Chemoimmunotherapy treatment strategies on a mathematical model of cancer evolution

TECNOLÓGICO NACIONAL DE MÉXICO

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Mathematical model of cancer with chemoimmunotherapy

The mathematical model of cancer chemoimmunotherapy presented by de Pillis et al. [1] describes the dynamics between the population of tumor cells $T(t)$, the NK cells $N(t)$, the effector cells $L(t)$, the circulating lymphocytes $C(t)$, the concentration of the chemotherapy drug (doxorubicin) $M(t)$ and the IL-2 (interleukin-2) $I(t)$.

$$\dot{T} = aT(1-bT) - cNT - DT - K_T(1-e^{-\delta_T M})T, \quad (1)$$

$$\dot{N} = f\left(\frac{e}{f}C - N\right) - pNT + \frac{p_N NI}{g_N + I} - K_N(1-e^{-\delta_N M})N, \quad (2)$$

$$\dot{L} = \frac{\theta mL}{\theta + I} + j\frac{T}{k+T}L - qLT + (r_1 N + r_2 C)T - \frac{uL^2 CI}{\kappa + I} - K_L(1-e^{-\delta_L M})L + \frac{p_I LI}{g_I + I} + v_L, \quad (3)$$

$$\dot{C} = \beta\left(\frac{\alpha}{\beta} - C\right) - K_C(1-e^{-\delta_C M})C, \quad (4)$$

$$\dot{M} = -\gamma M + v_M, \quad (5)$$

$$\dot{I} = -\mu_I I + \phi C + \frac{\omega LI}{\zeta + I} + v_I, \quad (6)$$

where $D = \frac{dL^l}{sT^l + L^l}$.

The dynamics of the system (1)-(6) is located in the non-negative ortant:

$$\boldsymbol{R}^6_{+,0} = \{T \geq 0, N \geq 0, L \geq 0, C \geq 0, M \geq 0, I \geq 0\}.$$

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 [2,4].

References

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Acknowledgments

This work was supported by TecNM with project number 9951.21-P titled "Computational modelling and in silico experimentation applied to the analysis and control of biological systems" (Modelizado computacional y experimentos in silico aplicados al análisis y control de sistemas biológicos).

Asymptotic stability at the tumor-free equilibrium point

We apply the Lyapunov's direct method [3] to establish sufficient conditions to ensure the elimination of the tumor in the chemoimmunotherapy system (1)-(6). For this, we propose the candidate Lyapunov function $h_6 = T$ and determine the Lie derivative as follows:

$$L_f h_6 = \left[a - abT - cN - \frac{dL^l}{sT^l + L^l} - K_T\left(1 - e^{-\delta_T M}\right)\right]T.$$

In addition, it is observed that $L_f h_6$ is negative definite, i.e., $L_f h_6 \leq 0$, if the following condition is fulfilled:

$$a - abT - cN - \frac{dL^l}{sT^l + L^l} - K_T\left(1 - e^{-\delta_T M}\right) < 0.$$

Considering the following statements about the boundaries of the populations of lymphocytes, NK and T cells, it is possible to obtain the solution of the inequality

$$C_{inf} \geq C_{inf^-} = \frac{\alpha}{\beta + K_C}, \qquad C_{sup} \leq C_{sup^+} = \frac{\alpha}{\beta},$$

$$N_{inf} \geq N_{inf^-} = \frac{eC_{inf^-}}{f + pb^{-1} + K_N}, \qquad N_{sup} \leq N_{sup^+} = \frac{eC_{sup^+}}{f - p_N},$$

$$L_{inf} \geq L_{inf^-} = \sqrt{\frac{v_L}{\sigma_6} + \frac{\sigma_7^2}{4\sigma_6^2}} - \frac{\sigma_7}{2\sigma_6}, \qquad \sigma_6 = uC_{sup^+},$$

$$\sigma_7 = qb^{-1} + K_L.$$

and accordingly, the next negative upper limit is defined for $L_f h_6$

$$L_f h_6 \leq \left[a - cN_{inf^-} - \frac{dL^l_{inf^-}}{sb^{-l} + L^l_{inf^-}} - K_T\left(1 - e^{-\delta_T M_{inf}}\right)\right]T \leq 0.$$

One can solve the following inequality with respect to the two treatment parameters and get the next two cases:

$$a - cN_{inf^-} - \frac{dL^l_{inf^-}}{sb^{-l} + L^l_{inf^-}} - K_T\left(1 - e^{-\delta_T M_{inf}}\right) < 0.$$

Case 1: With respect to chemotherapy treatment v_M:

$$v_M = M_{inf} > \frac{1}{\delta_T}\ln\left[-1 + \frac{a}{K_T} - \frac{cN_{inf^-}}{K_T} - \frac{dL^l_{inf^-}}{K_T\left(sb^{-l} + L^l_{inf^-}\right)}\right], \quad (7)$$

By replacing the value of the parameters, we obtain

$$v_M > v_{M_{inf}} = 0.3556 \ \frac{mg}{l \times day}.$$

Case 2: With respect to immunotherapy treatment v_L:

$$v_L > \frac{u\alpha}{\beta}\left[\sqrt[l]{\frac{sb^{-l}(f + pb^{-1} + K_N)(\beta + K_C)\left[a - K_T\left(1 - e^{-\delta_T v_M}\right)\right] - sb^{-l}ce\alpha}{(f + pb^{-1} + K_N)(\beta + K_C)\left[d - a - K_T\left(1 - e^{-\delta_T v_M}\right)\right] + ce\alpha}}\right]^2 \quad (8)$$

$$+ \left[\sqrt[l]{\frac{sb^{-l}(f + pb^{-1} + K_N)(\beta + K_C)\left[a - K_T\left(1 - e^{-\delta_T v_M}\right)\right] - sb^{-l}ce\alpha}{(f + pb^{-1} + K_N)(\beta + K_C)\left[d - a - K_T\left(1 - e^{-\delta_T v_M}\right)\right] + ce\alpha}}\right](qb^{-1} + K_L),$$

By replacing the value of the parameters, we obtain

$$v_L > v_{L_{inf}} = 8.5455 \times 10^8 \ \frac{cells}{l \times day}.$$

Asymptotic stability

If conditions (7) and (8) are met, then the tumor cell population is eradicated by the combined chemoimmunotherapy treatment. The latter implies asymptotic stability to plane $T = 0$.

