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Introduction

HIV is a viral infection that attacks the body's immune system. Although antiretroviral therapy is currently used to maintain a low viral load, no cure has been discovered for HIV. This research sought to explore a combination of gene therapy and latency reversing agents as a potential functional cure for HIV patients. We begin by building a system of differential equations to model an HIV infection under the combined treatment of CRISPR-Cas9 gene therapy, latency reversing agents (LRA), and antiretroviral therapy (ART). We then solve the corresponding optimal control problem to seek a functional cure by extending the remission time between treatments. The model presented below, based on the work found in [1, 2], describes the interactions between $CCR5^-$ cells, T_u, $CCR5^+$ cells, T_S, latently infected cells, L, actively infected cells I, and free virions V.

The Model

$$\frac{dT_u}{dt} = \lambda f - \delta_T T_u$$

$$\frac{dT_s}{dt} = \lambda(1-f) - \delta_T T_s - \beta T_S V$$

$$\frac{dL}{dt} = \epsilon\beta T_s V - (\alpha+\eta+\delta)L + \gamma I$$

$$\frac{dI}{dt} = (1-\epsilon)\beta T_s V - (\delta+c+\gamma)I + (\alpha+\eta)L$$

$$\frac{dV}{dt} = pI - cV$$

Basic Reproductive Ratio

We denote the disease-free equilibrium by $E_0 = (T_u^0, T_s^0, 0, 0, 0) = \left(\frac{\lambda f}{\delta_T}, \frac{\lambda(1-f)}{\delta_T}, 0, 0, 0\right)$ and calculate $\mathcal{R}_0$ using the next generation matrix method:

$$\mathcal{R}_0 = \frac{\beta\lambda p(1-f)(\alpha+\eta+\delta(1-\epsilon))}{\delta_T\delta_V((\alpha+\eta+\delta)(c+\delta)+\delta\gamma)}.$$

Global Stability

Theorem: When $\mathcal{R}_0 \leq 1$, the disease free equilibrium $(T_u^0, T_s^0, 0, 0, 0)$ is globally asymptotically stable.

To prove this theorem, we constructed the following Lyapunov function

$$\mathcal{L}(T_u, T_s, L, I, V) = \left(T_u - T_u^0 - T_u^0 \ln\left(\frac{T_u}{T_u^0}\right)\right) + \left(T_s - T_s^0 - T_s^0 \ln\left(\frac{T_s}{T_s^0}\right)\right)$$
$$+ \frac{\alpha+\eta}{\alpha+\eta+(1-\epsilon)\delta} L + \frac{\alpha+\delta+\eta}{\alpha+\eta+(1-\epsilon)\delta} I + \frac{\beta\lambda(1-f)}{\delta_T\delta_V} V.$$

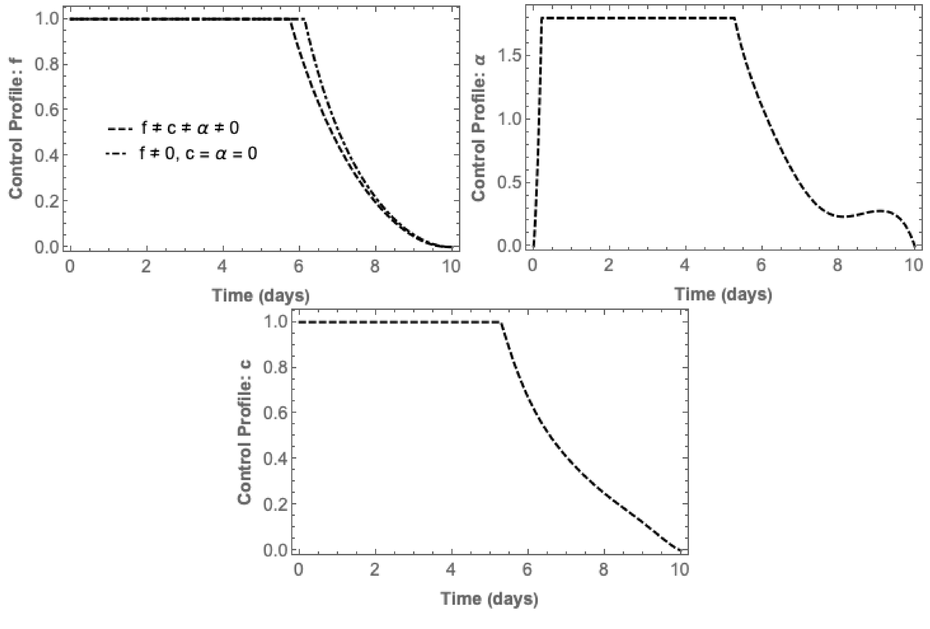
Theorem: When $\mathcal{R}_0 > 1$, the endemic equilibrium, denoted by $(T_u^*, T_s^*, L^*, I^*, V^*)$, is globally asymptotically stable.

To prove this theorem, we constructed a Lyapunov function similar to the one above:

$$\mathcal{L} = \left(T_u - T_u^* - T_u^* \ln\left(\frac{T_u}{T_u^*}\right)\right) + \left(T_s - T_s^* - T_s^* \ln\left(\frac{T_s}{T_s^*}\right)\right) + \left(\frac{\alpha+\eta}{\alpha+\eta+(1-\epsilon)\delta}\right)\left(L - L^* - L^* \ln\left(\frac{L}{L^*}\right)\right)$$
$$+ \left(\frac{\alpha+\eta+\delta}{\alpha+\eta+(1-\epsilon)\delta}\right)\left(I - I^* - I^* \ln\left(\frac{I}{I^*}\right)\right) + \left(\frac{\beta T_s^*}{\delta_V}\right)\left(V - V^* - V^* \ln\left(\frac{V}{V^*}\right)\right).$$

Optimal Control

Emphasizing a reduction in the latent reservoir, we find the following optimal functions $f(t), \alpha(t)$, and $c(t)$ that minimize the cost and side effects of gene therapy and LRA efficacy.



Numerical Results

Our simulations found that an optimal efficacy of gene therapy alone reduces the viral load by roughly 15% while a combination treatment of gene therapy and LRA reduces the viral load by roughly 50%. Additionally, we found that the latent reservoir was reduced by roughly 20% with gene therapy alone, but with a combination treatment strategy, the latent reservoir was reduced by a capacity of 80%.

Conclusion

Our results suggest that the use of gene therapy in conjunction with LRA and ART treatments could provide longer remission times compared to only one treatment option on its own. Current feasible remission times for individuals undergoing ART therapy is around seven days [1]. This fast relapse time creates a situation where individuals are forced to constantly stay on ART therapy. However, if the remission time could be prolonged, it could provide the opportunity for an individual with HIV to forgo ART treatment for a noticeable period of time. In future research, we hope to look at adding on other treatment strategies from [1] in combination with gene therapy and/or LRA treatment to compare the prolonged remission time found here with other potential treatments.

Acknowledgements

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