and determined both uninfected and infected steady-states. They utilized a model predictive control (MPC) method as an optimal strategy to achieve a balance between over-suppression and under-suppression.

In this research work, we propose a nonlinear integral sliding-mode control scheme for the first time based on the model developed in [40] to adjust the viral load and serum creatinine of the blood to satisfy standard clinical limitations. Using the proposed controller, the nonlinear behavior of this infection is taken into account in defining the control law for the immunosuppressive drug without any linearization of the model. The proposed method facilitates tracking of any desired concentration of $CD8^+$ T cells as an immune response that specifically targets the kidney in order to maintain the serum creatinine concentration below an acceptable clinical limit during the treatment period. The performance of closed-loop dynamics in the presence of different parameter values is evaluated and the robustness of the controller is shown for various cases via comprehensive sensitivity analysis.

In Section 2, the HCMV dynamic model is presented and relationships between its state variables and parameters are explained. The controller design and Lyapunov stability proof are formulated and described in Section 3. Simulations and numerical results for primary and reactivation cases, required control inputs, sensitivity analysis of the model parameters, and discussion on the antiviral therapy are mentioned in Section 4. Concluding remarks are finally explained in Section 5.

2. MATHEMATICAL MODEL OF TRANSPLANT RECIPIENTS

The dynamic model described in [40] is used here to analyze the HCMV infection in transplant recipients:

$$\dot{S} = \lambda_s\left(1-\frac{S}{\kappa_s}\right)S - \beta SV \tag{1}$$

$$\dot{I} = \beta SV - \delta_I I - mE_v I \tag{2}$$

$$\dot{V} = \rho_V \delta_I I - \delta_V V - \beta SV \tag{3}$$

$$\dot{E}_v = (1-\varepsilon)\left[\lambda_{EV} + \frac{\rho_{Ev} V}{V+\kappa_V}E_v\right] - \delta_{Ev}E_v \tag{4}$$

$$\dot{E_K} = (1-\varepsilon)\lambda_{EK} - \delta_{EK}E_K \tag{5}$$

$$\dot{C} = \lambda_C - \frac{\delta_C \kappa_{EK}}{E_K+\kappa_{EK}}C, \tag{6}$$

where $S(t)$ is the concentration of susceptible cells (Cells/μL-blood), $I(t)$ is the concentration of infected cells (Cells/μL-blood), $V(t)$ is the concentration of free HCMV (Copies/μL-blood), $E_v(t)$ is the concentration of HCMV-specific $CD8^+$ T cells (Cells/μL-blood), $E_K(t)$ is the concentration of allospecific effector $CD8^+$ T cells that specifically target kidney (Cells/μL-blood), and $C(t)$ is the serum creatinine concentration (mg/dL). It is clear that Eqs. (1)–(4), presenting the response of the immune system to the viral load, are coupled with Eqs. (5), (6), presenting the response of the immune system to the newly transplanted kidney [39].

The term βSV in Eqs. (1), (3) stands for the loss rate of both susceptible cells and viral load, in which they will be transformed into the infected ones in Eq. (2). If there is no virus, susceptible cells grow normally with the rate of $\lambda_s(1 - S/\kappa_s)S$. The terms $\delta_I I$ and $\delta_V V$ represent the natural death rate of infected cells and viruses, respectively. Moreover, infected cells' population decreases due to the immune response (E_v) against HCMV with the term mE_vI in Eq. (2). Also, the viral load increases with the death of infected cells through the term $\rho_V\delta_I I$ in Eq. (3). ε is the normalized control input acting as the immunosuppressive drug dosage per day, which reduces the immune system response affecting Eqs. (4), (5) in order to maintain the creatinine concentration (C) below its threshold for ideal kidney performance. Immune response (E_v) against HCMV increases in two ways; naturally with the rate λ_{EV} and also by acting against the viral load with the term $(\rho_{Ev}V/V+\kappa_V)E_v$, while its natural death rate is $\delta_{Ev}E_v$. Allospecific immune effector cells (E_K) have natural birth and death rates modeled with the terms λ_{EK} (related to the human leukocyte antigen system) and $\delta_{EK}E_K$, respectively. The serum creatinine level of the blood (C) is a measure for kidney performance. λ_C and $\delta_C\kappa_{EK}C/(E_K+\kappa_{EK})$ represent its production rate and death rate (in terms of the allospecific $CD8^+$ T cells' activity, E_K), respectively. Note that this model does not consider the HCMV-specific $CD4^+$ T cells for simplicity and the total period of treatment is considered 450 days [40]. The numerical values of the mentioned parameters are extracted from [40] and described in Table 1.

3. CONTROL SCHEME

In this section, the proposed sliding mode controller (SMC) is described to obtain a balance between normal kidney performance and proper immune system defence against the viral load. To achieve this goal, two constraints are defined on the state variables $V(t)$ (viral load) and $C(t)$ (serum creatinine of blood) that should be less than their defined thresholds to ensure that 1. viruses will not make dangerous situation and 2. the transplanted kidney is working properly.