Neural network controller vs pulse control to achieve complete eradication of cancer cells in a mathematical model

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1. Introduction

In this work, we study the global dynamics of a mathematical model of tumor-immune interactions developed by de Pillis *et al*. [1]. This model describes the dynamics of cancer cells, $T(t)$; natural killer (NK) cells, $N(t)$; and CD8⁺T effector cells, $L(t)$. The interactions of these cells' populations are given by the following set of ODEs:

$$\frac{dT}{dt} = aT(1 - bT) - cNT - D, \tag{1}$$

$$\frac{dN}{dt} = \sigma - fN + \frac{gT^2}{h+T^2}N - pNT, \tag{2}$$

$$\frac{dL}{dt} = -mL + \frac{jD^2}{k+D^2}L - qLT + rNT + s_L, \tag{3}$$

where

$$D = \frac{dL^\lambda}{sT^\lambda + L^\lambda}T.$$

Additionally, to explore the evolution of the system in presence of a treatment, we introduce into Equation (3) the adoptive cellular immunotherapy parameter s_L. This parameter allow us to control the cancer cells by the external treatment application. It is important to notice that $T = 0$ is considered a tumor-free state. Hence, we can obtain by an algebraic process the following tumor-free equilibrium point:

$$(T^*, N^*, L^*) = \left(0, \frac{\sigma}{f}, \frac{s_L}{m}\right).$$

Also, is important to consider that the dynamics of the system (1)-(3) is located in the nonnegative octant defined by

$$R^3_{+,0} = \{T(t), L(t) \geq 0, N(t) > 0\}.$$

[1] L. de Pillis, A. Radunskaya, C. Wiseman, "A validated mathematical model of cell-mediated immune response to tumor growth", Cancer research, 65(17), pp. 7950-7958, 2005.

Assumption

If a solution describing the growth of a cell population goes below the value of 1 cell, then it is possible to assume the complete eradication of such population [2].

[2] Valle Paul A., Coria Luis N., Plata Corina. Personalized Immunotherapy Treatment Strategies for a Dynamical System of Chronic Myelogenous Leukemia. Cancers 13.9 (2021): 22 pages.

2. Localization of compact invariant sets

Localizing domain. *If conditions $f - g > 0$ and $m - j > 0$ are fulfilled, then all compact invariant sets for the cancer-immunotherapy mathematical model (1)-(3) are located either inside or at the boundaries of the domain [3]:*

$$K_\Gamma = K_T \cap K_N \cap K_L,$$

where

$$K_T = \left\{0 \leq T(t) \leq T_{sup} = T_{max} - \frac{cN_{inf}}{ab} - \frac{dL^\lambda_{inf}}{sT^\lambda_{max} + L^\lambda_{inf}}\right\},$$

$$K_N = \left\{N_{inf} = \frac{\sigma}{f + pT_{max}} \leq N(t) \leq N_{sup} = \frac{\sigma}{f - g}\right\},$$

$$K_L = \left\{L_{inf} = \frac{s_L}{m + qT_{max}} \leq L(t) \leq L_{sup} = \frac{s_L + rN_{sup}T_{max}}{m - j}\right\},$$

$$T_{max} = \frac{1}{b}.$$

[3] Valle, P. A., Coria, L. N., Plata, C. and Salazar, Y., CAR-T Cell Therapy for the Treatment of ALL: Eradication Conditions and In Silico Experimentation, Hemato, Vol. 2, No. 3, pp. 441-462, 2021.

3. Tumor eradication and asymptotic stability

Applying the Lyapunov's direct method [4], we propose the following candidate Lyapunov function $h_4 = T$, and by computing its Lie derivative we obtain that $L_f h_4(0) = 0$ and $L_f h_4 < 0$ if the next condition holds

$$s_L > \frac{\rho_1}{b^2}\left(\frac{\rho_2 s}{1 - \rho_2}\right)^\lambda, \tag{4}$$

where

$$\rho_1 = bm + q,$$

$$\rho_2 = \frac{a}{d} - \frac{cb\sigma}{d(p + bf)},$$

and the condition $1 - \rho_2 > 0$ is also fulfilled. These results allows us to propose the next statement.

Asymptotic stability. *If conditions (4) and $1 - \rho_2 > 0$ hold, then the cancer cells population described by system (1)-(3) is eradicated by the immunotherapy treatment. The latter implies asymptotic stability to the plane $T = 0$.*

[3] Khalil, H. K., Nonlinear systems, Prentice-Hall, 3rd edn., 2002.

