on the interval (s,t), we use the generalized Legendre-Clebsch conditions to form the 3×3 matrix whose entries are given by

$$A_{ij} = (-1)^{\frac{h_j+1}{2}} \frac{\partial}{\partial v_i} \frac{d^{(\frac{h_i+h_j}{2}+1)}}{dt^{(\frac{h_i+h_j}{2}+1)}} \frac{\partial H}{\partial v_j}.$$

Here we have

$$A_{v_L,v_M,v_I} = \begin{pmatrix} -\eta_1 Q_L & \eta_1\eta_2\ominus & \eta_1\eta_3\circledast \\ \eta_1\eta_2\ominus & -\eta_2 Q_M & 0 \\ \eta_1\eta_3\circledast & 0 & -\eta_3 Q_I \end{pmatrix},$$

where Q_L, Q_M, Q_I, $\circledast$, and $\ominus$ are defined previously in (3.17) and (3.18).

This matrix is symmetric; in order for A_{v_L,v_M,v_I} to be positive semidefinite, we must have that

$$Q_L \leq 0,$$
$$Q_L Q_M \geq \eta_1\eta_2(\ominus)^2,$$
$$Q_L Q_M Q_I \leq \eta_1\eta_3 Q_M \circledast + \eta_1\eta_2 Q_I \ominus .$$

□

Conclusion. If the controls are singular either as a unit, in pairs, or as a triple, conditions are given for those controls to be minimizing. First, existence of the control triple is established. Within the characterization, the introduction of singular and/or bang-bang controls is given. It is worth noting that clinicians commonly give treatments in a bang-bang type scenario, i.e. give the drug combination for a period and then do not given any drug, c.f. [15], [33]. However, in this work, conditions are given such that a singular control vector would minimize the proposed objective functional. This could change the dynamic in which the chemotherapy and immunotherapy treatments are administered. Due to the interdependence on the conditions, we note that the characterizations of the singular control on the selected intervals are not explicitly determined. In future work, numerical analyses will be investigated to aid in graphically characterizing these singular control expressions.

4. Appendix A

In this section, we will give precise statements of the theorems used for proving the existence and finding the characterizations of optimal quadratic controls.

Theorem 4.1 (Fillipov-Cesari Theorem [14]). *Consider the following optimal control problem:*

$$\begin{aligned}
\min \quad & J = \int_0^T F(x(t), u(t), t)dt + S(x(T), T) \\
& \dot{x}(t) = f(x(t), u(t), t), \quad x(0) = x_0 \\
& g(x(t), u(t), t) \geq 0 \\
& h(x(t), t) \geq 0 \\
& a(x(T), T) \geq 0 \\
& b(x(T), T) = 0
\end{aligned}$$

where T is free on $[0, t_f]$. Assume that F,f,g,h,S,a, and b are continuous in all their arguments at all points (x, u, t). Define the (state-dependent) control region

$$\Omega(x, t) = \{u \in \mathbb{R}^m |\ g(x, u, t) \geq 0\} \subset \mathbb{R}^m$$

and the set

$$N(x, t) = \{(F(x, u, t) + \gamma, f(x, u, t))|\ \gamma \leq 0, u \in \Omega(x, t)\} \subset \mathbb{R}^{n+1}$$

where m and n are the number of control and state variables, respectively. Suppose that the following conditions hold:

(1) *There exits an admissible solution pair.*
(2) *$N(x, t)$ is convex for all $(x, t) \in \mathbb{R}^n \times [0, t_f]$.*

(3) *There exists $\delta > 0$ such that $\|x(t)\| < \delta$ for all admissible $\{x(t), u(t)\}$ and t.*
(4) *There exists $\delta_1 > 0$ such that $\|u\| < \delta_1$ for all $u \in \Omega(x, t)$ with $\|x\| < \delta$.*

Then there exists an optimal triple $\{T^*, x^*, u^*\}$ with $u^*(\cdot)$ measurable.

Theorem 4.2 (Pontraygin's Maximum/Minimum Principle [17])**.**
Let $\boldsymbol{u}(t) = [u_1(t), \ldots, u_m(t)]$ be a piecewise continuous control vector and $\boldsymbol{x}(t) = [x_1(t), \ldots, x_n(t)]$ be an associated continuous and piecewise differentiable state vector defined on the fixed time interval $[t_0, t_1]$ that minimizes

$$\int_{t_0}^{t_1} f(t, \boldsymbol{x}(t), \boldsymbol{u}(t))dt$$

subject to the differential equations

$$x_i(t) = g_i(t, \boldsymbol{x}(t), \boldsymbol{u}(t)), \quad i = 1, \ldots, n,$$

