IMMUNOSUPPRESSANT TREATMENT DYNAMICS IN RENAL TRANSPLANT RECIPIENTS: AN ITERATIVE MODELING APPROACH

NEHA MURAD, H. T. TRAN AND H. T. BANKS

Center for Research in Scientific Computation
North Carolina State University
Raleigh, NC 27695-8212, USA

R. A. EVERETT

Department of Mathematics and Statistics
Haverford College
Haverford, PA 19041, USA

ERIC S. ROSENBERG

Massachusetts General Hospital and Harvard Medical School
Departments of Pathology and Medicine
Boston, MA 02114, USA

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ABSTRACT. Finding the optimal balance between over-suppression and under-suppression of the immune response is difficult to achieve in renal transplant patients, all of whom require lifelong immunosuppression. Our ultimate goal is to apply control theory to adaptively predict the optimal amount of immunosuppression; however, we first need to formulate a biologically realistic model. The process of quantitively modeling biological processes is iterative and often leads to new insights with every iteration. We illustrate this iterative process of modeling for renal transplant recipients infected by BK virus. We analyze and improve on the current mathematical model by modifying it to be more biologically realistic and amenable for designing an adaptive treatment strategy.

Abbreviations:

| Abbreviation | Description |
|--------------|-------------|
| BKV          | BK virus    |
| GvHD         | Graft-Versus-Host Disease |
| GFR          | Glomerular Filtration Rate |
| HCMV         | Human Cytomegalovirus |
| HIV          | Human Immunodeficiency Virus |
| PVAN         | Polyomavirus type BK-associated Nephropathy |
| SOT          | Solid Organ Transplantation |

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1. **Introduction.** A patient undergoing a solid organ transplantation is usually put on a lifetime regime of immunosuppressive medications to prevent the body from rejecting the allograft [21]. However, these immunosuppressive treatments often leave the recipient susceptible to opportunistic pathogens including viruses. Achieving the delicate balance between under-suppression and over-suppression of the immune system is key to successful and sustainable transplantation. Currently, immunosuppressive treatment protocols in the United States are in a state of flux with varying treatment regimens across different organ transplant centers. One possible reason for this inconsistency is that centers are implementing individual or group based treatment protocols [11, 18].

Personalized medicine investigators attempt to find subgroups of similar patients who may need a different course of action or adaptively treat an individual patient based on their response to treatment [25]. One example, among many, of using mathematical models to enhance personalized treatment is the application of control theory to determine an optimal treatment strategy. There are several related biomedical applications of control theory in [13], such as determining the optimal treatment regimen for cancer patients undergoing chemotherapy in order to minimize tumor density as well as treatment side effects. The authors in [13] also apply control theory to human immunodeficiency virus (HIV)-infected patients undergoing chemotherapy and also to determine the optimal insulin injection level to better regulate blood glucose levels in diabetic patients. Further applications of control theory to HIV therapy strategies are presented in [1, 7, 22]. The authors in [26] present control problems related to cancer therapies, such as antiangiogenic treatments. There are several diseases that require immunosuppressant treatment, besides solid organ transplantation, in which control theory could potentially be beneficial. Allogeneic hematopoietic stem-cell transplant recipients receive immunosuppression therapy to diminish the risk of developing graft-versus-host disease (GvHD), the attack of donor T-cells on the host tissues [27]. Immunosuppression therapy is also one of the current treatment options for autoimmune diseases, which result from the body’s immune system attacking its own body [10].

Mathematical and statistical models can thus be important and beneficial tools that contribute to the improvement and optimization of treatment protocols. Modeling of any biological process is an iterative one, as seen in Figure 1. The biologist first presents a research question about some biological process as well as knowledge about biological relationships and mechanisms, often depicted by a schematic or diagram. The mathematician then represents the biological hypothesis of the relationships through a mathematical model. Analytic or numerical analysis of the model produces results which are interpreted and compared to the biological system, possibly leading to a change in the understanding of the biological relationships. The process is continuously repeated, sometimes through multiple research efforts, using the resulting biological insights (See [8] for more details on the iterative process of modeling).

In this study we first explain and analyze a previous model [5] which captures the biological mechanisms of the immune response in renal transplantation patients with respect to infection caused by the human polyomavirus type 1, named ‘BK virus’ (BKV). This is a common pathogen found in kidney transplantation patients and is normally controlled in immunocompetent individuals but can cause infections in the immunosuppressed. Our results show evidence of the lapses in biological understanding and implementation of the corresponding mathematical model. We
then attempt to address and correct for the discrepancies between the mathematical model and the biological system by revising components of the mathematical model, thereby illustrating the iterative process of modeling. Once a mathematical model is developed, it could in turn be used for control theory applications to predict optimal drug regimens, an important problem we intend to address in the future.

