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Cellular Immune Dynamics Under The Cancer Influence: Proposal of a Mathematical Model of Anti-Neoplastic Chemotherapy

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Abstract. Carcinogenesis is a formation process that causes modification in some genes through mutation of cells in the body. This process can be slow or happen quickly and aggressively, depending on individualizing peculiarities that can facilitate or inhibit tumor evolution. This pathology does not have specific causes and its study still generates many questions about the causative factors and the cellular interaction that allows such cellular proliferation of the disease. Based on this, this investigation seeks to understand the immune cell dynamics in the presence of tumor populations. To this end, we propose equations that aim to describe the behavior of specific cells and the production of cytokines, which are key elements acting in innate and adaptive immunity, contributing or hindering the spread of the pathogen in question. We also aim to understand and simulate the action of a specific drug, doxorubicin, applied in cycles, as an inhibitory agent in patients.

Key-words. Cancer, Immunological Dynamics, Numerical Simulation, Doxorubicin.

1 Introduction

Oncogenesis is the first stage of carcinogenesis, when genetic changes occur, transforming healthy cells into tumor cells, through the mutation [9]. Among the various causes of this pathology, there are internal and external factors. These factors can interact in different ways, resulting in an aggressive process with a rapid evolution. Unfortunately, in this first stage of the disease it is not possible to clinically detect a tumor [2], which means that many studies are developed with the objective of understanding the individual's tumor immune dynamics.

Several researches also indicate a greater vulnerability of elderly people to the carcinogenic process. This is because natural aging is one of the causes of the loss of cell repair, which makes the elderly more susceptible to the proliferation of tumor cell populations and, consequently, an inefficient activity of the response [15]. In addition, studies in the medical literature indicate that, in the early stages of cancer, a correct diagnosis and adequate treatment allow a higher rate of patient survival, which makes such research fundamental for the advancement of science in this area.

Based on this, several researchers seek to understand these processes through mathematical models capable of reproducing the tumor interaction and the innate and adaptive immune system, as a way of predicting pathological behavior using numerical simulations [3, 7, 13]. In addition, the aggressiveness of chemotherapeutic drugs in patients also makes it extremely important to predict their action on tumors, allowing a more detailed analysis by the physician in relation to which

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chemotherapeutic drug to use and the duration of treatment to which the physician will submit the patient.

As a way of explaining the model proposed here, we explain a little about the immune systems involved: the innate and the adaptive. Both systems work together in an attempt to block the individual against potential pathogens, exterminating infectious elements in the human body [11]. The cells belonging to the innate immunity system act without the need to include elements or supports outside the body. In contrast, adaptive immunity corresponds to the activation of highly enhanced cells, especially as they make use of immune memory. The union of these two systems is responsible for the synthesis of interleukins and proteins in the action of the immune response [3] in combating tumor proliferation [11, 19].

The proposed mathematical model involves equations that represent immune, precancerous and tumor cells. The model is based on changes in models [1, 17]. In addition, we also present an equation that represents the performance of the chemotherapy drug doxorubicin, widely used in the treatment of different types of cancer. The application in cycles simulated here is in accordance with protocols published in the medical literature, as well as the respective parameters used.

2 Mathematical Model

In this section, we present equations for populations of macrophages of types I and II, natural-killer cells (NKs), as well as adaptive immune cells (T-Helper and T-cytotoxic), equations referring to polymorphonuclear leukocytes in addition to precancerous and carcinogenic cells. In this way, the growth rate of type I, type II, precancerous and cancerous cells will be described as:

- Type I immune signal = activation + proliferation - necrosis - apoptosis,
- Type II immune signal = activation + proliferation - apoptosis,
- Cancerous cells = proliferation + recruiting - necrosis - apoptosis,
- Precancerous cells = production - apoptosis.

All the cells mentioned above are correlated with pro- and anti-inflammatory interleukins through the inclusion of differentiated equations, so that they can act as both inhibitors and promoters of tumor-spread in the patient. The cytokines discussed here are dynamic cytokines [6] and consist of a group of proteins capable of promoting cell communication, acting directly on the proliferation and activation of immune cells [19]. We also assume that these cytokines assume a quasi-stationary state, as proposed in [20].

In addition, it is necessary to address some factors that have been taken into account:

- $C_i = \dfrac{C}{(k+C)}$ represents the saturation effect of cancer cells. In this equation, k is the average saturation level of stimulated cancer cells due to the immune response [7];
- Tumor and immune cells are considered to have logistic growth under a rate α_i, up to a carrying capacity β_i [12];
- Cells that have some direct interaction with tumor cells need to be deactivated. Such deactivation happens at a rate δ_i and all modeled cells have a half-life period (semi-disintegration) μ_i^{-1}.

