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Optimal Control Applied to a Mathematical Model for Vancomycin-Resistant Enterococci

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OPTIMAL CONTROL APPLIED TO A MATHEMATICAL MODEL FOR VANCOMYCIN-RESISTANT ENTEROCOCCI

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ABSTRACT

OPTIMAL CONTROL APPLIED TO A MATHEMATICAL MODEL FOR VANCOMYCIN-RESISTANT ENTEROCOCCI

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Enterococci bacteria that cannot be treated effectively with the antibiotic vancomycin are termed Vancomycin-Resistant Enterococci (VRE). In this thesis, we develop a mathematical framework for determining optimal strategies for prevention and treatment of VRE in an Intensive Care Unit (ICU). A system of five ordinary differential equations describes the movement of ICU patients in and out of different states related to VRE infection. Two control variables representing the prevention and treatment of VRE are incorporated into the system. An optimal control problem is formulated to minimize the VRE-related deaths and costs associated with controls over a finite time period. Pontryagin's Minimum Principle is used to characterize optimal controls by deriving a Hamiltonian expression and differential equations for five adjoint variables. Numerical solutions to the optimal control problem illustrate how hospital policy makers can use our mathematical framework to investigate optimal cost-effective prevention and treatment schedules during a VRE outbreak.

Contents

Chapter 1

Introduction to Optimal Control for Ordinary Differential Equations

In this thesis, we study a system of coupled ordinary differential equations which represent the dynamics of a spreading bacterial infection in a hospital's Intensive Care Unit. We introduce two control variables within the system of equations as a way to drive the infection dynamics to a desired state. Optimal control theory is applied to determine an optimal cost-effective allocation of controls through time. In this first chapter, we look at optimal control theory applied to a single ordinary differential equation (ODE) and a single control variable for a better understanding of the topic. A detailed introduction to optimal control theory can be found in [23].

We denote $x(t)$ as the state variable and $u(t)$ as the control variable. Both variables are functions of time. Typically, the state variable has a physical interpretation (e.g. population size at time t). An ODE is constructed to describe the changing dynamics of the state variable, $x(t)$. These dynamics are affected by the control variable in the sense that

$$x'(t) = g(t, x(t), u(t)) \tag{1.1}$$

where $u(t)$ belongs to a set of admissible controls, U. We assume the control set U

consists of Lebesgue integrable functions.

The goal of an optimal control problem is represented by an objective functional, which is typically formulated as minimizing (or maximizing) an integral expression in terms of both the state and control variables. Our ambition is to find an optimal control $u^*(t) \in U$ and the corresponding state $x^*(t)$ that minimize (or maximize) the objective functional. The optimal control problem can be represented as

$$\min_{u \in U} \int_0^T f(t, x(t), u(t)) \, \mathrm{d}t \tag{1.2}$$

subject to

$$x'(t) = g(t, x(t), u(t)) \tag{1.3}$$

$$\text{where } x(0) = x_0 \text{ and } x(T) \text{ is free.} \tag{1.4}$$

An optimal control, denoted by $u^*(t) \in U$, achieves the minimum. Under the assumption that f and g are continuously differentiable in their arguments, one can state the first order necessary conditions in the simplest form by Pontryagin's Minimum Principle. Around 1950, Pontryagin, along with collaborators, developed optimal control theory for ODE's [40]. They developed the important concept of introducing an adjoint function that attaches the right hand side (RHS) of the differential equation in (1.1) with the objective functional in (1.2).

Theorem 1. Pontryagin's Minimum Principle: *If $u^*(t)$ and $x^*(t)$ are optimal for (1.2)-(1.4), then there exists an adjoint variable $\lambda(t)$ such that*

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

at each time, where the Hamiltonian H is defined by

$$H(t, x(t), u(t), \lambda(t)) = f(t, x(t), u(t)) + \lambda(t) g(t, x(t), u(t))$$

and

$$\lambda'(t) = \frac{-\partial H(t, x(t), u(t), \lambda(t))}{\partial x},$$

$$\lambda(T) = 0.$$

The final time condition on the adjoint variable is called the transversality condition. This principle creates the current problem to optimize the Hamiltonian pointwise as a method for finding a control that minimizes the objective functional subject to the state ODE and initial conditions. A simpler way to define the Hamiltonian is

$$\begin{aligned} H(t, x, u, \lambda) &= f(t, x, u) + \lambda g(t, x, u) \\ &= (\text{integrand}) + (\text{adjoint}) \times (\text{RHS of ODE}) \end{aligned}$$

One can generate the necessary conditions by optimizing H with respect to u at u^*. The necessary conditions are

$$\begin{aligned} &\frac{\partial H}{\partial u} = 0 \Rightarrow f_u + \lambda g_u = 0 \text{ (optimality condition)} \\ &\lambda' = -\frac{\partial H}{\partial x} \Rightarrow \lambda' = -(f_x + \lambda g_x) \text{ (adjoint equation), and} \\ &\lambda(T) = 0 \text{ (transversality condition).} \end{aligned}$$

We can also consider second-order conditions. For minimization, we have

$$\frac{\partial^2 H}{\partial u^2} > 0 \text{ at } u^*$$

and for maximization, we have

$$\frac{\partial^2 H}{\partial u^2} < 0 \text{ at } u^*.$$

In the majority of biological models, the controls will be bounded as a result of specific applications. Pontryagin's Minimum Principle still holds when the controls are restricted within the bounds

$$a \leq u(t) \leq b.$$

After introducing an adjoint variable, we now have three unknowns, u^*, x^*, and λ. The concatenation of the state and adjoint differential equations, boundary conditions, and control characterization are referred to as the optimality system. Solutions to the optimality system, more than often, cannot be solved analytically, but can be approximated numerically.

Chapter 2

VRE: An Antibiotic-Resistant Bacterium

2.1 Background

In today's society, antibiotic resistance acquired in a hospital setting is a major health care concern. Nosocomial infections caused by resistant bacteria represent approximately 100,000 deaths every year in hospitals located in the United States [47]. One of the top Center for Disease Control (CDC) health concerns, and the focus of this study, is Vancomycin-Resistant Enterococci (VRE) infections [54].

Vancomycin is an antibiotic that is used to treat bacteria that are resistant to penicillin and penicillin derivatives. Enterococci are spherical bacteria that are normally found living in digestive and genital tracts, bloodstreams, and wounds. These bacteria are adaptable to wide range of pH levels and temperatures [29, 47]. As a result, enterococci are hard to treat without the use of antibiotics.

There are severe mortality costs associated with VRE infections [2, 8, 13, 24, 27, 37, 44, 48]. Among VRE infected patients who are critically ill or VRE infected patients who have had a liver transplant, there is an associated death rate of up to 70% [1, 30, 33]. The presence of VRE bacteria is most common in immuno-compromised patients and

VRE also has the ability to transfer to other bacteria such as Methicillin-Resistant Staphylococcus Aureus (MRSA) [20, 25]. VRE has a high contamination rate and is difficult to treat [29, 47].