2. Recent modeling efforts in kidney transplantation. Several research groups have recently contributed to developing mathematical models to study the mechanisms of the complex biological process involving solid organ transplantation (SOT), specifically kidney transplantation.

Funk et al. [17] use simple mathematical equations to investigate the relationship between BKV replication and polyomavirus type BK-associated nephropathy (PVAN), one of the most common viral complications to develop in renal transplant recipients. It is a prominent cause of renal transplant dysfunction and graft loss. Since PVAN was first reported in 1995, an occurrence rate from 1% to 10% has been reported in renal transplant patients [19]. Prevalence of PVAN is mainly attributable to BK virus. Around 90% of the world’s general population has some form of Polyomavirus BK (BKV) present in their reno-urinary tract. However, as long as the immune response is functional, there is usually no sign of clinically significant viral replication. The authors in [17] assume the BK virus grows and decays exponentially and then present the corresponding equations to calculate the viral doubling times and half-lives. The generation time and basic reproductive ratio ($R_0$) equations are also given. The authors then perform a retrospective mathematical analysis on 15 individual patient datasets with the given equations. Their results indicate rapid replication of the BK virus, elucidating the progressive nature of PVAN, contrary to the general perception in clinical practice. The authors also propose the use of $R_0$ as a measure of the efficiency of anti-viral interventions in future studies.
The authors of [15] extend this work and first perform statistical analysis on datasets from 223 kidney transplant recipients to help understand the relationship between BKV in the plasma and urine. The authors present a dynamical model that considers four cell populations and two virus populations: uninfected kidney tubular epithelial cells, infected tubular epithelial cells, plasma virus, uninfected urothelial cells, infected urothelial cells, and urine virus. Antiviral interventions are represented as a time-dependent function that affects the growth of both viral populations. The basic reproductive ratio for the kidney and urinary compartments are determined and used in parameter sensitivity analysis. The authors simulate the mathematical model to explore the dynamics of BKV for various scenarios and compare simulation results to 7 individual kidney transplant patient datasets.

Kepler et al. [24] also consider the effect of the immune response on the viral infection in the presence of immunosuppression therapy. The authors specifically consider human cytomegalovirus (HCMV) infection (one of eight known human herpes viruses) in SOT recipients and present a model that describes the dynamics of the viral load, immune response, actively-infected cells, susceptible cells, and latently-infected cells. The authors show that the model can describe the three types of infection: primary, latent, and reactivation. Model simulations are given for varying amounts of immunosuppression. Due to the limited amount of corresponding data in literature, the authors do not compare their model to patient data. However, the authors state how inverse problems can be performed with individual datasets to estimate parameter values for individual patients, providing insights into the heterogeneity in disease progression.

Banks et al. [4] modify the model in [24] to include the body’s immune response to a donor kidney. Their model considers susceptible cells, infected cells, free HCMV, HCMV-specific CD8+T-cells, allospecific CD8+T-cells that target the donor kidney, and serum creatinine, a biological marker for renal function. Due to a lack of data, model validation is not provided; model simulations with varying antiviral and immunosuppressive drug efficacy are produced only to verify that results match clinical trends. The authors then use simulated data to demonstrate an optimal control problem to design an adaptive anti-viral and immunosuppressant treatment schedule that balances over-suppression and under-suppression of the immune system.

Due to the high rate of incidence of BKV infection in transplant patients and the lack of effective BK virus-specific therapy, the authors in [5] adapt the model from [4] to consider renal transplant recipients infected with BKV. Here, we present qualitative analysis of this model (using model simulations) and modifications in the context of the iterative modeling process.

3. Iteration I: Preliminary model.

3.1. Data collection and biological model. Data used to fit the model and obtain some of the model parameters in [5] was collected at Massachusetts General Hospital from a renal transplant patient TOS003 diagnosed with BKV in the first 3 months of kidney transplantation. (This data was collected with approval of the
MGH human subjects (IRB) committee. Furthermore data was shared with NCSU in a de-identified manner. Eight BK viral plasma load (DNA copies/mL) measurements and sixteen plasma creatinine level (mg/dL) measurements were collected. Creatinine levels are used as a surrogate for GFR (Glomerular Filtration Rate), to measure kidney function. Due to the sparsity of data collected, we do not estimate parameters for Iteration II of our modeling efforts; instead, we use most of the parameters from literature.