Thus, the model is composed by the following equations:

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- Equation for Type I and II Macrophages:

$$\frac{dM_1}{dt} = \rho_m I_\alpha C_i + \frac{\alpha_m M_1 \left(1 - \frac{M_1}{\beta_m}\right)}{1 + \eta_3(I_\beta + I_{23})} - \delta_m M_1 C - \mu_m M_1, \tag{1}$$

$$\frac{dM_2}{dt} = \rho_m I_{10} C_i + \frac{\alpha_m M_2 \left(1 - \frac{M_2}{\beta_m}\right)}{1 + \eta_1 I_\gamma} - \mu_m M_2, \tag{2}$$

- Equation for Natural Killers:

$$\frac{dN_K}{dt} = \rho_K I_\alpha C_i + \frac{\alpha_K N_K \left(1 - \frac{N_K}{\beta_K}\right)}{1 + \eta_3(I_\beta + I_{23})} - \delta_K N_K C - \mu_K N_K, \tag{3}$$

- Equation for cytotoxic T-cells:

$$\frac{dT_C}{dt} = \rho_8 I_{12} C_i + \frac{\alpha_t T_C \left(1 - \frac{T_C}{\beta_t}\right)}{1 + \eta_3 I_\beta} - \delta_t T_C C - \mu_8 T_C, \tag{4}$$

- Equation for T-Helpers (Th0, Th1, Th2 and Th17):

$$\frac{dT_0}{dt} = \rho_t I_{12} C_i + \frac{\alpha_t T_0 \left(1 - \frac{T_0}{\beta_t}\right)}{1 + \eta_3 I_\beta} - \delta_t T_0 C - \mu_t T_0, \tag{5}$$

$$\frac{dT_1}{dt} = \rho_t I_{12} T_0 + \frac{\alpha_t T_1 \left(1 - \frac{T_1}{\beta_t}\right)}{1 + (\eta_3 I_\beta + \eta_2 I_4)} - \delta_t T_1 C - \mu_t T_1, \tag{6}$$

$$\frac{dT_2}{dt} = \rho_t I_4 T_0 + \frac{\alpha_t T_2 \left(1 - \frac{T_2}{\beta_t}\right)}{1 + \eta_3 I_\beta} - \mu_t T_2, \tag{7}$$

$$\frac{dT_{17}}{dt} = \rho_t I_6 T_0 + \frac{\alpha_t T_{17} \left(1 - \frac{T_{17}}{\beta_t}\right)}{1 + \eta_1(I_2 + I_{16})} - \mu_t T_{17}, \tag{8}$$

- Equation for Granulocytes (Eosinophils, Mast Cells and Basophils):

$$\frac{dE}{dt} = \phi_E(I_5) C_i + \frac{\alpha_E E \left(1 - \frac{E}{\beta_E}\right)}{1 + \eta_3 I_\beta} - \delta_E E C - \mu_E E, \tag{9}$$

$$\frac{dM_A}{dt} = \phi_{M_A} I_\alpha C_i + \frac{\alpha_{M_A} M_A \left(1 - \frac{M_A}{\beta_{M_A}}\right)}{1 + \eta_3 I_\beta} - \delta_{M_A} M_A C - \mu_{M_A} M_A, \tag{10}$$

$$\frac{dB}{dt} = \phi_B(I_8) C_i + \frac{\alpha_B B \left(1 - \frac{B}{\beta_B}\right)}{1 + \eta_3 I_\beta} - \delta_B B C - \mu_B B, \tag{11}$$

- Equation for precancerous cells and tumor cells:

$$\begin{aligned}\frac{dP_C}{dt} &= (\delta_m M_1 + \delta_K N_K + \Delta_t(T_0 + T_C + T_1) + \delta_E E + \delta_{M_A} M_A + \delta_B B)C \\ &\quad - (\Lambda_C(T_C + N_K))P_C - (\theta_I + \mu_I)P_C,\end{aligned} \tag{12}$$

$$\begin{aligned}\frac{dC}{dt} &= \alpha_C C\left(1 - \frac{C}{\beta_C}\right) + \theta_C M_2 C + \theta_I P_C + \\ &\quad \left(-\left[\frac{\Lambda_C(M_1 + N_K + T_C + T_1 + E + B + M_A)}{1 + \eta_3 I_B}\right] C - \mu_C C\right).\end{aligned} \tag{13}$$

In addition to existence and uniqueness, the aforementioned model should not harm biological conditions and, therefore, non-negative restrictions are demonstrated in the solutions, but omitted in this document.