There are also severe monetary costs attributable to VRE. Hospitals use a reliable and cheap method to screen the patients to see if VRE is present. Rectal swabs are taken from the patient, on an every other day interval, to be grown on agar plates [12, 29, 42]. However, this test takes several days for confirmation, potentially resulting in an increased length of stay for the patients. When a patient is recognized as being colonized with VRE, hospitals must spend money on preventative measures, such as quarantining these patients from others and changing gowns and gloves before and after seeing these patients. Also, money is spent reducing the size of the colony of VRE in the patient. One way to do this is to subject the patient to chlorhexidine baths [12, 35, 46]. If the VRE colonization is severe enough to cause physical signs of infection, treatment for the infection is an option. However, there are only a few drugs the can treat VRE infection and they are very expensive. The two most commonly used drugs are Tygacil and Linezolid.

In this thesis, we present a mathematical framework for determining an optimal cost-effective balance of preventative care of colonized individuals and treatment of infected individuals to reduce VRE-related deaths within a hospital's ICU. The framework allows for parameters that are specific to individual hospitals. The framework may be used by hospital policy makers to investigate how to optimally allocated resources given specific monetary constraints.

2.2 Biological Model

We adopt and modify a recent VRE model developed in Yahdi et al. [50]. The model follows a population of individuals within an Intensive Care Unit (ICU) of a hospital. Individuals within the population exist in one of five different states, based on their

VRE infection stage and access to care. The first infection stage is for patients who do not have VRE. In this stage, all patients are susceptible to develop VRE. The second infection stage is for patients that are colonized with VRE. In this stage, patients produce a positive culture of the VRE bacteria but do not have symptoms of an infection. The second stage is further divided into colonized patients with no preventative care and colonized patients with preventative care. The final infection stage is for patients who have a VRE infection. In this final stage, patients have a high density of VRE bacteria and show symptoms of an infection. This stage is further divided into infected patients with no treatment and infected patients that are receiving treatment. A total of five states are used to describe the ICU population.

Notation for each state and a brief description are listed below.

- **Susceptible, S**: Represents the proportion of the ICU population that do not produce a positive culture of VRE. There is no natural immunity to VRE. Patients who have been decolonized or cured of VRE are susceptible to contract VRE again [16, 29].

- **Colonized, X**: Represents the proportion of the ICU population that have positive VRE cultures and are not receiving any preventative care. Hospital funds, severity of colonization, etc. are not sufficient to place these individuals under preventative care.

- **Colonized with preventative care, Y**: Represents the proportion of the ICU population that have positive VRE cultures and are currently receiving preventative care. CDC requires VRE colonized patients to be put under contact isolation to prevent further spread. Hospital funds, severity of colonization, etc. are sufficient to be place these individuals under preventative care.

- **Infected, V**: Represents the proportion of the ICU population that show symptoms of an infection due to high-density VRE colonies and are not receiving

treatment. Insufficient funds or resources prevent these patients from receiving treatment.

- **Infected with treatment, W**: Represents the proportion of the ICU population that show symptoms of an infection due to high-density VRE colonies and are receiving treatment. There are several drugs to treat VRE infection, such as Tygacil and Linezolid.

For this biological model we incorporate all possible VRE-related transitions in and out of the ICU and between the five states introduced above. A brief description of the movement in and out of each of the five states is provided below.

- **Transitions into S (susceptible)**: The majority of patients enter the ICU VRE free and are therefore placed into the S state. Colonized patients in states X or Y who have spontaneously cured from VRE colonization or have been cleared of their VRE colony from preventative care return immediately to the susceptible state. There is no natural immunity to VRE. In addition, infected patients in state W who have been cured due to treatment will move to the susceptible state.

- **Transitions out of S**: Patients can leave the S state by leaving the ICU. Patients can also transfer from S to one of the colonized states, X or Y, if they have positive VRE cultures.

- **Transitions into X (colonized)**: Patients can enter the X state by entering the ICU already colonized. Individuals in the S state who produce a positive culture of VRE, but do not fit criteria for preventative care, are placed into state X. It is possible for colonized patients in state Y who stop preventative care to transfer into the X state due to, but not limited to, monetary reasons or reduced severity of the colonization. Furthermore, infected patients in states V and W can become infection-free but still be colonized with VRE and therefore they may transition to the X state.

- **Transitions out of X**: Patients can leave the X state by leaving the ICU. Patients in the X state can be spontaneously cured of their colonization and transition to the susceptible stage. Transitions from X to Y occur when a colonized patient's VRE colony size dramatically increases, causing them to be put under preventative care. Alternatively, new hospital funds can increase the number of patients who can receive preventative care. Patients in the X state can show a sign of infection causing them to move to one of the infected states V or W.

- **Transitions into Y (colonized with preventative care)**: Patients can enter the ICU as colonized and under preventative care. Susceptible patients who produce a positive culture and fit preventative care criteria transition to the Y state. The severity of a colonization in an individual in state X can cause a patient to be put under preventative care, thus moving them to the Y state. Lastly, infected patients in states V and W can move to state Y if they become infection-free but still have a severe colonization and require preventative care.

- **Transitions out of Y**: Patients can leave the Y state by leaving the ICU. Patients in the Y state can be cured of VRE colonization due to preventative care, yet remain in the ICU, in the susceptible state S. Hospital policies and limited resources can cause patients to be removed from preventative care, moving them out of the Y state and into the X state. Furthermore, patients in Y who show signs of infection transfer to one of the infected states, V or W.

- **Transitions into V (infected without treatment)**: Patients can enter the V state by entering the ICU with a VRE infection. Colonized patients in states X or Y who show signs of infection but do not need immediate treatment transition to state V. Limited funding can cause infected patients in state W to stop treatment and move to the V state.

- **Transitions out of V**: Patients can leave the V state by leaving the ICU. Patients can spontaneously cure from the infection and transition from the V state to the S state. If patients are cleared from infection but are still colonized, then they will transition to one of the colonized states, X or Y. If the infection of a patient in state V worsens, the patient may start treatment and therefore transition to the W state.

- **Transitions into W (infected with treatment)**: Patients can enter the W state by entering the ICU with a VRE infection and treatment. Once colonized patients in the X or Y states show signs of infection and are in need of treatment, they are transferred into W. Patients in the V state with progressing infection may transition to the W state by receiving treatment.

- **Transitions out of W**: Patients can leave the W state by leaving the ICU. Patients in the W state can be cured from the infection due to treatment and therefore move to the susceptible state S. If patients are cleared from infection but are still colonized, then they will return to one of the colonized states, X or Y. Patients in the W state may stop receiving treatment and move to the V state due to monetary issues or the fact that some current drugs used to treat VRE can only be used for seven to ten consecutive days.