The authors in [5] describe a model schematic of the compartmentalized biological model as shown in Figure 2. Since no effective anti-viral treatment exists for BKV, the authors in [5] modify the model in [4] to only consider the efficiency of immunosuppressant treatment. Additionally, the authors model the effect of the susceptible cells on creatinine clearance and on the allospecific CD8+T-cell population growth. As opposed to Funk et al. [15], the authors in [5] do not consider the urothelial cells and only consider infection in tubular epithelial cells, in part due to the availability of data. While this makes the model more specific, one can hope to expand the current model scope to include urothelial cells once relevant data becomes available.

![Figure 2. Model diagram of the BKV virus affecting renal cells [5].](image)

3.2. Mathematical model. The mathematical model in [5] describes the concentrations of susceptible cells ($H_S$), infected cells ($H_I$), free BKV ($V$), BKV-specific CD8+T-cells ($E_V$), allospecific CD8+T-cells ($E_K$) that target the kidney, and serum creatinine ($C$), by the following system of ordinary differential equations:
\[ \dot{H}_S = \lambda_{HS} \left( 1 - \frac{H_S}{\kappa_{HS}} \right) H_S - \beta H_S V \]  
\[ \dot{H}_I = \beta H_S V - \delta_{HI} H_I - \delta_{EH} E_V H_I \]  
\[ \dot{\bar{V}} = \rho_V \delta_{HI} H_I - \delta_V V - \beta H_S V \]  
\[ \dot{E}_V = (1 - \epsilon_I) [\lambda_{EV} + \rho_{EV}(V)E_V] - \delta_{EV} E_V \]  
\[ \dot{E}_K = (1 - \epsilon_I) [\lambda_{EK} + \rho_{EK}(H_S)E_K] - \delta_{EK} E_K \]  
\[ \dot{C} = \lambda_C - \delta_C(E_K, H_S)C, \]

where

\[ \rho_{EV}(V) = \frac{\bar{\rho}_{EV} V}{V + \kappa_{V}}, \]

\[ \rho_{EK}(H_S) = \frac{\bar{\rho}_{EK} H_S}{H_S + \kappa_{KH}}, \]

\[ \delta_C(E_K, H_S) = \frac{\delta_{C0}\kappa_{EK}}{E_K + \kappa_{EK}} \cdot \frac{H_S}{H_S + \kappa_{CH}}. \]

The initial conditions are given by,

\[ (H_S(0), H_I(0), V(0), E_V(0), E_K(0), C(0)) = (H_{S0}, H_{I0}, V_0, E_{V0}, E_{K0}, C_0). \]  

Susceptible cells proliferate logistically at maximum rate \( \lambda_{HS} \) with the carrying capacity \( \kappa_{HS} \). The term \( \beta H_S V \) represents the loss of susceptible cells due to infection, causing growth in the infected cell population and loss of free virions. For simplicity, the authors in [5] assume one virion infects one susceptible cell, creating one infected cell. The parameter \( \beta \) represents the infection rate of \( H_S \) by \( V \). Infected cells lyse at rate \( \delta_{HI} \) due to the cytopathic effect of the BK virus, releasing \( \rho_V \) free virions. The infected cell population can also decrease due to elimination by the BK-specific CD8+T-cells at rate \( \delta_{EH} \). The body naturally clears virions from the blood at rate \( \delta_V \).

The authors in [5] assume both a virus-dependent and virus-independent growth rate of the BKV-specific CD8+T-cell population. The parameter \( \lambda_{EV} \) represents the virus-independent source rate for \( E_V \). The virus-dependent growth rate is represented by the Michaelis-Menten function \( \rho_{EV}(V)E_V \), where \( \bar{\rho}_{EV} \) represents the maximum proliferation rate and \( \kappa_V \) represents the half saturation constant (See [2] or [23] for information on half saturation constants and Michaelis-Menten kinetics). The parameter \( \delta_{EV} \) represents the death rate of the BKV-specific CD8+T-cells. Similarly it is assumed that growth rate of the allospecific CD8+T-cell population is both susceptible cell-dependent and susceptible cell-independent. The parameter \( \lambda_{EK} \) represents the susceptible cell-independent source rate for \( E_K \). The susceptible cell-dependent growth rate is represented by the Michaelis-Menten term \( \rho_{EK}(H_S)E_K \), where \( \bar{\rho}_{EK} \) represents the maximum proliferation rate and \( \kappa_{KH} \) represents the half saturation constant. The parameter \( \delta_{EK} \) represents the death rate of the allospecific CD8+T-cells that target the kidney.

