In silico modelling for the treatment of gastric cancer

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I. Mathematical model of intestinal-type gastric adenocarcinoma growth with ACI

We propose a qualitative mathematical model composed of three first-order Ordinary Differential Equations (ODEs), which describes some survival mechanisms of intestinal-type gastric adenocarcinoma and the interaction of the immune system. The model consists of three types of cell populations, gastric cancer cells, Dendritic Cells (DCs), and T cells. We cover interesting aspects such as cell cannibalism and the prolonged presence of *Helicobacter Pylori* (H. Pylori) that could stimulate tumor growth and survival beyond its initial carrying capacity. We explore the effects of Adoptive Cellular Immunotherapy (ACI) by incorporating a treatment parameter into the model.

2.1. Biological assumptions.

In order to construct our model, biological assumptions are established to limit the complexity of the problem:

1. In the absence of an immune response and a proper treatment, the gastric cancer cells grow logistically.
2. There is evidence in [1] to support the statement that gastric cancer cells cannibalize neutrophils. Further, in other tumor types, malignant cells have also been shown to cannibalize other effector cells such as T cells. Therefore, cannibalism is considered a mechanism to suppress the immune response.
3. There is a proliferation of gastric cancer cells due to the presence of bacterium H. Pylori, which contribute to the formation of gastric adenocarcinoma [2].
4. The DCs remain in a homeostatic state. Nonetheless, these cells become activated and grow logistically through stimulation of their cellular receptors by identifying tumor antigens of gastric cancer cells [3].
5. The DCs die by apoptosis after presenting tumor antigens to the T cells [3].
6. Activated T cells are capable of eliminating gastric cancer cells by cell lysis.
7. There is a natural death of T cells. Furthermore, these cells are eventually inactivated after a certain number of encounters with gastric cancer cells [3].
8. The total tumor cells population eliminated by ACI treatment is a factor of the number of T cells supplied which we represent as a treatment parameter.

2.2. Model equations.

The model describes the interactions between gastric cancer cells $x(t)$, DCs $y(t)$ and T cells $z(t)$ by the following ODEs:

$$\dot{x} = \underbrace{\alpha_x x(1-\beta_x x)}_{\text{Logistic growth of } x} + \underbrace{\eta_x x}_{\text{Growth by H. Pylori}} + \underbrace{\delta_x xz}_{\text{Cell cannibalism}} - \underbrace{\gamma_x xz}_{\text{Immune response by } z} \quad (1)$$

$$\dot{y} = \underbrace{\alpha_y y(1-\beta_y y)}_{\text{Logistic growth of } y} + \underbrace{\delta_y xy}_{\text{DCs activation by } x} - \underbrace{\gamma_y yz}_{\text{DCs death by T cells interaction}} \quad (2)$$

$$\dot{z} = \underbrace{\delta_z yz}_{\text{T cells activation by DCs}} - \underbrace{\gamma_z xz}_{\text{T cells inactivation by } x} - \underbrace{\mu_z z}_{\text{Natural death}} + \underbrace{\alpha_z}_{\text{ACI treatment}} \quad (3)$$

It should be noted that the dynamics of the system (1)-(3) is located in the nonnegative orthant defined by

$$\mathbb{R}^3_{+,0} = \{x(t) \geq 0,\ y(t) \geq 0,\ z(t) \geq 0\}.$$

The dimension per unit for all cell populations is 10^{11} cells, and the time scale is considered to be in months. For simulation purposes, we used an artificial intelligence software called Eureqa [4] to estimate the parameter values. **Figure 1** illustrates the interactions between cells populations, H. Pylori, and the treatment.

II. Localization of Compact Invariant Sets

The method of Localization of Compact Invariant Sets (LCIS) it is useful to study the short- and long-time dynamics of any ODEs system by computing the so-called *localizing domain* [5]. In **Theorem 1**, we summarize our results concerning the LCIS for the intestinal-type gastric adenocarcinoma system (1)-(3).

Theorem 1. *If conditions $\gamma_x > \delta_z$ and $\Upsilon \geq \delta_z/\gamma_y$ are satisfied, then all compact invariant sets of the system (1)-(3) are located either inside or at the boundaries of the following compact localizing domain:*

$$K_{xyz} = K_x \cap K_y \cap K_z,$$

where

$$K_x = \left\{0 \leq x(t) \leq x_{\text{sup}} = \frac{\alpha_x + \eta_x}{\alpha_x \beta_x} - \frac{(\gamma_x - \delta_x)}{\alpha_x \beta_x} z_{\text{inf}}\right\},$$

$$K_y = \left\{0 \leq y(t) \leq y_{\text{sup}} = \frac{1}{\beta_y} + \frac{\delta_y}{\alpha_y \beta_y} x_{\text{max}} - \frac{\gamma_y}{\alpha_y \beta_y} z_{\text{inf}}\right\},$$

$$K_z = \left\{z_{\text{inf}} = \frac{\alpha_z}{\mu_z + \gamma_z x_{\text{max}}} \leq z(t) \leq z_{\text{sup}} = \frac{\alpha_z}{\mu_z} + \frac{\Upsilon(\mu_z + \alpha_y + \delta_y x_{\text{max}})^2}{4\alpha_y \beta_y \mu_z}\right\}.$$