In silico experimentation

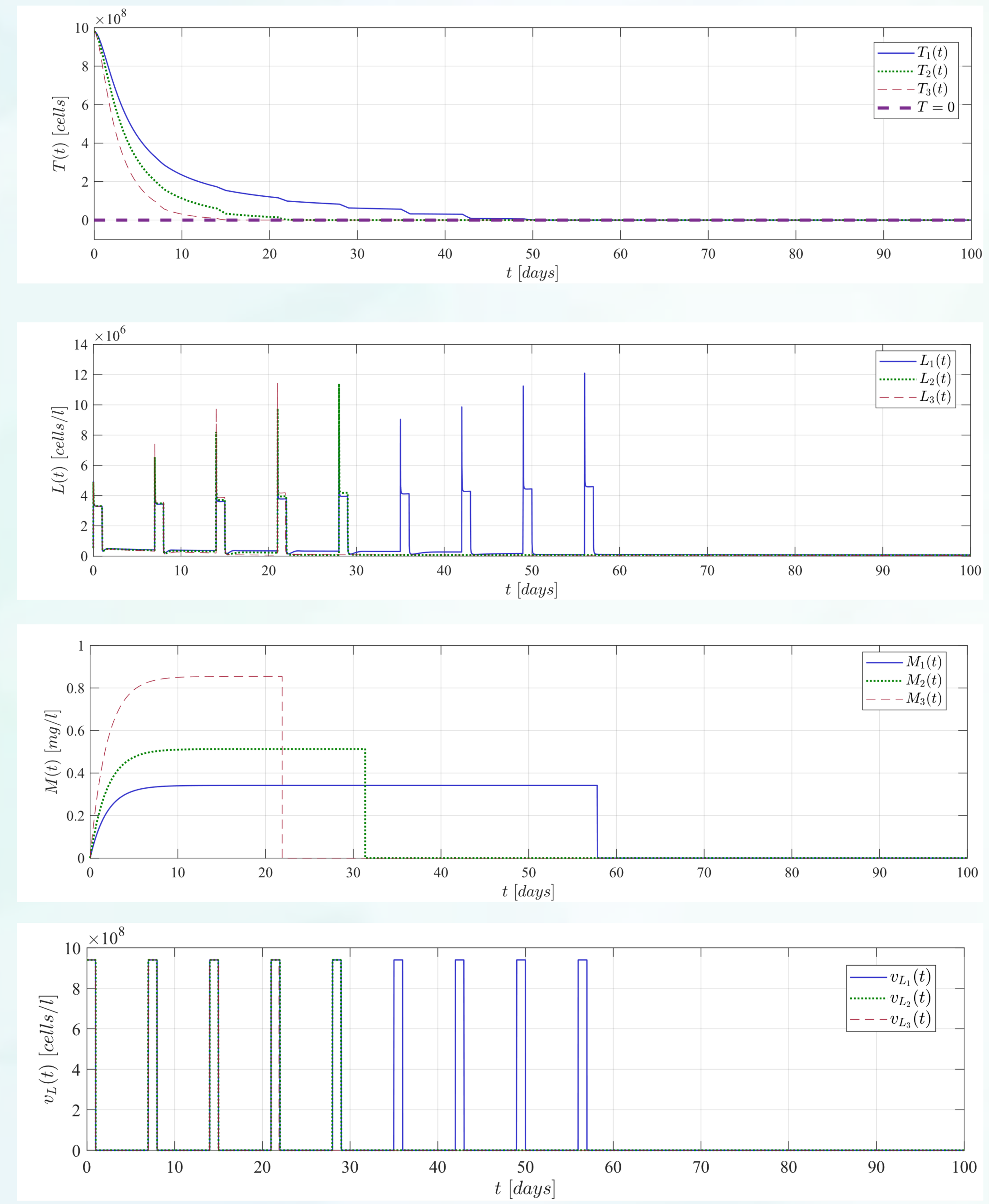

Figure 1. Elimination of tumor cells when the chemotherapy treatment is applied at a concentration of $0.5 \ v_{M_{inf}}$ in $M_1(t)$, $0.75 \ v_{M_{inf}}$ in $M_2(t)$ and $1.25 v_{M_{inf}}$ in $M_3(t)$ and the immunotherapy treatment is applied in pulses for 7 days.

Conclusions

Through the localization of compact invariant sets method [4], Lyapunov's direct method [3] and in silico experimentation, we achieved to both demonstrate the asymptotic stability of the tumor-free equilibrium point of the system. According to the numerical simulations, the tumor cell population is asymptotically eliminated when using a concentration of chemotherapy $v_M > v_{M_{inf}}$ and immunotherapy $v_L > v_{L_{inf}}$ (in pulses for 7 days) in a period of less than 100 days.