The growth of the immune system inversely depends on the immunosuppressive treatment. This dependence is given by the term \( (1 - \epsilon_I) \), where \( \epsilon_I \in [0, 1] \) represents
the efficiency of immunosuppressive drugs. A drug efficiency of 0% \( (\epsilon_I = 0) \) indicates that treatment does not affect the immune system and the CD8+ T-cells grow normally; a drug efficiency of 100% \( (\epsilon_I = 1) \) is assumed to cause the CD8+ T-cells of the immune system to decrease exponentially. The dosage, type, and concentration of drugs often change over the course of treatment. Therefore, for simplicity, \( \epsilon_I \) is defined by the following piecewise constant function

\[
\epsilon_I(t) = \begin{cases} 
\epsilon_1 & t \in [0, 21] \\
\epsilon_2 & t \in (21, 60] \\
\epsilon_3 & t \in (60, 120] \\
\epsilon_4 & t \in (120, 450].
\end{cases}
\]

The parameter \( \lambda_C \) represents the constant production rate of serum creatinine. A damaged kidney is not able to filter waste from the blood as effectively, causing a build-up of creatinine. Thus it is assumed that the loss of serum creatinine depends on both the susceptible cells and the allospecific CD8+ T-cells that target the kidney, with \( \delta_{C0} \) representing the maximum clearance rate of serum creatinine. As the allospecific CD8+ T-cells that target the kidney increase (indicating damage to the kidney), the creatinine clearance rate \( \delta_C \) decreases to 0, resulting in creatinine build-up. As the susceptible cell population increases (indicating a healthier kidney), the creatinine clearance rate \( \delta_C \) increases, which in turn decreases the creatinine concentration in the body. The parameters \( \kappa_{EK} \) and \( \kappa_{CH} \) represent half saturation constants. A description of the state variables and parameters are given in Tables 1 and 3 respectively. For more details on the analysis of this model see [5].

**Table 1. Description of state variables.**

| State   | Description                                           | Unit   |
|---------|-------------------------------------------------------|--------|
| \( H_S \) | Concentration of susceptible graft cells              | cells/mL |
| \( H_I \) | Concentration of infected graft cells                 | cells/mL |
| \( V \)   | Concentration of free BKV                             | copies/mL |
| \( E_V \) | Concentration of BKV-specific CD8+ T-cells            | cells/mL |
| \( E_K \) | Concentration of allospecific CD8+ T-cells that target kidney | cells/mL |
| \( C \)   | Concentration of serum creatinine                     | mg/dL   |

### 3.3. Statistical error model.

The authors in [5] assume the simplest statistical error model, an absolute error model, where the variances of the error for each observable (viral load and creatinine) are equal and constant over time. That is, the authors account for the uncertainty in the dataset by the following statistical error model

\[
Y_i^1 = f_1(t_i^1; \theta_0) + \xi_i^1, \quad i = 1, 2, \ldots, n_1,
\]

\[
Y_j^2 = f_2(t_j^2; \theta_0) + \xi_j^2, \quad j = 1, 2, \ldots, n_2.
\]

The functions \( f_1(t_i^1; \theta_0) \) and \( f_2(t_j^2; \theta_0) \) represent the model solution for viral load and creatinine at times \( t_i^1 \) and \( t_j^2 \) respectively, assuming a “true” or nominal parameter set \( \theta_0 \). The existence of this “true” parameter set is a standard assumption in statistical models [6].

The \( \xi_i^1 \), \( \xi_j^2 \) terms represent the measurement error that causes the measurements to differ from the model solution with the “true” parameter set. We assume the
$n_1 \times 1$ and $n_2 \times 1$ random vectors $\mathbf{E}^1$ and $\mathbf{E}^2$ respectively, are independent and identically distributed with mean zero and $\text{Var}(\mathbf{E}_i^1) = \sigma_{01}^2$ and $\text{Var}(\mathbf{E}_j^2) = \sigma_{02}^2$. The authors in [5] assume $\sigma_{01}^2 = \sigma_{02}^2$ (Note the model is log scaled). The corresponding method for parameter estimation is ordinary least squares (OLS).

In [3], we build on the works of [5] and consider a more general (and possibly more biologically realistic) statistical error model. We assume the variances of observation errors are not equal and allow for the errors to depend on the size of the observed quantity. That is, we assume the following statistical error model, a relative error model, given by

$$
Y_{i_1}^1 = f_1(t_{i_1}; \theta_0) + f_1(t_{i_1}; \theta_0)\gamma_1 \mathbf{E}_i^1, \quad i = 1, 2, \ldots, n_1,
$$

$$
Y_{j_2}^2 = f_2(t_{j_2}; \theta_0) + f_2(t_{j_2}; \theta_0)\gamma_2 \mathbf{E}_j^2, \quad j = 1, 2, \ldots, n_2,
$$

for $\gamma_k \geq 0, k = 1, 2$. The measurement error term now can depend on the size of the model solution of the observables. Note that if both $\gamma_1 = 0$ and $\gamma_2 = 0$, the two statistical error models are equivalent. The corresponding method for parameter estimation, assuming a relative error model, is iterative weighted least squares (IWLS).