initial conditions

$$x_i(t_0) = x_{i0}, \quad i = 1, \ldots, n \quad (x_{i0} \textit{ fixed}),$$

terminal conditions

$$\begin{gathered} x_i(t_1) = x_{i1}, \quad i = 1, \ldots, p, \\ x_i(t_1) \geq x_{it}, \quad i = p+1, \ldots, q \quad (x_{i1}, i = 1, \ldots, q \textit{ fixed}), \\ x_i(t_1) \textit{free}, \quad i = q+1, \ldots, n, \end{gathered}$$

and control variable restriction

$$\boldsymbol{u}(t) \in U, \quad U \text{ a given set in } \mathbb{R}^m.$$

We assume that $f, g, \partial f/\partial x_j$, and $\partial g_i/\partial x_j$ are continuous functions of all their arguments, for all $i = 1, \ldots, n$ and $j = 1, \ldots, n$. Then there exists a constant λ_0 and continuous functions $\lambda(t) = (\lambda_1(t), \ldots, \lambda_n(t))$, where for all $t_0 \leq t \leq t_1$ we have $(\lambda_0, \lambda(t)) \neq (0, 0)$ such that for every $t_0 \leq t \leq t_1$,

$$H(t, \boldsymbol{x}^*(t), \boldsymbol{u}(t), \lambda(t)) \leq H(t, \boldsymbol{x}^*(t), \boldsymbol{u}^*(t), \lambda(t)),$$

where the Hamiltonian function H is defined by

$$H(t, \boldsymbol{x}, \boldsymbol{u}, \lambda) = \lambda_0 f(t, \boldsymbol{x}, \boldsymbol{u}) + \sum_{i=1}^{n} \lambda_i g_i(t, \boldsymbol{x}, \boldsymbol{u}).$$

Except at points of discontinuity of $\boldsymbol{u}^*(t)$,

$$\lambda'(t) = -\partial H(t, \boldsymbol{x}^*(t), \boldsymbol{u}^*(t), \lambda(t))/\partial x_i, \quad i = 1, \ldots, n.$$

Finally, the following transversality conditions are satisfied:

$$\begin{gathered} \lambda_i(t_1) \quad \textit{no conditions}, \quad i = 1, \ldots, p, \\ \lambda_i(t_1) \geq 0 \quad (= 0 \textit{ if } x_i^*(t_1) > x_{i1})) \quad i = p+1, \ldots, q, \\ \lambda_i(t_1) = 0, \quad i = q+1, \ldots, n. \end{gathered}$$

In addition, the modifications to (4.2) generated by the terminal inequality are given in Kamien and Schwartz [17], p. 160: *If $K(x_q(t_1),\dots,x_n(t_1))\geq 0$ is required, then the transversality conditions*

$$\begin{aligned}\lambda_i(t_1) &= p\ \partial K/\partial x_1, \quad i=q,\dots,n,\\ p &\leq 0,\\ pK &= 0\end{aligned}$$

are necessary.

Theorem 4.3 (Generalized Legendre-Clebsch Conditions [23])**.** *Assume that $\mathbf{u}(t)$ and $\mathbf{x}(t)$ are defined for (2.1)-(2.6) on $[0,t_f]$. Suppose $\mathbf{u}(t)\in$ interior Ω and each $\mathbf{u_i}$ is singular of degree $\frac{h_i+1}{2}$ on the subinterval (t_0,t_1). If $\mathbf{u}(t)$ is minimal, then there exists a $\lambda(t)$ satisfying the PMP on $[0,t_f]$ such that on the subinterval (t_0,t_1),*

$$\frac{\partial}{\partial \mathbf{u_i}}\frac{d^k}{dt^k}\frac{\partial}{\partial \mathbf{u_j}}H(\lambda(t),\mathbf{x}(t),\mathbf{u}(t))=0$$

for $k=0,\dots,\frac{h_i+h_j}{2}, 1\leq i,j\leq l$ (where l is the dimension of the control space). Moreover, if $h_i<\infty$ for $i=1,\dots,k\leq l$, then the $k\times k$ matrix whose i,j entry is

$$(-1)^{\frac{h_j+1}{2}}\frac{\partial}{\partial \mathbf{u_i}}\frac{d^{(\frac{h_i+h_j}{2}+1)}}{dt^{(\frac{h_i+h_j}{2}+1)}}\frac{\partial}{\partial \mathbf{u_j}}H(\lambda(t),\mathbf{x}(t),\mathbf{u}(t))$$

where $1\leq i,j\leq k$, must be symmetric and nonnegative definite.

Note that a given symmetric real matrix is nonnegative definite (i.e. positive semidefinite) if and only if all of its upper-left minors are positive; that is, for a given $n\times n$ matrix

$$A_{n\times n}=\begin{pmatrix} A_{11} & \dots & A_{1n}\\ \vdots & \ddots & \vdots\\ A_{n1} & \dots & A_{nn}\end{pmatrix},$$

we have that

$$A_{11}\geq 0,\quad \begin{vmatrix} A_{11} & A_{12}\\ A_{21} & A_{22}\end{vmatrix}\geq 0,\quad \begin{vmatrix} A_{11} & A_{12} & A_{13}\\ A_{21} & A_{22} & A_{23}\\ A_{31} & A_{32} & A_{33}\end{vmatrix}\geq 0,$$

etc.