We made two modifications to the model put forth by Yahdi et al. [50]. First, we simplified the model by assuming the proportion of patients moving from colonized with preventative care (Y) to infected with treatment (W) is equivalent to the proportion of patients moving from colonized (X) to infected with treatment (W). Thus, one parameter (r) represents the proportion of people moving from both colonized states to the infected with treatment state. Second, we made the model more realistic by including a parameter (γ_p) which represents the movement of individuals from the colonized with preventative care state (Y) to the susceptible state (S). The new parameter accounts

for spontaneous curing and an increased curing rate attributed to preventative care.

2.3 Mathematical Model

We construct a mathematical model for an ICU population based on the above biological description of the five VRE-related states and transitions between the states. The mathematical model consists of five state variables (S, X, Y, W, V) and a set of parameters that realistically represents the factors that would lead to the progression or recession of VRE infection. Figure 2.1 illustrates the dynamics of the mathematical model. The parameters used in the model are defined in detail in a later section. For a brief summary of the parameters, see Table 2.1.

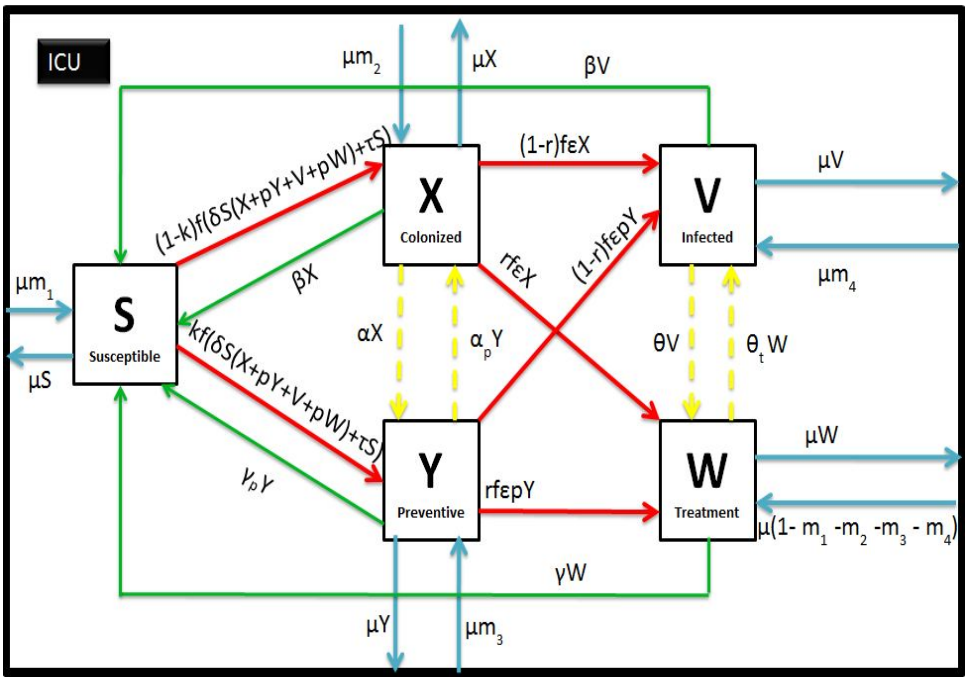

Figure 2.1: VRE MODEL

The mathematical model is written as a system of coupled ordinary differential equations (ODEs) based on the incoming and outgoing rates of the five states over time. Our system consists of five differential equations with nineteen independent parameters.

The ODE system with initial values and necessary conditions are given below.

$$\begin{aligned}
\frac{dS}{dt} &= \mu(m_1 - S) + \beta(X + V) + \gamma_p Y + \gamma W - f(\delta S(X + pY + V + pW) + \tau S) \\
\frac{dX}{dt} &= \mu(m_2 - X) + (1 - k)f(\delta S(X + pY + V + pW) + \tau S) + \alpha_p Y - X(\beta + \alpha + f\epsilon) \\
\frac{dY}{dt} &= \mu(m_3 - Y) + kf(\delta S(X + pY + V + pW) + \tau S) + \alpha X - Y(\alpha_p + \gamma_p + fp\epsilon) \\
\frac{dV}{dt} &= \mu(m_4 - V) + (1 - r)f\epsilon(X + pY) + \theta_t W - V(\theta + \beta) \\
\frac{dW}{dt} &= \mu(1 - m_1 - m_2 - m_3 - m_4 - W) + rf\epsilon(X + pY) + \theta V - W(\theta_t + \gamma)
\end{aligned}$$

The system has the following initial conditions:

$$S(0) = S_0, X(0) = X_0, Y(0) = Y_0, V(0) = V_0, W(0) = W_0$$

where S_0, X_0, Y_0, V_0, and W_0 are given initial values for each of the five states, and $S_0 + X_0 + Y_0 + V_0 + W_0 = 1$.

There are nineteen independent parameters in our model. Biologically realistic ranges for these parameters were gathered from recent data found in professional journals, including National Institutes of Health and Clinical Trails website, Harvard School of Public Health, and other scientific journals. Ranges were chosen to reflect the diversity among all ICUs. A list of all nineteen parameters, their brief description, mean values, ranges, and the source(s) used to find these values can be found in Table 2.1. A more in depth description of the parameters with units is listed below.

- μ (day^{-1}) represents the general ICU admission rate, while m_1, m_2, m_3, m_4, m_5 represent the proportion admitted into each of the five states. Note $m_5 = 1 - m_1 - m_2 - m_3 - m_4$.

- δ (day^{-1}) represents a contamination rate. This parameter encompasses all factors leading to contamination. This includes contact with health care workers, contact with other patients, etc.

- β (day^{-1}) represents spontaneous curing. VRE colonizations and infections can vary in severity, and it is possible for patients to be cured naturally over time.

- τ (day^{-1}) represents the rate at which susceptible individuals become colonized with VRE by antibiotic use alone. Previous antibiotic use or misuse is a risk factor for contracting VRE infection, including frequency and length of antibiotic use.

- γ (day^{-1}) represents the rate of curing due to treatment: Antibiotics such as Tygacil and Linezolid can clear the infection.

- γ_p (day^{-1}) represents the rate of curing due to preventative care. Isolation, chlorhexidine baths, and compliance with hand washing, limited contact, and new stethoscopes can clear colonizations.

- α and α_p (day^{-1}) represent the transition rates from colonized without preventative care (X) to colonized with preventative care (Y) and vice versa. These transitions are subject to limited resources, high density of VRE, previous surgeries, etc.

- θ and θ_t (day^{-1}) represent the transition rates from infected patients without treatment (V) to infected patients with treatment (W), and vice versa. These transitions occur when a patient's infection severity increases or decreases or when a patient stops or starts antibiotics that can only be administered for a certain amount of time.

- ϵ (day^{-1}) represents the rate of infection. This parameter encompasses any factor that can lead to VRE infection such as previous surgeries, prior hospital stays, previous nosocomial infections, etc.

- f (unitless) represents the bacteria's fitness. Fitness relates to the bacteria's ability to colonize. If it is easy for the bacteria to live with the plasmid, then

the patient experiences an increased probability of colonization. In this case, f takes a value that is close to one. If it is difficult for the bacteria to live with the plasmid, then the bacteria regresses to a nonresistant strain and the patient experiences a reduced probability of colonization. In this case, f takes a value that is close to zero.