In [3], we use a second order difference-based method to eliminate statistical error model misspecification by selecting the correct statistical error model directly from the data. We show how modified residuals from the inverse problem can then be used to detect discrepancies in mathematical model formulation. However, we also point out in [3] that due to sparsity of data available to us, it is difficult to ascertain which statistical model is suitable for this specific dataset.

3.4. Model analysis. The authors of [5] numerically analyze the model by performing an inverse problem with the data to estimate parameters. That is, the authors seek to find a parameter set that minimizes the distance between the collected data and mathematical model. However, the model has a large number of parameters (29 parameters) and thus not all the parameters can be reliably estimated with such a small dataset of 24 observations. Thus, the authors of [5] implement an iterative procedure to determine the most sensitive parameters. An inverse problem is then performed to estimate the 5 most sensitive parameters, and the resulting model solutions provide a reasonable fit to the data (see [5] for details). However, in [3] we present examples which illustrate that a good fit is not necessarily enough to conclude the accuracy of a model. We conclude that further data collection endeavors are needed to reduce the uncertainty in parameter choices made for the model.

Our primary motivation of mathematically modeling the immune response to the allograft and BK virus is to eventually formulate a control problem to adaptively predict patient specific optimal immunosuppressant dosage as treatment progresses. Specifically, the immunosuppressant dosage level should keep viral loads low (less than 10,000 copies/ml [12][28][29]) and creatinine levels within a healthy range (0.6 – 1.1 mg/dL [4]). Figure 3 depicts the general dynamics of both the BK virions and CD8+ T-cells for varying amounts of immunosuppressants.

As a first step towards a feedback control strategy, we implemented a simple open loop control problem (where the output has no influence or effect on the control input). The results (not shown) provided inadequate validation to the mathematical model’s robustness for formulation and design of the control. Hence, we considered
Cell density vs treatment

Figure 3. Plot illustrating the balance between under and over suppression of the immune response.

A simpler test: to simulate model solutions for the highest and lowest immunosuppressant dosage and observe the model dynamics. Note that, for all simulations, we assume a constant immunosuppression efficiency (i.e., $\epsilon_1 = \epsilon_2 = \epsilon_3 = \epsilon_4$ in (2)), whereas the authors in [5] considered different constant values for immunosuppression dosage, $\epsilon_1 = 0.1009, \epsilon_2 = 0.3658, \epsilon_3 = 0.5999,$ and $\epsilon_4 = 0.3649$.

Recall that a drug efficiency of 0% ($\epsilon_I = 0$) implies that the immune system is not compromised and the body fights the virus effectively (i.e., BK viral loads are under control and there is negligible infection); however the immune response treats the kidney transplant as a foreign object and attacks it, killing the susceptible cells and causing the creatinine levels to increase. On the other hand, a drug efficiency of 100% ($\epsilon_I = 1$) causes the immune system to significantly decrease (Note this is an extreme case of immunosuppression therapy and is usually not prescribed for individuals). While it is no longer a threat to the allograft, the immune system is now unable to defend itself against outside infections (in our case BKV infection), causing an increase in viral load. These dynamics are summarized in Table 2.

Table 2. Summary of cell dynamics under influence of immunosuppression.

| $\epsilon$ | CD8+ T-cells | BKV | Infected cells | Susceptible cells | Creatinine |
|------------|--------------|-----|----------------|-------------------|-----------|
| Low        | ↑            | ↓   | ↓              | ↓                 | ↑         |
| High       | ↓            | ↑   | ↑              | ↓                 | ↑         |
The model solutions in Figure 4 describe that the viral load, the infected cells and the susceptible cells are all fairly impervious to the immune response which is contradictory to the dynamics depicted in Table 2. Furthermore, Figure 4b illustrates that creatinine is sensitive to the control where in fact it should be increasing for both extremes of immunosuppression, a phenomenon not captured by the current model (1).

We also notice from the model solutions with $\epsilon_I = 1$ in Figure 4, both the BK viral load and infected cell population increase as expected, but then decrease. A large viral load indicates BK virus-associated nephropathy (viral loads $> 185,000$ copies/mL) [12], where the kidney susceptible cells are damaged due to infection. The decrease observed in Figures 4a and 4d implies that there are no more remaining susceptible cells for the virus to infect. However, we see in Figure 4c that the susceptible population remains around carrying capacity, suggesting a discrepancy between the model and biological understanding.