III. Tumor clearance and global stability

We propose the candidate Lyapunov function $h_5 = x$ and perform the corresponding mathematical analysis to establish that the Lie derivative of the function h_5 is negative semidefinite, i.e., $L_f h_5 \leq 0$, if the following condition is fulfilled:

$$\alpha_z > \frac{\mu_z(\alpha_x + \eta_x)}{\gamma_x - \delta_x} + \frac{\gamma_z(\alpha_x + \eta_x)^2}{\alpha_x \beta_x (\gamma_x - \delta_x)} \quad (4)$$

by assuming the condition $\gamma_x > \delta_z$ also holds. **Figure 2** illustrates the temporal dynamics of the system (1)-(3) without and with ACI treatment. For $\alpha_z = 0$, the tumor gastric mass is cycled in approximately 9 months. During 2 or 3 months, the tumor reaches a value close to its maximum carrying capacity and then descends to almost zero in a state known as tumor latency [3]. The system (1)-(3) converges to the tumor-free equilibrium point given by

$$P_0 = \left(0, 0, \frac{\alpha_z}{\mu_z}\right).$$

The solution of the cancer cells population converges to zero in short time when condition (4) is satisfied.

IV. Conclusions

The mathematical model exhibits periodic oscillations in the absence of treatment. These oscillations illustrates patterns related to tumor latency and recurrence, which partially coincide with the recurrence time observed in patients with gastric adenocarcinomas [6]. We present a sufficient condition of global asymptotic stability of the tumor-free equilibrium point P_0, which implies the elimination of the gastric adenocarcinoma.

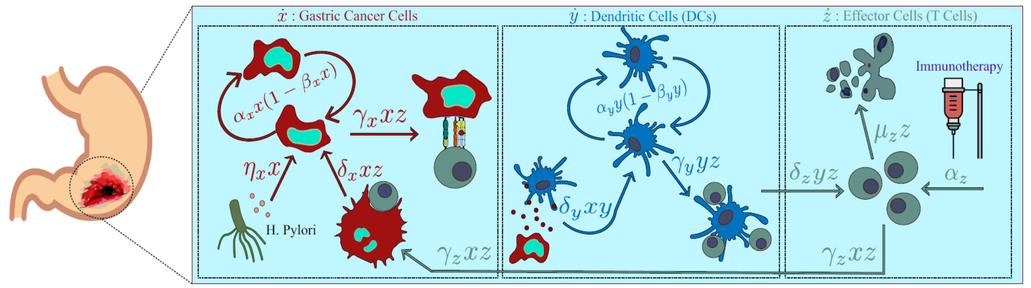

Figure 1. Interactions between gastric cancer cells [$x(t)$], DCs [$y(t)$], T cells [$z(t)$] and ACI treatment.

In silico experimentations.

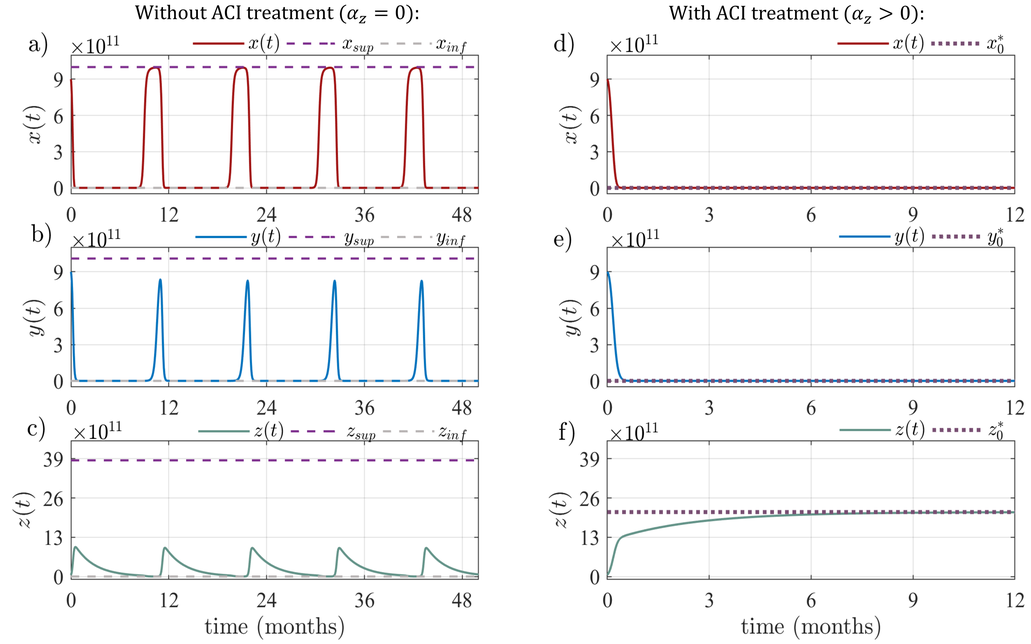

Figure 2. Solutions of the system (1)-(3). For $a_z = 0$, the solutions of the system (1)-(3) are shown in panels *a* to *c*. For $a_z = 8.9$, the solutions are shown in panels *d* to *f*.

References.

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