- r (unitless) represents the proportion of individuals in the colonized states, X and Y, that receive treatment when infection occurs. Thus, $(1-r)$ represents the proportion that do not receive treatment when infection occurs.

- p (unitless) represents the hospital's and health-care workers' compliance with preventative care. This includes compliance regulations, hand hygiene, changing of gloves and gowns, chlorhexidine baths, health-care workers contact rate with other patients, etc.

- k (unitless) represents the proportion of individuals in the susceptible state S that receive preventative care when colonization occurs. Thus, $(1-k)$ represents the proportion that do not receive preventative care when colonization occurs.

	Description	**Mean**	**Range**	**Reference**
μ	General admission rate	0.0956	$0.03 \leq \mu \leq 0.14$	[11, 26, 32]
μ_V	Death rate for infected patients without treatment	0.04353	$0 \leq \mu_V \leq 0.7$	[13, 14, 36]
μ_W	Death rate for infected patients with treatment	0.00166	$0 \leq \mu_W \leq 0.7$	[13, 14, 36]
δ	Contamination rate	0.29845	$0.2657 \leq \delta \leq 0.3312$	[22]
m_1	Proportion of new ICU patients that are susceptible	0.7	$0 \leq m_1 \leq 1$	[11, 32]
m_2	Proportion of new ICU patients that are colonized without preventative care	0.1	$0 \leq m_2 \leq 1$	[11, 32]
m_3	Proportion of new ICU patients that are colonized with preventative care	0.1	$0 \leq m_3 \leq 1$	[11, 32]
m_4	Proportion of new ICU patients that are infected without treatment	0.05	$0 \leq m_4 \leq 1$	[11, 32]
β	Rate of spontaneous curing	0.095	$0.03 \leq \beta \leq 0.16$	[18, 20, 22, 32]
τ	Rate of infection due to antibiotic use alone	0.302	$0.07 \leq \tau \leq 0.65$	[11, 26]
γ	Rate of curing due to treatment	0.46	$0 \leq \gamma \leq 0.46$	[26]
γ_p	Rate of curing due to preventative care	0.15	$0 \leq \gamma_p \leq 0.33$	[10]
α	Movement rate from X to Y	0.2	$0 < \alpha < 0.5$	[32]
α_p	Movement rate from Y to X	0.1	$0 < \alpha_p < 0.5$	[32]
θ	Movement rate from V to W	0.2	$0 < \theta < 0.5$	[32]
θ_t	Movement rate from W to V	0.1	$0 < \theta_t < 0.5$	[32]
ϵ	Factors leading to infection	0.2083	$0 < \epsilon < 1$	[11, 32]
f	Fitness of bacteria	0.75	$0.5 \leq f \leq 1$	[41]
r	Proportion of newly infected who receive treatment	0.2	$0 < r < 1$	[32]
p	Compliance	0.5	$0 \leq p \leq 1$	[11, 32]
k	Proportion of newly colonized who receive preventative treatment	0.2	$0 < k < 1$	[32]

Table 2.1: Summary Table of Parameters

Chapter 3

Optimal Control for VRE Model

3.1 Optimal Control Problem

Our goal is to minimize the total costs due to preventative care and treatment while also minimizing the deaths attributed to VRE over a period of T days. We introduce two control variables; both are functions of time. The control $u_1(t)$ is associated with preventative care and the parameter k. The control $u_2(t)$ is associated with treatment and the parameter r. The control variables are bounded such that $0 \leq u_1(t) \leq 1.0$ and $0 \leq u_2(t) \leq 1.0$. Controls u_1 and u_2 are associated with multipliers η_1 and η_2 respectively. The controls are assumed to affect the parameters linearly, so when no control is applied (i.e, $u(t) = 0$), k and r are at baseline values and when control is applied (i.e, $u(t) > 0$) k and r are multiplied by $(1 + \eta_1 u_1)$ and $(1 + \eta_2 u_2)$, respectively. We define the set of admissible controls as

$$U = \{0 \leq u(t) \leq 1 \text{ for } 0 \leq t \leq T \mid u \text{ is Lebesgue integrable}\}.$$

The control variables are included within our system of differential equations as

indicated below.

$$\frac{dS}{dt} = \mu(m_1 - S) + \beta(X + V) + \gamma_p Y + \gamma W - f(\delta S(X + pY + V + pW) + \tau S) \quad (3.1)$$

$$\frac{dX}{dt} = \mu(m_2 - X) + (1 - (1 + \eta_1 u_1)k) f(\delta S(X + pY + V + pW) + \tau S) + \alpha_p Y - X(\beta + \alpha + f\epsilon) \quad (3.2)$$

$$\frac{dY}{dt} = \mu(m_3 - Y) + (1 + \eta_1 u_1) k f(\delta S(X + pY + V + pW) + \tau S) + \alpha X - Y(\alpha_p + \gamma_p + fp\epsilon) \quad (3.3)$$

$$\frac{dV}{dt} = \mu(m_4 - V) + (1 - (1 + \eta_2 u_2) r) f\epsilon(X + pY) + \theta_t W - V(\theta + \beta) \quad (3.4)$$

$$\frac{dW}{dt} = \mu(1 - m_1 - m_2 - m_3 - m_4 - W) + (1 + \eta_2 u_2) r f \epsilon(X + pY) + \theta V - W(\theta_t + \gamma) \quad (3.5)$$

The system has the following initial conditions:

$$S(0) = S_0, X(0) = X_0, Y(0) = Y_0, V(0) = V_0, W(0) = W_0 \quad (3.6)$$

where S_0, X_0, Y_0, V_0, and W_0 are given initial values for each of the five states, and $S_0 + X_0 + Y_0 + V_0 + W_0 = 1$.

Given controls u_1 and u_2 in U, there exists (S, Y, X, V, W) satisfying system (3.1)-(3.6). Existence is due to the fact that state variables are bounded, i.e.,

$$0 \leq |S(t)| \leq 1,\ 0 \leq |X(t)| \leq 1,\ 0 \leq |Y(t)| \leq 1,\ 0 \leq |V(t)| \leq 1,\ 0 \leq |W(t)| \leq 1,$$

and therefore the right hand side of each differential equation in (3.1)-(3.5) can be written as $|f(t, z)| \leq a(t) + b(t)|z(t)|$ where z represents the state variable and $a(t)$ and $b(t)$ are non-negative integrable functions. Thus, standard results in [28] provide existence of solutions to the state system.