3 Model with Chemotherapy Treatment

Doxorubicin hydrochloride is a drug widely used in the chemotherapy treatment of cancer, especially in breast, bladder, lung carcinomas, bone and soft tissue sarcomas, as well as in Hodgkin's and non-Hodgkin's lymphomas and neuroblastomas [5]. Although this substance acts in a significant way, with high tumoricidal efficacy, preventing the cell replication of tumors, it has as one of the side effects a considerable drop in the individual's immunity, in addition to being quite harmful to the heart muscle. There are no safe doses for doxorubicin due to its cumulative effect, which may vary by type of cancer and gender. We will consider here systemic chemotherapy, which is introduced into the bloodstream, that is, administered intravenously in a rapid infusion, in order to reach cancer cells throughout the body, through the administration of doxorubicin hydrochloride.

Unfortunately, this drug destroys, in addition to cancer cells, healthy cells and this is one of the reasons why the side effects are so strong in patients [5]. The existence of this harmful effect is represented in each population equation through a negative portion representing the death of healthy cells. Thus, it is necessary to have a saturation term evidencing the chemotherapeutic effect of the drug doxorubicin on the immune system: $(1 - e^L)$. For each cell type, this portion will be multiplied by a respective factor: $D_\varphi(1 - e^L)$, where $\varphi = M_1, M_2, N_K, T, E, B, M_A, P_C$ and C, depending on the cell type in question. The addition of this portion in each cell population allows us to adjust the model to the doxorubicin hydrochloride data. In addition, we will include a new equation, which represents the concentration of doxorubicin hydrochloride (L):

$$\frac{dL}{dt} = -\gamma L + \upsilon_L(t), \tag{14}$$

where $\upsilon_L(t)$ represents the amount of doxorubicin injected per day, per liter of blood (in mg/l per day) and the portion $-\gamma L$ represents the excretion and elimination of drug toxicity. Note that, in this case, the resistance of tumor cells to the drug in question will be neglected, as well as the role of immune memory.

For the simulated model, we also took into account the half-life of the drug, with the γ elimination rate of doxorubicin [16]. For the numerical simulation, parameters reported in human and murine studies were considered, since many biological data involving specific cell populations are still scarce in the literature. Thus, the equations presented above were modified in order to aggregate the effects of chemotherapy in each biological population:

$$
\begin{cases}
\dfrac{dM_1}{dt} = \rho_m I_\alpha C_i + \dfrac{\alpha_m M_1\left(1-\dfrac{M_1}{\beta_m}\right)}{1+\eta_3(I_\beta+I_{23})} - \delta_m M_1 C - \mu_m M_1 - K_{M_1} - D_{M_1}(1-\mathrm{e}^{-\phi_{M_1}L})M_1,\\
\dfrac{dM_2}{dt} = \rho_m I_{10} C_i + \dfrac{\alpha_m M_2\left(1-\dfrac{M_2}{\beta_m}\right)}{1+\eta_1 I_\gamma} - \mu_m M_2 - D_{M_2}(1-\mathrm{e}^{-\phi_{M_2}L})M_2,\\
\dfrac{dN_K}{dt} = \rho_K(I_\alpha) C_i + \dfrac{\alpha_K N_K\left(1-\dfrac{N_K}{\beta_K}\right)}{1+\eta_3(I_\beta+I_{23})} - \delta_K N_K C - \mu_K N_K - D_{N_K}(1-\mathrm{e}^{-\phi_{N_K}L})N_K,\\
\dfrac{dT_C}{dt} = \rho_8 I_{12} C_i + \dfrac{\alpha_t T_C\left(1-\dfrac{T_C}{\beta_t}\right)}{1+\eta_3 I_\beta} - \delta_t T_C C - \mu_8 T_C - D_{T_C}(1-\mathrm{e}^{-\phi_{T_C}L})T_C,\\
\dfrac{dT_0}{dt} = \rho_t I_{12} C_i + \dfrac{\alpha_t T_0\left(1-\dfrac{T_0}{\beta_t}\right)}{1+\eta_3 I_\beta} - \delta_t T_0 C - \mu_t T_0 - D_{T_0}(1-\mathrm{e}^{-\phi_{T_0}L})T_0,\\
\dfrac{dT_1}{dt} = \rho_t I_{12} T_0 + \dfrac{\alpha_t T_1\left(1-\dfrac{T_1}{\beta_t}\right)}{1+(\eta_3 I_\beta+\eta_2 I_4)} - \delta_t T_1 C - \mu_t T_1 - D_{T_1}(1-\mathrm{e}^{-\phi_{T_1}L})T_1,\\
\dfrac{dT_2}{dt} = \rho_t I_4 T_0 + \dfrac{\alpha_t T_2\left(1-\dfrac{T_2}{\beta_t}\right)}{1+\eta_3 I_\beta} - \mu_t T_2 - D_{T_2}(1-\mathrm{e}^{-\phi_{T_2}L})T_2,\\
\dfrac{dT_{17}}{dt} = \rho_t I_6 T_0 + \dfrac{\alpha_t T_{17}\left(1-\dfrac{T_{17}}{\beta_t}\right)}{1+\eta_1 I_\gamma} - \mu_t T_{17} - D_{T17}(1-\mathrm{e}^{-\phi_{T_{17}}L})T_{17},\\
\dfrac{dE}{dt} = \phi_E(I_5) C_i + \dfrac{\alpha_E E\left(1-\frac{E}{\beta_E}\right)}{1+\eta_3 I_\beta} - \delta_E E C - \mu_E E - D_E(1-\mathrm{e}^{-\phi_E L})E,\\
\dfrac{dM_A}{dt} = \varphi_1(I_\alpha) C_i + \dfrac{\alpha_{M_A} M_A\left(1-\frac{M_A}{\beta_{M_A}}\right)}{1+\pi_2 C} - \delta_{M_A} M_A C - \mu_{M_A} M_A - D_{M_A}(1-\mathrm{e}^{-\phi_{M_A}L})M_A,\\
\dfrac{dB}{dt} = \varphi_1(I_8) C_i + \dfrac{\alpha_B B\left(1-\frac{B}{\beta_B}\right)}{1+\pi_2 C} - \delta_B B C - \mu_B B - D_B(1-\mathrm{e}^{-\phi_B L})B,\\
\dfrac{dP_C}{dt} = (\delta_m M_1 + \delta_K N_K + \Delta_t(T_0+T_C+T_1) + \delta_E E + \delta_{M_A} M_A + \delta_B B)C\\
\qquad - (\Lambda_C(T_C+N_K))P_C - (\theta_I+\mu_I)P_C - D_{P_C}(1-\mathrm{e}^{-\phi_{P_C}L})P_C,\\
\dfrac{dC}{dt} = \alpha_C C\left(1-\dfrac{C}{\beta_C}\right) + \theta_C M_2 C + \theta_I P_C\\
\qquad - \left[\dfrac{\Lambda_C(M_1+N_K+T_C+T_1+E+B+M_A)}{1+\pi_2 C}\right] C - \mu_C C - D_C(1-\mathrm{e}^{-\phi_C L})C.
\end{cases}
\tag{15}
$$