These findings from our analysis prompted us to delve further in understanding the biological interpretation and the parameter values for this model.

3.5. Biological interpretation of model and changes in understanding.

Based on our findings in the previous section, we renewed our effort to understand the biological interpretation of the mathematical model and analysis from [5]. Enumerated below is a list of biological discrepancies in the model.

1. The mammalian kidney is a non-regenerative organ. While the kidneys can self-repair certain small sections of the nephron, loss of nephrons due to chronic kidney injury is irreversible, resulting in permanent damage and impaired renal function [9, 14, 20]. In model (1) the logistic growth term represents the regeneration and proliferation of susceptible kidney cells. This term is not representative of the true biological phenomenon.

2. The factors contributing to the decay in the susceptible cell population as seen in (1a) are due to infection by the BK virus. However, a large population of allo-specific CD8+ T-cells also attack susceptible cells, causing a decrease in both the total $H_S$ population and kidney function (observed via creatinine levels). This biological mechanism is not captured in model (1).

3. The estimated initial condition for viral load in [5] was approximately 50,000 copies/mL which is higher than the threshold viral load for initial detection of viremia (10,000 copies/mL [12, 28, 29]). This would imply that the patient had an active viral infection just before and during their kidney transplantation.

4. Iteration II: Improved model.

4.1. Mathematical model. Based on our model analysis and our renewed biological understanding, we propose another iteration of modeling which encapsulates our new observations. The updated BKV model is presented below:

\begin{align*}
\dot{H}_S &= -\chi(E_K > E_K^*)\beta_H S E_K - \chi(V > V^*)\beta_H S V \\
\dot{H}_I &= \chi(V > V^*)\beta_H S V - \delta_H I H_I - \chi(E_V > E_V^*)\delta_{EH} E_V H_I
\end{align*}

(3a)
\[
\dot{V} = \rho_V \delta_H H_I - \delta_V V - \chi_{(V>V^*)} \beta H_S V
\]  
(3c)

\[
\dot{E}_V = (1 - \epsilon_I) [\lambda_{EV} + \rho_{EV}(V) E_V] - \delta_{EV} E_V
\]  
(3d)

\[
\dot{E}_K = (1 - \epsilon_I) [\lambda_{EK} + \rho_{EK}(H_S) E_K] - \delta_{EK} E_K
\]  
(3e)

\[
\dot{C} = \lambda_C - \delta_C(H_S) C
\]  
(3f)

where

\[
\rho_{EV}(V) = \frac{\hat{\rho}_{EV} V}{V + \kappa_V},
\]  
(3g)

\[
\rho_{EK}(H_S) = \frac{\hat{\rho}_{EK} H_S}{H_S + \kappa_{KH}},
\]  
(3h)

\[
\delta_C(H_S) = \delta_{C0} \cdot \frac{H_S}{H_S + \kappa_{CH}}.
\]  
(3i)

As before initial conditions are given by,

\[
(H_S(0), H_I(0), V(0), E_V(0), E_K(0), C(0)) = (H_{S0}, H_{I0}, V_0, E_{V0}, E_{K0}, C_0).
\]  
(3j)

Following the justification presented in Section 3.5, the logistic term in (1a) has been removed. The additional term \(\hat{\beta} H_S E_K\) represents the loss of healthy susceptible cells when under attack from allo-specific CD8 + T-cells. The parameter \(\hat{\beta}\) represents the death rate of \(H_S\) by \(E_K\). The term \(\beta H_S V\) continues to represent the infection of susceptible cells by free virions. However, we additionally assume that for trace levels of both allospecific CD8 + T-cells and viral load, the susceptible cells are not destroyed and are constant. That is, at trace population levels there is negligible interaction. We approximate this phenomenon mathematically with the following characteristic or indicator function \(\chi\)

\[
\chi(x > x^*) = \begin{cases} 
1, & \text{for } x > x^* \\
0, & \text{otherwise.} 
\end{cases}
\]  
(4)

Again we see the presence of the characteristic function with the infection term \(\beta H_S V\) in equation (3b), indicating that for low levels of viral load there is no infection. The infected cell population can also decrease due to elimination by the BK-specific CD8+T-cells at rate \(\delta_{EH}\) only when there is a sufficient number of immune cells present, hence the characteristic function. The dynamics of BK virus remain the same as in (1) except for the additional characteristic term in (3c).