Given the mathematical model with controls in (3.1)-(3.6), we formulate an objective functional that best fits the purpose of this research. We introduce μ_v and μ_w, the death rates attributed to VRE for the infected without treatment (V) and infected with treatment (W), respectively. Thus, we seek to find u_1^* in U and u_2^* in U satisfying

$$\min \int_0^T (A\mu_V V + B\mu_W W + Cu_1^2 + D(\eta_1 u_1 k f(\delta S(X + pY + V + pW))) + Eu_2^2 + G(\eta_2 u_2 r f \epsilon(X + pY))) \, \mathrm{d}t \tag{3.7}$$

subject to (3.1) - (3.6). Here A, B, C, D, E, and G are constants representing the costs associated with death, preventative care, and treatment. Quadratic terms are often used to represent non-linear costs. Cost coefficients A and B represent costs associated with death, C and D represent costs associated with preventative care, and E and G represent costs associated with treatment of infected individuals. Coefficients A, B, D, and G are viewed as costs per person, while C and E are coefficients on the quadratic terms and their values are chosen accordingly. Costs can vary dramatically between different hospitals. We estimate values of costs based on available literature. Table 3.1 displays the values of A, B, C, D, E, and G that we have chosen to use in our simulations.

	Description	**Starting Values**	**Range Value**	**REF**
A	Cost for death in V	\$150,000	variable	-
B	Cost for death in W	\$150,000	variable	-
C	Quadratic cost for preventative care	\$10	$10 \leq C \leq 100$	-
D	Linear cost for preventative care	\$3,850	$500 \leq C \leq 6000$	[8, 39]
E	Quadratic cost for treatment	\$100	$10 \leq E \leq 100$	-
G	Linear cost for treatment	\$11,150	$1000 \leq C \leq 36000$	[8, 39]
η_1	Multiplier for control u_1	3	-	-
η_2	Multiplier for control u_2	3	-	-

Table 3.1: Summary Table of Objective Function Coefficients

3.2 Optimality System

It can be shown that there exists an optimal pair u_1^* in U and u_2^* in U. Existence relies on several conditions. First, the set of solutions to the state system is non-empty. Second, each of the differential equations in (3.1)-(3.5) is linear in the control variables u_1 and u_2. Third, the control set U is closed. Fourth, the integrand in the objective functional is convex on U. Results in [15] (page 68) show that optimal controls exist if these conditions are satisfied.

Pontryagin's Minimum Principle is applied to solve for the optimal controls. The principle states that we can solve the optimal control problem by solving the corresponding optimality system. The optimality system consists of the adjoint equations, the transversality conditions, and the control characterizations.

To generate the optimality system, we follow the methodology outlined in Chapter 1. We first form the Hamiltonian. The Hamiltonian is the sum of the integrand of the objective functional and expressions involving the adjoint variables and the state differential equations. In each expression, an adjoint variable is multiplied by the right hand side of corresponding state's differential equation with controls. Each of the five state variables in our system of differential equations has an associated adjoint variable. For example, λ_S corresponds to state S and therefore, in the Hamiltonian, λ_S is multiplied by the right hand side of the differential equation for S. The complete Hamiltonian is stated below.

$$
\begin{aligned}
H = {} & A\mu_v V + B\mu_w W + Cu_1^2 + D(\eta_1 u_1 k f(\delta S(X + pY + V + pW))) + Eu_2^2 + \\
& G(\eta_2 u_2 r f \epsilon(X + pY)) + \lambda_S \big[\mu(m_1 - S) + \beta(X + V) + \gamma_p Y + \gamma W - \\
& f(\delta S(X + pY + V + pW) + \tau S)\big] + \lambda_X \big[\mu(m_2 - X) + \\
& (1 - (1 + \eta_1 u_1)k) f(\delta S(X + pY + V + pW) + \tau S) + \alpha_p Y - X(\beta + \alpha + f\epsilon)\big] + \\
& \lambda_Y \big[\mu(m_3 - Y) + (1 + \eta_1 u_1) k f(\delta S(X + pY + V + pW) + \tau S) + \alpha X - \\
& Y(\alpha_p + \gamma_p + fp\epsilon)\big] + \lambda_V \big[\mu(m_4 - V) + (1 - (1 + \eta_2 u_2) r) f\epsilon(X + pY) + \theta_t W - \\
& V(\theta + \beta)\big] + \lambda_W \big[\mu(1 - m_1 - m_2 - m_3 - m_4 - W) + (1 + \eta_2 u_2) r f \epsilon(X + pY) + \\
& \theta V - W(\theta_t + \gamma)\big]
\end{aligned}
$$

A system of differential equations is then formulated to describe the adjoint variables. The differential equation governing an adjoint variable is determined by the negative partial derivative of the Hamiltonian with respect to the corresponding state variable.

$$\frac{d\lambda_S}{dt} = -\frac{\partial H}{\partial S} = \mu\lambda_S - f(\delta(X+pY+V+pW)+\tau)((1-(1+\eta_1 u_1)k)\lambda_X + (1+\eta_1 u_1)k\lambda_Y - \lambda_S) \tag{3.8}$$

$$\frac{d\lambda_X}{dt} = -\frac{\partial H}{\partial X} = \mu\lambda_X + f[\delta S(\lambda_S - (1-(1+\eta_1 u_1)k)\lambda_X - (1+\eta_1 u_1)k\lambda_Y) - \epsilon((1-(1+\eta_2 u_2)r)\lambda_V + (1+\eta_2 u_2)r\lambda_W - \lambda_X)] + \beta(\lambda_X - \lambda_S) + \alpha(\lambda_X - \lambda_Y) \tag{3.9}$$

$$\frac{d\lambda_Y}{dt} = -\frac{\partial H}{\partial Y} = \mu\lambda_Y + fp[\delta S(\lambda_S - (1-(1+\eta_1 u_1)k)\lambda_X - (1+\eta_1 u_1)k\lambda_Y) - \epsilon((1-(1+\eta_2 u_2)r)\lambda_V + (1+\eta_2 u_2)r\lambda_W - \lambda_Y)] + \alpha_p(\lambda_Y - \lambda_X) + \gamma_p(\lambda_Y - \lambda_S) \tag{3.10}$$

$$\frac{d\lambda_V}{dt} = -\frac{\partial H}{\partial V} = \mu\lambda_V + f\delta S(\lambda_S - (1-(1+\eta_1 u_1)k)\lambda_X - (1+\eta_1 u_1)k\lambda_Y) + \beta(\lambda_V - \lambda_S) + \theta(\lambda_V - \lambda_W) - A\mu_v \tag{3.11}$$

$$\frac{d\lambda_W}{dt} = -\frac{\partial H}{\partial W} = \mu\lambda_W + f\delta Sp(\lambda_S - (1-(1+\eta_1 u_1)k)\lambda_X - (1+\eta_1 u_1)k\lambda_Y) + \gamma(\lambda_W - \lambda_S) + \theta_t(\lambda_W - \lambda_V) - B\mu_w \tag{3.12}$$

The transversality condition implies every adjoint has a final time condition equal to zero.

$$\lambda_S(T) = 0,\ \lambda_X(T) = 0,\ \lambda_Y(T) = 0,\ \lambda_V(T) = 0,\ \lambda_W(T) = 0 \tag{3.13}$$

To characterize optimal controls u_1^* and u_2^* we set the partial derivative of the Hamiltonian with respect to each control equal to zero, then solve for u_1^* and u_2^*, respectively.

$$\frac{\partial H}{\partial u_1} = 0 => \ u_1^* = \frac{\eta_1 k f(\delta S(X+pY+V+pW)+\tau S)(\lambda_x - \lambda_y - D)}{2C} \tag{3.14}$$

$$\frac{\partial H}{\partial u_2} = 0 => \ u_2^* = \frac{\eta_2 r f \epsilon(X+pY)(\lambda_v - \lambda_w - G)}{2E} \tag{3.15}$$

The optimality system supplies necessary conditions for solutions to the optimal control

problem. Our optimality system cannot be solved analytically for u_1^* and u_2^*, so we explore numerical approximations to solutions.