4. Neural network controller

In order to estimate a value of the immunotherapy treatment s_L capable of eradicate the tumor cells, we propose a one-layer functional-link neural network controller with 10 neurons on its hidden layer, designed by applying the neural network approximation property and Lyapunov's stability theory [5]. We obtain the following control law and neural network weight tuning algorithms

$s_L = \widehat{W}^T\phi(x) + K_v r$, with an activation function $\phi(x) = tanh(x)$,

$\dot{\widehat{W}} = H\phi(x)r^T$, with H a positive definite design matrix,

where

$$e = T - T_d,$$

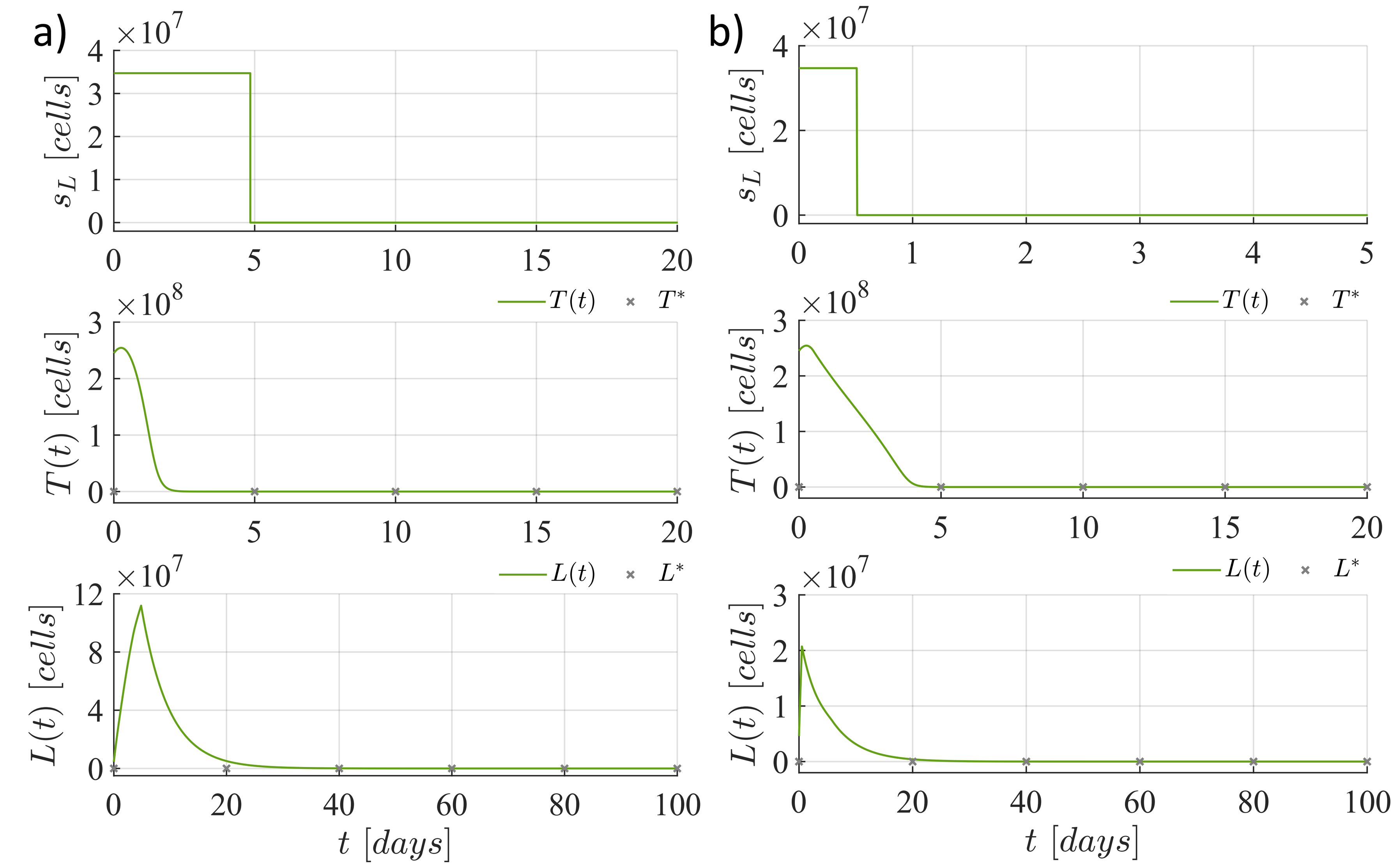
$$r = \dot{e} + \Lambda e,$$

$$K_v r = K_v\dot{e} + K_v\Lambda e.$$

[4] Lewis, F., Jagannathan, S. and Yesildirak, A., Neural network control of robot manipulators and non-linear systems, CRC Press, 1998.