The parameter \(\epsilon_I \in [0, 1]\) continues to represent the efficiency of immunosuppressive drugs where we assume a drug efficiency of 0% (\(\epsilon_I = 0\)) indicates that the treatment does not affect the immune system and a drug efficiency of 100% (\(\epsilon_I = 1\)) is the highest dose that curbs the immune response fully. However, we also know that the dosage, type, and concentration of drugs often change over the course of treatment. With devising a control problem formulation as our eventual goal in improving this model, we replace the stepwise function from the previous iteration (2) with a single control parameter, \(\epsilon_I\), which we aim to be able to control and predict over time.
In model (1) the loss of creatinine was assumed to be a function of both the susceptible cells and the allo-specific CD8+T-cells that target the kidney. Our revised model more explicitly incorporates the effect of allo-specific CD8+T-cells on the healthy susceptible cells in (3a), and thus we do not need the $E_K$ dependent decay function in (3i). Note that the model is very sensitive to the threshold concentrations, $V^*$, $E_K^*$ and $E_V^*$. We chose a $V^*$ value that was significantly below detection level for BK Virus related viremia (10,000 copies/mL [12, 28, 29]). Thresholds $E_K^*$ and $E_V^*$ were deduced from total populations of CD8+T-cells observed during numerical simulations.

A description of the state variables and parameters are given in Tables 1 and 3 respectively.

Below are the detailed justifications for parameter value changes, as shown in Table 3.

A. The value for parameter $\kappa_V$ changed from 180 to $10^6$ copies/mL. Recall that $\kappa_V$ represents the half saturation constant in the term $\rho_{EV}(V) = \frac{\bar{\rho}_{EV}V}{V + \kappa_V}$.

In Figure 4, we notice that viral loads reach approximately $4 \times 10^5$ copies/mL. If $\kappa_V << 4 \times 10^5$, $\rho_{EV}(V) \approx \bar{\rho}_{EV}$, a constant. Equivalently, if $\kappa_V \approx 4 \times 10^5$,
Table 3. Original (Iteration I) and new model (Iteration II) parameters.

| Parameter | Description | Unit | Iteration I | Iteration II | Justification |
|-----------|-------------|------|-------------|--------------|---------------|
| $\lambda_{LB}$ | Proliferation rate for $L_B$ | /day | 0.04 | - | See A |
| $\gamma$ | Half saturation constant | copies/mL | 100 | $10^6$ | |
| $\mu_{LB}$ | Saturation constant | cells/mL | 1025 | - | |
| $\beta$ | Attack rate on $L_B$ by $E_K$ | mL/(cells·day) | 0.002 | 285 | |
| $\lambda_{EK}$ | Source rate of $E_K$ | cells/(mL·day) | 0.001 | - | |
| $\rho$ | Infection rate of $E_K$ by $V$ | mL/(copies·day) | $8.22 \times 10^{-4}$ | $8.22 \times 10^{-4}$ | [4] |
| $\delta_{EK}$ | Death rate of $E_K$ | /day | 0.03 | 0.09 | |
| $\delta_{CL}$ | Death rate of $H_E$ by $V$ | /day | 0.085 | 0.085 | |
| $\kappa_{LV}$ | Production rate for $C$ | ng/(mL·day) | 0.01 | 0.01 | |
| $\rho_V$ | # Virions produced by $H_I$ before death | copies/cells | 4922.4 | 15000 | $3 - 44 000$ [16] |
| $\delta_{EV}$ | Elimination rate of $H_I$ by $V$ | mL/(mL·day) | 0.0018 | 0.0018 | |
| $\kappa_{EK}$ | Half saturation constant | cells/mL | 0.2 | - | |
| $\nu_{E}$ | Natural clearance rate of $V$ | /day | 0.04 - 0.05 | 0.04 - 0.05 | [5, 15, 16] |
| $\kappa_{CH}$ | Half saturation constant | cells/mL | 10 | $10^6$ | See A |
| $\lambda_{EV}$ | Source rate of $E_V$ | cells/(mL·day) | 0.001 | 285 | [4] |
| $\delta_{EV}$ | Death rate of $E_V$ | /day | 0.14 | 0.17 | |
| $\kappa_{EV}$ | Half saturation constant | cells/mL | 84.96 | $10^3$ | |
| $\mu_{EV}$ | Maximum proliferation rate for $E_V$ | /day | 0.25 | 0.36 | |
| $E_V^*$ | Threshold concentration of BKV specific CD8+ T-cells | cells/mL | - | 2500 | |
| $E_{V}^*$ | Threshold concentration of BKV specific CD8+ T-cells | cells/mL | - | 500 | |

Table 4. Initial conditions both original (Iteration I) and new (Iteration II).