Chapter 4

Numerical Solutions

4.1 Numerical Algorithm

As mentioned previously, it may not be possible to solve the optimality system explicitly. Alternatively, we use numerical methods to approximate solutions and display results. An iterative scheme is implemented in MATLAB® to to solve the optimality system with initial conditions for the state variables and final time conditions for the adjoint variables. A Runge-Kutta method of the fourth-order is used within the iterative scheme.

The iterative scheme can be generalized by the following steps.

1. Establish initial guesses for the control variables.

2. Given initial conditions for the states, approximate solutions for the state equations using the Runge-Kutta method.

3. Given the state solutions from the previous step and the final time conditions on the adjoints, approximate the solutions for the adjoint equations using the Runge-Kutta method.

4. Update the values of the control variables by averaging the previous value and

the new value arising from the control characterization.

5. Repeat steps 1-4 until successive values of all the states, adjoints, and control(s) are sufficiently close.

This final step for determining convergence requires that values of states, adjoints, and controls from two successive iterations satisfy the relation

$$\frac{||v - oldv||}{||v||} \leq \bar{\epsilon}$$

where $\bar{\epsilon}$ is the accepted tolerance, v is the vector of current values, $oldv$ is the vector of values from the previous iteration, and $||\cdot||$ refers the the sum of the absolute value of the elements within v.

4.2 Simulations

Using the steps listed above, we numerically solve the optimality system and display optimal VRE dynamics. We look at optimal controls and associated VRE dynamics over a period of $T = 30$ days. For the simulations displayed here, we use the mean values of each parameter (see Table 2.1) and initial conditions $S(0) = 0.8, X(0) = 0.05, Y(0) = 0.05, V(0) = 0.05, W(0) = 0.05$. Our objective is to start with an initial set of cost coefficients (see Table 3.1) and vary one cost coefficient at a time to investigate how optimal controls change with different costs. The figures that are shown below display the same four plots for different cost coefficients. The top left plot displays the proportion of ICU patients that are susceptible through time. The top middle plot represents the proportion of ICU patients who are colonized through time. In this graph, the red line represents colonized patients with preventative care and the blue line represents colonized patients without preventative care. The top right plot displays the proportion of ICU patients who are infected through time. In this graph, the red

line represents infected patients receiving treatment, the blue line represents infected patients who are not receiving treatment, and the black line represents all infected patients (i.e., sum of red and blue lines). Finally, the bottom plot represents the level of each control applied through time. In this graph, the green line represents control u_1 (associated with preventative care) and the blue line represents control u_2 (associated with treatment).

In addition to displaying the optimal controls and corresponding VRE dynamics through time, we compute the total VRE-related deaths and total costs of controls over the 30-day period. The differential equation

$$\frac{d\bar{D}}{dt} = \mu_v V + \mu_w W \qquad \bar{D}(0) = 0$$

was used to track total deaths over time. Here, $\bar{D}$ represents the cumulative death attributed to VRE.

$$\begin{aligned} \frac{d\bar{C}}{dt} =& Cu_1^2 + D(\eta_1 u_1 k f(\delta S(X + pY + V + pW)))+ \\ & Eu_2^2 + G(\eta_2 u_2 r f \epsilon(X + pY)) \\ \bar{C}(0) =& 0 \end{aligned}$$

Here, $\bar{C}$ represents the cumulative cost attributed to VRE control. The total deaths and total costs for all simulations are summarized in Table 4.1.

Figure 4.1 illustrates the solution to our system (3.1)-(3.5) when no controls are applied. In this simulation, we set both controls equal to zero for the duration of the simulation, i.e., $u_1(t) = 0$ and $u_2(t) = 0$ for $0 \leq t \leq 30$. This scenario represents baseline ICU conditions in which no additional resources are allocated towards preventative care and treatment. Given that no control is being applied, the total VRE-related death rate is 0.1650. Throughout the 30 days of this simulation, the proportion of ICU patients infected with VRE is consistently ≈ 0.2.

We now simulate model dynamics with optimal controls. We start with an initial set of values for the cost coefficients in the objective functional, $A = \$150,000$, $B = \$150,000$, $C = \$10$, $D = \$3,850$, $E = \$100$, $G = \$11,150$. Figure 4.2 displays the optimal controls and the associated VRE dynamics. For this simulation, control u_2 is at a moderate level of approximately 0.4, while u_1 is not applied at all during the 30 days. This control strategy means that parameter r is multiplied by 2.2 and parameter k remains at baseline throughout the 30 days. Given this control strategy, the total VRE-related death rate is reduced to 0.1308. The total costs associated with the controls are \$4,607.84. Throughout the 30 days of this simulation, the proportion of ICU patients infected with VRE remains consistently just below 0.2.

For the second simulation, we reduce the linear cost of preventative care, D, to \$1,000 and keep the remaining cost coefficients the same. Figure 4.3 displays the optimal controls and corresponding VRE dynamics. As a result of reducing the cost of preventative care, both u_1 and u_2 are applied during the 30 days. By reducing D to \$1,000, u_1 is now applied at maximum level (i.e., $u_1(t) = 1.0$) and u_2 is applied at a level of ≈ 0.40 until day 26. Given this control strategy, the total VRE-related death rate is reduced to 0.1182. The total costs associated with the controls are \$4,057.49. Throughout the 30 days of this simulation, the proportion of total infected patients is ≈ 0.15 until control is turned off on day 26.

For the third simulation, we keep the same cost coefficients used in the second simulation, except we increase the quadratic cost for preventative care, C, to \$50. Figure 4.4 displays the optimal controls and corresponding VRE dynamics. Control u_1 is initially applied at maximum level and u_2 is initially ≈ 0.1. However, on the fifth day both controls have the same value and remain at ≈ 0.5 for the majority of the time. This scenario represents one in which resources are available for both preventative care and treatment, but neither option is being applied at extreme values for a long period of time. Given this control strategy, the total VRE-related death rate is reduced to

0.1248. The total costs associated with the controls are \$4,480.64. Throughout the 30 days of this simulation, the proportion of total infected patients remains at ≈ 0.15 until control is turned off on day 26.