5. Conclusions

By applying the LCIS method and Lyapunov's stability theory, we derive sufficient conditions on the parameter s_L to achieve tumor clearance and asymptotic stability of the tumor-free equilibrium point. As shown in Figure 1, all strategies are capable to eliminate cancer cells population, once the tumor is eradicated the treatment is turned off, $s_L = 0$, then the solutions of the system converges to the tumor-free equilibrium point. As shown in Table 1, our results suggest that a pulse application satisfying the condition (4) reduces the adoptive cellular immunotherapy treatment consumption considerably. Secondly, the neural network controller estimates a bigger initial doses, then the treatment value approaches to 0 and the tumor cells decrease until its eradication. Nonetheless, further investigation is needed to properly formulate an administration protocol for the therapy.



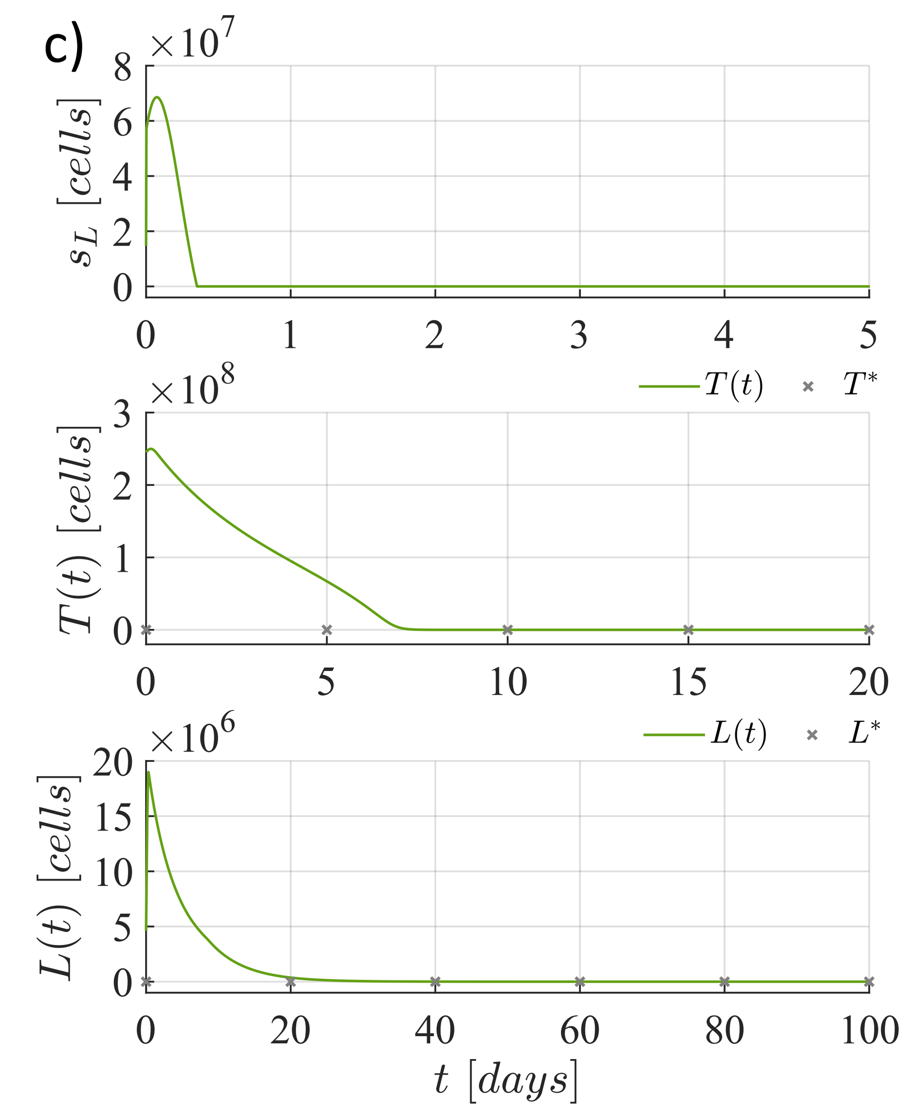


Figure 1. To illustrate our results, we propose and initial condition for cancer cells $T(0) = 2.451 \times 10^8$ and the following treatment application methods:
a) Immunotherapy treatment applied constantly satisfying conditions for asymptotic stability until cancer cells eradication.
b) Immunotherapy treatment applied by a pulse satisfying conditions for asymptotic stability.
c) Immunotherapy treatment applied is the value s_L estimated by the neural network controller with $K_v = 0.6$, $\Lambda = 0.1$ and $T_d = 0$.

Table 1. Comparison between treatment application strategies.

Application method	Total treatment supplied	Days to achieve cancer eradication
Constant application	1.682×10^8 *cells*	4.85 *days*
Application by a pulse with 51.2% duty cycle	1.778×10^7 *cells*	6.98 *days*
Treatment estimated by the neural network controller	1.558×10^7 *cells*	9.84 *days*

Acknowledgments

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