4 Numerical Simulations

In this section we present some numerical results considering that the population of cancer cells and cells belonging to the innate system are greater than zero for $t = 0$ and the population of cells referring to the adaptive immune system is zero. All parameters used were taken from experiments

reported in the medical literature. The population growths of tumor cells without treatment are shown in the first graph of Figure 1, using the fourth-order Runge-Kutta numerical method.

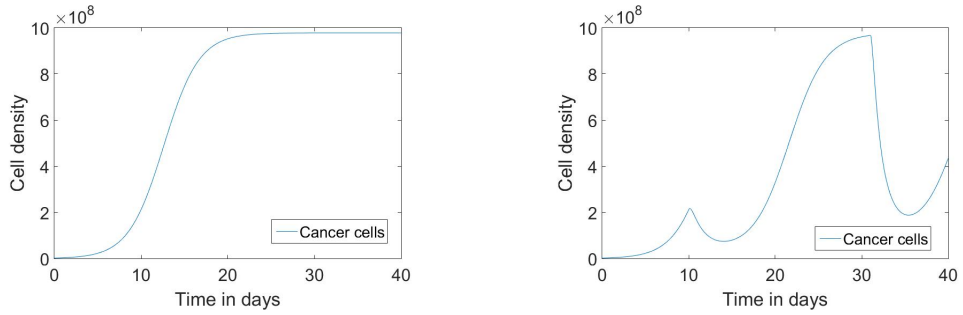

Figure 1: Population growth of tumor cells without and with treatment, respectively.

For the case mentioned in the previous section, we present here the proposed model considering the same input conditions, adding only the parameters used referring to the concentrations of the chemotherapeutic agent [8] and its administration with pauses [18]. The protocol followed here corresponds to the application of the drug intravenously every 21 days, starting on day 10 as can be seen in the second graph of Figure 1. As mentioned in [10], this drug is not always effective in decimating the pathology since several protocols make administration of two or more drugs or therapies together. Furthermore, this model does not yet show the effects of dendritic cells, which will be the next step in this work and have a significant influence on treatment. In any case, we obtained results (Figure 1) compatible with those already published in the literature [4, 14].

5 Conclusion

In this work we present a mathematical model that evidences the behavior of the dynamics of the innate-adaptive immune response in cancer patients. Besides, through extensive biological research, we have included the role of interleukins through equations that relate such cell populations. Furthermore, we present equations that represent the antineoplastic chemotherapy treatment, as well as its effects on the cell populations studied. Numerical simulation of this system returns results that correspond to those presented in [4, 14].

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