Finally, in the fourth simulation we keep the same cost coefficients used in the third simulation except we reduce the quadratic cost coefficients for both preventative care and treatment, C and E respectively, to \$10. Figure 4.5 displays the optimal controls and corresponding VRE dynamics. With this change in cost, both u_1 and u_2 are being fully applied at maximum levels for most of the 30-day period. The effect of this scenario is such that both parameters k and r are quadrupled in valued, going from 0.2 (baseline) to 0.8 (with controls). Given this control strategy, the overall total VRE-related death rate is reduced to 0.0789. The total costs associated with the controls are \$8,570.23. Throughout the 30 days of this simulation, the proportion of total infected patients remains just above 0.1 until control is turned off on day 26.

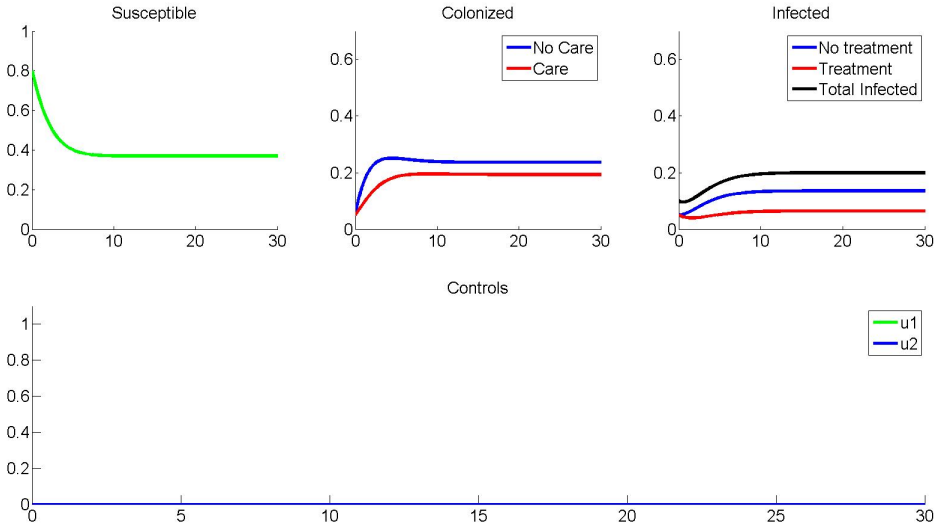

Figure 4.1: Solution to VRE model with no control

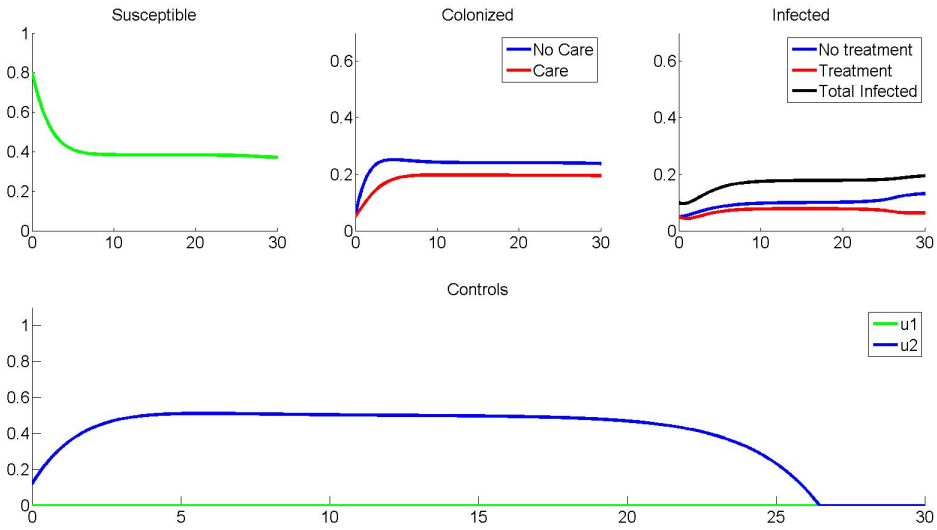

Figure 4.2: Simulation 1: VRE model with optimal controls using A = B = \$150,000, C = \$10, D = \$3,850, E = \$100, G = \$11,150

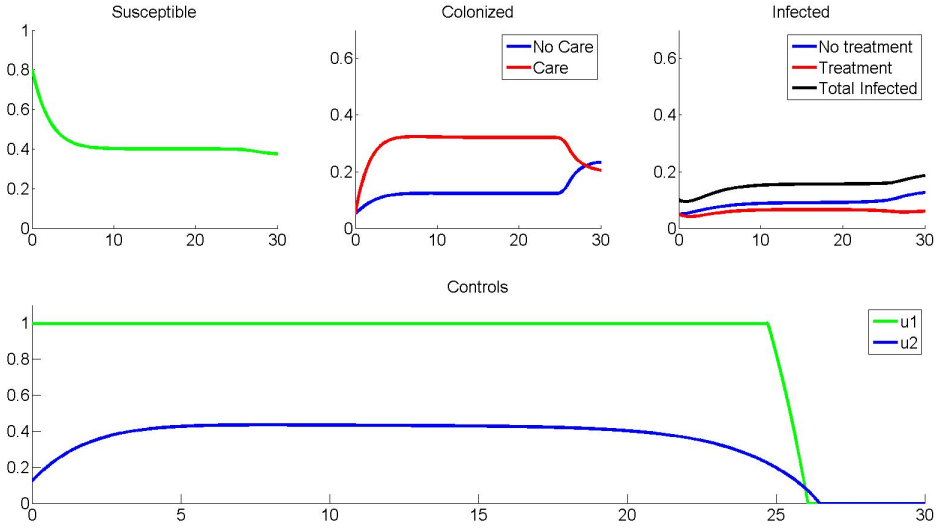

Figure 4.3: Simulation 2: VRE model with optimal controls using A = B = \$150,000, C = \$10, D = \$1,000, E = \$100, G = \$11,150

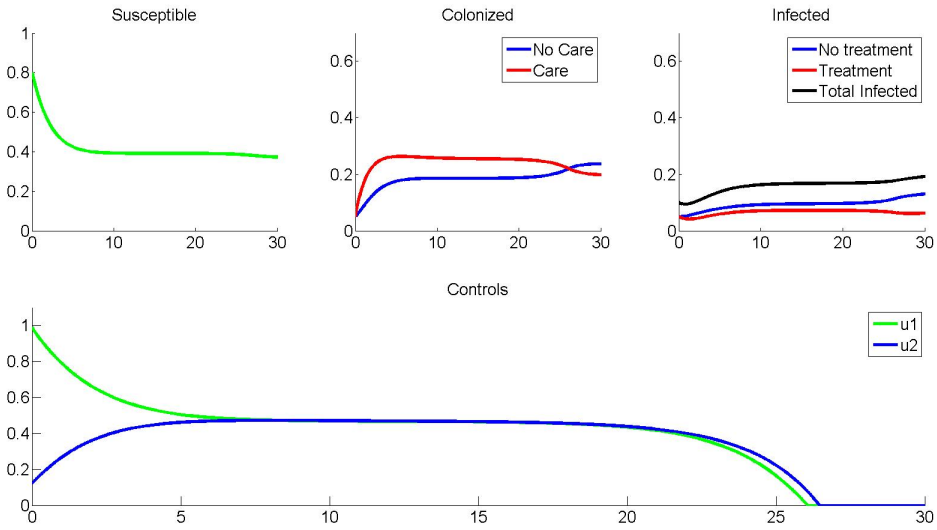

Figure 4.4: Simulation 3: VRE model with optimal controls using A = B = \$150,000, C = \$50, D = \$3,850, E = \$100, G = \$11,150

