Computers and Mathematics with Applications 71 (2016) 2338–2351

Contents lists available at ScienceDirect

Computers and Mathematics with Applications

journal homepage: www.elsevier.com/locate/camwa

Feedback control of the immune response of renal transplant recipients with inequality constraints

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ARTICLE INFO

Article history:
Available online 2 January 2016

Keywords:
Feedback control
Model predictive control
Inequality constraint
Extended Kalman filter
Ensemble Kalman filter
Renal transplant

ABSTRACT

This paper describes a model of the immunologic response of latent viruses and a donor kidney in a renal transplant recipient. An optimal control problem with state variable inequality constraints is considered to maintain the balance between over-suppression where latent viruses are reactivated and under-suppression where the transplanted kidney is rejected. A feedback methodology based on the model predictive control (MPC) method is proposed to design (sub)optimal treatment regimes. In addition, the problem of implementing the MPC methodology and nonlinear Kalman filter with inaccurate or incomplete observation data and long measurement periods is addressed. The results of numerical simulations show that a (sub)optimal dynamic immunosuppression therapy method can help strike a balance between the over-suppression and under-suppression of the immune system.

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1. Introduction

Based on the United States Renal Data System's (USRDS) 2013 Annual Data Report [1], approximately 616,000 patients received their treatment for end-stage renal disease (ESRD) in 2011 in the US, and 116,000 began their treatment in the same year. In addition, there were almost 11 times more patients treated for ESRD in 2011 than in 1980. ESRD is the complete or almost complete failure of the kidney. Common symptoms of the disease include fatigue, headaches, weight loss without trying, the loss of appetite, and nausea, among others. Dialysis or kidney transplantation is the best treatment for the disease. Based on the Organ Procurement and Transplantation Network (OPTN) data [2], there were 15,412 cases of renal transplantation in the US in 2013.

In general, the recipient's immune system is a major obstacle to renal transplantation between genetically non-identical patients. The immune system treats a donor kidney as a non-self and immediately or chronically rejects it. Therefore, the lifelong administration of some immunosuppressive drug is essential to reduce the risk of rejection. However, immunosuppression therapy methods can make transplant recipients much more susceptible to opportunistic infections and reactivate latent viruses such as human cytomegalovirus (HCMV) and the Epstein–Barr virus (EBV) and so on. Severely immunosuppressed patients have an HCMV disease that can be defined as the active infection of HCMV, whereas the disease rarely occurs in immunocompetent patients. HCMV infection is a serious threat to recipients of kidney transplants and graft health [3,4]. In the absence of any antiviral therapy, an active HCMV infection occurs in approximately 75% of all organ

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http://dx.doi.org/10.1016/j.camwa.2015.12.020
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Table 1
Descriptions of state variables.

States	Description (concentration)	Units
S	Susceptible cells	Cells/μL-blood
I	Infected cells	Cells/μL-blood
V	Free HCMV	Copies/μL-blood
E_V	HCMV-specific CD8+ T cells	Cells/μL-blood
E_K	Allospecific CD8+ T cells that targets kidney	Cells/μL-blood
C	Serum creatinine	mg/dL

transplant recipients in the first year, and HCMV infection can reduce the survival rate in transplant patients [5,6]. Therefore, it is crucial for renal transplant recipients to achieve a delicate balance between over-suppression (reactivation of the latent virus HCMV) and under-suppression (rejection of the transplanted kidney). Unfortunately, however, there is no general consensus on which immunosuppressive strategies are optimal. Each transplant center establishes its own guidelines for the immunosuppressive strategies based on its experience and local preferences.

Mathematical models provide powerful tools for understanding many complex biological systems and investigating disease dynamics and control. This paper explores optimal immunosuppressive treatment schemes using a mathematical model describing the dynamics of the immune response to the HCMV infection in conjunction with optimal control theory. Many researchers have started to explore optimal control theory with mathematical models to suggest optimal treatment strategies for HIV, tuberculosis, and vector-born diseases, among others [7,8,3,9,10]. Some have investigated feedback control that can be determined in a real-time fashion based on full or partial observations of the state [11–14]. While existing control studies have focused only on minimizing or maximizing a cost functional to derive optimal treatment schemes, this paper considers an optimal control problem with state variable inequality constraints to maintain a good balance between over-suppression and under-suppression. In addition, the paper performs a qualitative analysis of a mathematical model and proposes a feedback methodology based on both model predictive control (MPC) and nonlinear Kalman filter to overcome some shortcomings induced by low-frequency sampling and incomplete observations. MPC, also known as receding horizon control (RHC), solves a finite-horizon open-loop control problem iteratively such that the current state is sampled at the measurement time [15]. Several studies provide a good overview of theoretical and practical viewpoints associated with MPC [16–19]. To apply the MPC method, full information on the current state is required. In a clinical setting, however, only partial information on the state is given because of a lack of technical skills to quantify all state variables. To address this issue, this paper employs nonlinear Kalman filtering methodologies, namely the extend Kalman filter (EKF) and the ensemble Kalman filter (EnKF). The EKF and EnKF are recursive algorithms that produce estimates of the optimal state of the nonlinear system by using a series of observed data with noise [20,21].

The rest of this paper is organized as follows: Sections 2 and 3 introduce and analyze a mathematical model describing the dynamics of the immune response to both the HCMV infection and a donor kidney in a renal transplant recipient. Section 4 formulates an optimal control problem with state variable inequality constraints and then derives a new optimal control problem with a modified objective functional that minimizes the systemic cost of immunosuppressive drugs and penalty terms. In addition, the section addresses a feedback control problem based on both the MPC and the nonlinear Kalman filters to derive the best immunosuppressive strategies. Section 5 presents the results of numerical simulations demonstrating a good balance between over-suppression and under-suppression, and Section 6 concludes.

2. The model

The model describes the dynamics of the immune response to both the HCMV infection and a donor kidney in a renal transplant recipient [3]. Table 1 shows the state variables in the model.

The model is given by the following system of ordinary differential equations:

$$\begin{aligned}
\dot{S} &= \lambda_S \left(1 - \frac{S}{\kappa_S}\right) S - \beta S V \\
\dot{I} &= \beta S V - \delta_I I - m E_V I \\
\dot{V} &= \rho_V \delta_I I - \delta_V V - \beta S V \\
\dot{E_V} &= (1-\epsilon)\left[\lambda_{EV} + \frac{\rho_{EV} V}{V + \kappa_V} E_V\right] - \delta_{EV} E_V \\
\dot{E_K} &= (1-\epsilon)\lambda_{EK} - \delta_{EK} E_K \\
\dot{C} &= \lambda_C - \frac{\delta_C \kappa_{EK}}{E_K + \kappa_{EK}} C,
\end{aligned} \tag{2.1}$$

with the initial condition $(S(0), I(0), V(0), E_V(0), E_K(0), C(0))^T$.

Susceptible cells S follow a logistic growth function with the carrying capacity κ_S and the intrinsic increasing rate λ_S in the absence of any infection. If they become infected by HCMV, then the loss rate of susceptible cells can be denoted by βSV.

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