TABLE 1
Parameters Values of the HCMV Dynamic Model for Kidney Transplantation [40].

Parameters	Value
λ_s	10^{-3} per day
κ_s	400 cells/μL-blood
β	2×10^{-4} μL-blood/(copies day)
δ_I	0.2 per day
m	0.048571 μL-blood/(cells day)
ρ_V	9.6 copies/cells
δ_V	0.2 per day
λ_{EV}	0.5 cells/(μL-blood day)
ρ_{Ev}	1 per day
κ_V	20 copies/μL-blood
δ_{Ev}	0.05 per day
λ_{EK}	0.5 cells/(μL-blood day)
δ_{EK}	0.1 per day
λ_C	0.2 mg/(dL day)
κ_{EK}	8 cells/μL-blood
δ_C	0.2 per day

3.1. Design of an Integral Sliding Mode Controller

A proper SMC firstly needs a definition for the sliding surface, which its stability could be proven by the Lyapunov theorem. In this work, an integral sliding surface is formulated in terms of tracking error as follows:

$$s = \tilde{e} + \int_0^t \tilde{e}\, dt, \tag{7}$$

which $\tilde{e} = E_K - E_{Kd}$ is the tracking error with respect to the desired concentration of allospecific effector CD8$^+$ T cells (E_{Kd}). The main characteristic of this sliding surface is having a stable behaviour for the error dynamics. Therefore, the control law is developed such that the system response tends to this stable surface. Due to the existence of one control input as the immunosuppressive drug dosage, only one desired trajectory for E_K is defined based on [26]:

$$E_{Kd} = \left(E_{K0} - E_{Kf}\right) \exp(-at) + E_{Kf} \tag{8}$$

such that the constraint for being below the threshold value of 1.2 for $C(t)$ [40] is satisfied. Therefore, we consider $C_f = 1.1875$ as the final steady-state value to make sure that it will be less than the mentioned threshold.

TABLE 2
Magnitudes of Desired Parameters in Eqs. (8) and (9).

Parameters	Value
E_{Kf}	1.5
C_f	1.1875
a	0.12

Accordingly, the final magnitude of E_K is obtained based on Eq. (6) as

$$0 = \lambda_C - \frac{\delta_C \kappa_{EK}}{E_{Kf} + \kappa_{EK}} \times 1.1875 \rightarrow E_{Kf} = 1.5 \tag{9}$$

where E_{K0} and E_{Kf} are the initial and final (steady-state) values of allospecific CD8$^+$ T cells, respectively. The magnitudes of these desired values are presented in Table 2, where C_f is the final value of the serum creatinine in blood and a is the reduction rate of E_K in Eq. (8) during the treatment period.

3.2. Lyapunov Stability Proof

Now, we consider a quadratic Lyapunov function candidate V in terms of distance from the sliding surface as follows:

$$V = \frac{1}{2} s^2, \tag{10}$$

in which s is the sliding surface defined in (7). The Lyapunov candidate (10) is positive definite, and it is needed to be proven that its time derivative is negative definite:

$$\dot{V} = s\dot{s} = s(\dot{e} + e) = s\left(\dot{E}_K - \dot{E}_{K_d} + E_K - E_{Kd}\right) \tag{11}$$

For this purpose, we design the control input ε such that $\dot{V} \leq -\eta s \tanh(s)$, which η is a positive constant. As a result, we first obtain $\varepsilon_{\mathrm{eq}}$ that makes $\dot{s} = 0$ based on Eqs. (5), (8), and (11):

$$\varepsilon_{eq} = \frac{\lambda_{EK} - \delta_{EK} E_K + a\left(E_{K0} - E_{Kf}\right)\exp(-at) + E_K - \left(E_{K0} - E_{Kf}\right)\exp(-at) - E_{Kf}}{\lambda_{EK}} \tag{12}$$

This control signal will lead the system to reach the desired trajectory. However, it works when the system is on the sliding surface, in the absence of any disturbances. Thus, to obtain the desired value for $\dot{V}$ to guarantee the stability, the following controller is proposed:

$$\varepsilon = \varepsilon_{eq} + \frac{k}{\lambda_{EK}} \tanh(s), \tag{13}$$