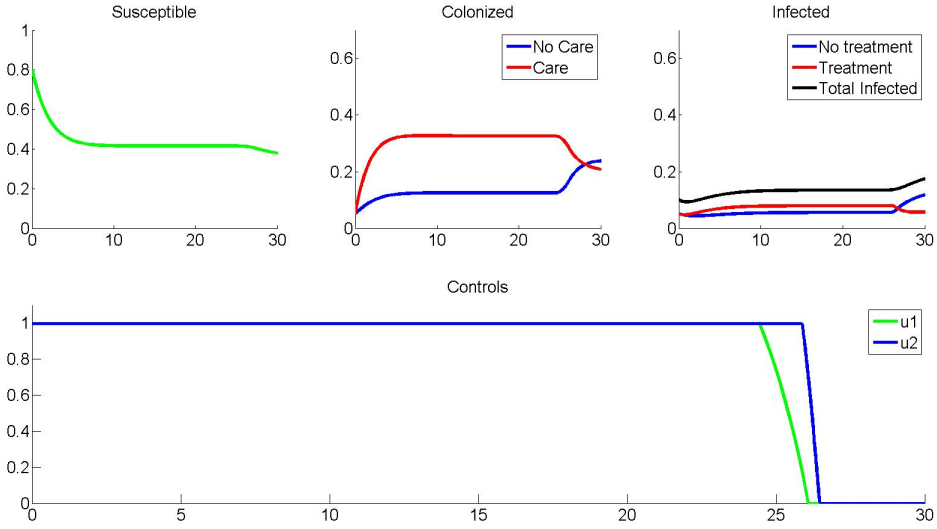

Figure 4.5: Simulation 4: VRE model with optimal controls using A = B = \$150,000, C = \$10, D = \$1,000, E = \$10, G = \$11,150

Simulation	**Total Death**	**Total Costs**
No Control (Baseline)	0.1650	\$0
1	0.1308	\$4,607.84
2	0.1182	\$4,057.49
3	0.1248	\$4,480.64
4	0.0789	\$8,570.23

Table 4.1: Summary of death rate and costs of control for each 30-day simulation

Throughout our investigation of various cost coefficients, we notice that, regardless of costs, both u_1 and u_2 are turned off around day 26. The reason behind this event is that there is no benefit (in terms of reducing death) of applying control on the last couple of days. Therefore, it is optimal to turn the controls off. If we want to eliminate this phenomena, then we could add a salvage term (e.g., $V(T)+W(T)$) to the objective functional. This additional term then changes our goal to not only reducing the number of deaths over time, but also reducing the total number of infected individuals at the final time.

In our investigation of optimal controls, we also look at the maximum costs that can be associated with a control before it is optimal to apply no control. Given $A = \$150,000$, $B = \$150,000$, $C = \$10$, $E = \$100$, we simulated optimal controls for different values of G and D. First, we assumed that the linear cost for treatment remains at $G = \$11,150$. In this scenario, if $D \leq \$1,800$, then it is optimal to apply $u_1(t) > 0$ for some duration of time. However, if $D > \$1,800$, then it is optimal that $u_1 \equiv 0$. Subsequently, we assumed the linear cost for preventative care remains at $D = \$3,850$. In this scenario, if $G \leq \$14,500$, then it is optimal to apply $u_2(t) > 0$ for some duration of time. If $G > \$14,500$ then it is optimal that $u_2 \equiv 0$. Thus, for these particular parameters, we consider $G = \$14,500$ and $D = \$3,850$ to be threshold values for the costs of controls.

Further analysis can be achieved by varying the values of the nineteen independent parameters, initial conditions of the state variables, and duration of control (T).

Chapter 5

Conclusions

In this thesis, we present a novel application of optimal control theory to solve a biological problem. The goal is presented as minimizing an integral expression written in terms of state variables and control variables. To characterize optimal solutions we use techniques in optimal control theory developed by Pontryagin [40]. Pontryagin's Minimum Principle states that if there are optimal state and control variables, then there exists an adjoint variable that minimizes an expression called the Hamiltonian. The Principle also states how to characterize the adjoint variables. Pontryagin's Minimum Principle takes the complicated problem of minimizing the objective functional subject to the state ODE and initial conditions and simplifies it to minimizing the Hamiltonian point-wise.

We investigated cost-efficient strategies for mitigating the spread of Vancomycin-Resistant Entercocci (VRE) within an Intensive Care Unit (ICU) using a mathematical model and optimal control theory. We started with a biological model of VRE describing the movement of individuals between different infection stages. We converted the biological model into a mathematical model with five state variables (S, X, Y, V, W) and nineteen independent parameters. The mathematical model was written as a system of five ordinary differential equations based on incoming and outgoing rates of the five state variables. We introduced two control variables, $u_1(t)$ and $u_2(t)$ into our

mathematical model. The control u_1 relates to the proportion of newly colonized patients receiving preventative care and control u_2 relates to the proportion of newly infected patients receiving treatment. Next, we formulated an objective functional as the minimization of an integral expression describing the total VRE-related deaths and total costs associated with controls over a finite time period. We then used an extension of Pontryagin's Minimum Principle to solve for optimal controls, u_1^* and u_2^* in terms of state and adjoint variables. We wrote an iterative numerical scheme, which included a fourth-order Runge-Kutta, in MATLAB® to solve the optimality system, which consisted of ODEs and initial conditions for the state variables, ODEs and final time conditions for the adjoint variables, and the control characterizations. Using this mathematical framework, we investigated cost-effective strategies for the control of VRE spread within the ICU by running numerous simulations, changing one cost parameter at time, and tracking the total VRE-related death rates and total costs for control.

Our research provides a flexible mathematical framework for determining cost-effective schedules for treatment and preventative care during a VRE outbreak within an ICU. With VRE being a top health concern of the Center for Disease Control, our research presents a solution to a problem that is of concern to many hospitals. The flexibility of our model allows health care workers to adjust the nineteen parameters to replicate the dynamics observed in a specific hospital ICU. Subsequently, policy makers may use results of the mathematical model and optimal control problem to make cost efficient decisions regarding the use of preventative care and treatment to reduce the spread of VRE. This analysis has the potential to not only reduce hospital costs but also reduce the impact that VRE has on the hospital patients. Lastly, the research presented in this thesis can provide a mathematical framework that will be useful for studying the control of other antibiotic-resistant bacteria such as MRSA.

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