5. Appendix B

In this section, we will state the equations P_L, P_M, and P_I used in the characterizations of controls v_L, v_M, and v_I, respectively.

$$\begin{aligned}P_L = &\frac{d\lambda_1}{dt}\frac{\partial D}{\partial L}T-\frac{d\lambda_6}{dt}\left(\frac{\omega I}{\zeta+I}\right)\\ &+\left[\lambda_1 T\frac{\partial^2 D}{\partial T\partial L}+\lambda_1\frac{\partial D}{\partial L}-\frac{\epsilon_L}{\eta_1}\left(q-\frac{jk}{(k+T)^2}\right)\right]\frac{dT}{dt}\\ &+\left[\frac{\epsilon_L}{\eta_1}\left(\frac{\theta m}{(\theta+I)^2}+\frac{p_I g_I}{(g_I+I)^2}-2u_0LC\frac{\kappa}{(\kappa+I)^2}\right)-\lambda_6\frac{\omega\zeta}{(\zeta+I)^2}\right]\frac{dI}{dt}\\ &-2u_0L\frac{\epsilon_L}{\eta_1}\left(\frac{I}{\kappa+I}\right)\frac{dC}{dt}-\delta_L K_L e^{-\delta_L M}\frac{\epsilon_L}{\eta_1}\frac{dM}{dt}\end{aligned}$$

$$+\left[\lambda_1 T\frac{\partial^2 D}{\partial L^2}-2u_0C\frac{\epsilon_L}{\eta_1}\left(\frac{I}{\kappa+I}\right)\right]$$
$$\times\Big[-\frac{\theta mL}{\theta+I}-qLT+r_1NT+r_2CT+\frac{p_ILI}{g_I+I}-\frac{u_0L^2CI}{\kappa+I}$$
$$+\frac{jTL}{k+T}-K_L(1-e^{-\delta_L M})L\Big],$$

$$P_M=\delta_T K_T e^{-\delta_T M}\left(\lambda_1\frac{dT}{dt}+T\frac{d\lambda_1}{dt}\right)+\delta_N K_N e^{-\delta_N M}\left(\lambda_2\frac{dN}{dt}+N\frac{d\lambda_2}{dt}\right)$$
$$+\delta_L K_L e^{-\delta_L M}\left(\lambda_3\frac{dL}{dt}+L\frac{d\lambda_3}{dt}\right)+\delta_C K_C e^{-\delta_C M}\left(\lambda_4\frac{dC}{dt}+C\frac{d\lambda_4}{dt}\right)$$
$$-\gamma M\Big[\delta_T K_T\lambda_1 T(-\delta_T e^{-\delta_T M})+\delta_N K_N\lambda_2 N(-\delta_N e^{-\delta_N M})$$
$$+\delta_L K_L\lambda_3 L(-\delta_L e^{-\delta_L M})+\delta_C K_C\lambda_4 C(-\delta_C e^{-\delta_C M})\Big]$$

,

$$P_I=-\frac{d\lambda_2}{dt}\left(\frac{p_Ng_NN}{(g_N+I)^2}\right)-\frac{d\lambda_3}{dt}\left[\frac{\theta mL}{(\theta+I)^2}+\frac{p_Ig_IL}{(g_I+I)^2}-\frac{u_0\kappa L^2C}{(\kappa+I)^2}\right]$$
$$-\frac{dN}{dt}\left(\frac{\lambda_2p_Ng_N}{(g_N+I)^2}\right)-\frac{dC}{dt}\left(\frac{\lambda_3u_0\kappa L^2}{(\kappa+I)^2}\right)$$
$$+\frac{dL}{dt}\left[-\frac{\lambda_3\theta m}{(\theta+I)^2}-\frac{\lambda_3p_Ig_I}{(g_I+I)^2}+\frac{2\lambda_3u_0\kappa LC}{(\kappa+I)^2}+\frac{\epsilon_I\omega\zeta}{\eta_3(\zeta+I)^2}\right]$$
$$+\left[\frac{2\lambda_2p_Ng_NN}{(g_N+I)^3}+\frac{2\lambda_3\theta mL}{(\theta+I)^3}+\frac{2\lambda_3p_Ig_IL}{(g_I+I)^3}-\frac{2\lambda_3u_0\kappa L^2C}{(\kappa+I)^3}-\frac{2\epsilon_I\omega\zeta L}{\eta_3(\zeta+I)^3}\right]$$
$$\times\left(-\mu_II+\phi C+\frac{\omega LI}{\zeta+I}\right).$$

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