| State | Iteration I IC | Iteration II IC | Justification |
|-------|----------------|----------------|---------------|
| $H_{E0}$ | $5 \times 10^5$ cells/mL | 1025 cells/mL | Assume $H_{E0} = \kappa_{HS}$ from [4] |
| $H_{I0}$ | 60 cells/mL | $2 \times 10^{-16}$ cells/mL | Trace infection before transplant |
| $V_0$ | $5 \times 10^5$ copies/mL | 1200 copies/mL | Minimal V of 10,000 copies/mL for low BK viremia detection [12, 28, 29] |
| $E_{K0}$ | 0.04 cells/mL | $2 \times 10^{-16}$ cells/mL | Negligible amounts of Allospecific CD8+ T-cells |
| $E_{V0}$ | 0.4 cells/mL | 100 cells/mL | Low level of BKV specific CD8+ T-cells |
| $C_0$ | 1.05 mg/dL | 0.7 mg/dL | Range 0.6 - 1.1 | [4] |

$\rho_{EV}(V) \approx \frac{\rho_{EV}}{2}$. These choices for $\kappa_V$ make the BK dependent growth rate of $E_V$ impervious to viral load values. Thus we set $\kappa_V = 10^6$ in order to capture the sensitivity of the growth rate of $E_V$ to $V$. Similarly we notice that susceptible cell populations are primarily between orders of magnitude $10^2$ cells/mL and $10^3$ cells/mL; hence, we choose $\kappa_{KH} = 10^3$ and $\kappa_{CH} = 10^4$.

B. The authors in [5] assume low source rates $\lambda_{EV}$ and $\lambda_{EK}$ for BKV specific and allospecific cells respectively, resulting in the BKV load proliferating at a much higher rate compared to the CD8+T-cells. Thus, the BKV dynamics become impervious to the immune response, rendering it insensitive to the control over time. The authors in [4] consider $\lambda_{EV} = \lambda_{EK} = 0.5$ cells/μL·blood-day. Using the conversion 1 cell/μL·blood-day = 570 cells/mL·plasma-day, we obtain $\lambda_{EV} = \lambda_{EK} = 285$ cells/mL·plasma-day.

4.2. Model analysis and biological interpretation. Figure 5 contains model solutions with parameter values in Tables 1 and 3. We examine the solutions for both models for varying levels of immunosuppressant efficiency to determine if our current mathematical model more accurately represents the biological process. The simulations show higher sensitivity to drug dosage with the modified model in Iteration II. We also notice that for the improved model for both higher and lower dosages of immunosuppressant, the kidney function fails, as seen from the rise in creatinine levels (either due to infection or rejection). There are intermediate values of immunosuppressant dosages for which the creatinine levels stay low. Lastly, we pick a low initial viral load as we assume that the transplant recipient does not have an active BKV infection just before and during transplantation. We can see
that the modified model solutions are more biologically representative of the true dynamics as described in Table 2. In Figure 5 we consistently use the following line markers to depict the curves:

\[ \begin{align*}
\text{--- } \epsilon_1 = 0.8 & \quad \text{--- } \epsilon_1 = 0.6 \\
\text{--- } \epsilon_1 = 0.4 & \quad \text{--- } \epsilon_1 = 0.2
\end{align*} \]

5. **Discussion.** To illustrate the iterative modeling process, we analyze and modify a mathematical model of the immune response in renal transplant recipients.
infected with BK virus. Motivated by the problem of implementing a control strategy for individual patients, our investigation of the preliminary model indicates a discrepancy between the model and the biological process, prompting another iteration of modeling. The modified model now represents the biological process of infection and organ rejection more accurately, as seen in Figure 5.
Future work involves possible further improvements to this model. For instance, as more data (viral load and creatinine measurements) becomes available we should obtain more confidence in the parameters. Using a diverse data set spanning over several patients one would also be able to conduct further analysis to see if the parameters change substantially for different patients. We are currently exploring the specific effects of individual immunosuppressant drugs on the mechanisms of the immune response by understanding how each of these drugs individually and in combination with others inhibit the functioning of the CD8+ T-cells. This might lead to an improvement in the understanding of how immunosuppressed CD8+ T-cells grow and decay in the presence of foreign cells, and in turn might lead to another iteration of modeling.

With this new model, we are now currently developing the adaptive optimal control problem to determine the optimal level of immunosuppressive therapy for individual patients to balance over-suppression and under-suppression. The authors in [4] present this control problem in the context of HCMV-infected kidney transplant recipients. Unlike HCMV infection, the lack of an approved antiviral therapy for symptomatic BKV nephropathy makes the task of carefully monitoring the level of immunosuppression an even more challenging but imperative one.

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E-mail address: nnumrad@ncsu.edu
E-mail address: reverett@haverford.edu
E-mail address: tran@ncsu.edu
E-mail address: htbanks@ncsu.edu
E-mail address: EROSENBERG1@mgh.harvard.edu