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A Preliminary Volterra Lotka Model Analysing Cancer, Intracellular Parasite, and Immune Cells Interaction

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Abstract: In this paper, we investigate the dynamics of immune and tumor cell densities in the presence of a parasite using the prey-predator Volterra-Lotka model in a biological system, assuming that the parasite is either a down or up-regulator of the induced immune cells. Thus, we analysed the model for equal and non equal initial conditions and report their impact on the populations growth.

Keywords: Immune cells, Tumor growth, Parasites, Volterra-Lotka

1 Introduction

The human immune system develops complex mechanisms based on signaling secretory molecules production to recruit and propagate populations of cells against infectious diseases and cancer. Defending and protecting the body by orchestrating specific and non-specific immune responses pose a range of challenges to the immune system, especially, when the immune response does not accomplish the goal. The host must be programmed into a destruction restraint phase in order to diminish the pathological effects [1,2]. Some Helminths [2,3,4], protozoa [5,6,7], and cancer cells [8] have been suggested to develop such a kind of circumvention strategies. On the one hand, escaping the immune devastation is based on a molecular interaction with the host and interestingly many parasites benefit from the host molecular signals for their development [9, 10]. Protozoa such as Plasmodium falciparum, Trypanosoma cruzi, Toxoplasma gondii, and helminths like Trichinella spiralis may evade the immune system, passively and or actively, by either epitopes mutation, antigenic variation, or pertaining inactivity as illustrated by Schmid-Hempel [11]. Recently, researchers demonstrated that some intestinal worms give a surprising boost to the immune system [12]. Their discovery showed that lymph nodes include more immune cells when the host is infected with a specific invader like a parasite. This work has significant implications for our understanding of how the immune system responds to a coexistence of parasite and cancer. On the other hand, tumor development has been associated with the expression or the mutation of various genes due to internal including gene over-expression, amplification, or mutation [7] or external factors like helminths or protozoa infection [13,14,15]. The relationship between a parasite, cancer, and the immune system is under investigation [16]. Some parasites are suggested to modulate the human immune response associated with cancer growth [6,7,8,9, 11]. However, the mechanisms of action triggered by the parasites and some of their products involved in modulating cancer development are diverse and not yet fully described [5]. Protozoa such as Trypanosoma cruzi [9] and Toxoplasma gondii [11] may suppress the tumor growth by inducing apoptosis through activating the cytotoxic T cells (CD8/NK cells, and helminths-like Echinococcus granulomas [15,16,17], Taenia crassiceps [17] and Trichinella spiralis [18,19,20] induce down-regulating molecules to the neoplastic growth such as antibodies, and chemokines. Researchers have been working theoretically and experimentally to manage the parasitic infections and deadly cancers. The study [20] provided a comprehensive overview of the different approaches used to model the tumor-immune system interaction dynamics. A considerable amount of studies had been done by the researchers [20,21,22,23], through utilizing differential equations to investigate the

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interaction among tumor cells and different types of immune cells [24,25,26,27,28]. Some other separate studies were done on a host-parasite relationship modelling and all were retrieved in an entire chapter [29]. In this work, we investigate a theoretical model by considering a tumor-host interface where tumor cells and immune cells co-exist with a parasitic infection. Using the prey-predator scheme, we investigate the temporal dynamics of the immune, tumor, and parasite cell densities in terms of maximum growth rates, maximal cell densities, and lumped competition rates. Our goal is to study the effect of an intracellular parasitic infection on the immune system in the presence of a cancer, where the parasitic effect is introduced in our model as a regulator rate denoted by ξ. While this model is yet fundamental, it might pave the way for intervening applications that can benefit from the presence of certain parasites for the interest of cancer patients. Our paper is structured as follows: in section 2, we present the model. Hence, we describe the temporal dynamics of cancer, immune, and parasite densities, using the competitive Volterra-Lotka model. The analysis is reported in section 3 followed by a discussion and concluding remarks. Finally, the current paper proposes the model while the analytical study of the stability and the phase portrait are under investigation.

2 Model

2.1 Cells Dynamics

Firstly, we describe the dynamics of tumor and immune cells using the competitive Volterra Lotka model. By denoting respectively, the immune cells by I and the tumor cells by T, at a time t and in a spatial location x, we can write:
$\frac{\partial S}{\partial t} = \alpha\Phi(x,t) + G[S] + D$
In addition
: $\frac{\partial^2 S}{\partial^2 x} e(t) = \mu k(t) + \nu \frac{dk(t)}{dt}$

where (S) denotes the vector with components representing the population densities of the immune and tumor cells; respectively, in concomitant with a parasite population that influences the interaction of cancer with the immune response. (G) is the non-linear population kinetics function, and (D) is a matrix of diffusion coefficients supposed to be positive. In this model, we assume that the cells grow initially according to a Malthusian law. For more details about tumor cells growth mechanism, we suggest [30]. We also consider that the densities of the cells are uniform so that the diffusion is neglected along the x-direction (an x-axis within the cell). In the Volterra-Lotka model, the human body is believed to be an ecological system in which all types of interactions occur between human cells and pathological (or beneficial) agents through various complex mechanisms with prey-predator behavior. In general, the dynamic of (M) interacting organisms is given by:

$$\frac{dx_i}{dt} = r_i x_i (1 - \frac{\sum_{j=1}^{M} \alpha_{ij} x_j}{K_i}) \tag{1}$$

for $i = 1, ..., M$ and where, the population density of a cell x_i in time is denoted by $x_i = x_i(t)$, (r_i) and (K_i) are the growth rates and the carrying capacities; respectively. The term (α_{ij}) is the non-linear interactive effect of the cell (j) on (i). In addition, each population density of a given cell will show logistic growth in the absence of competition and will tend towards its carrying capacity for large temporal scale (t goes to infinity). Secondly, we investigate the interactions of tumor cells and immune cells during the parasitic infection. Thus. the relation between the immune cells and and parasites is a kind of predator-prey relationship.The analysis of tumor-immune cells prey-predator system in conjugation with the parasite-immune cells system can be represented by the following equations:

$$\begin{aligned}
\frac{dT}{dt} &= r_T T(1 - \frac{T}{K_T}) - \frac{r_T \beta_{TI}}{K_T} TI \\
\frac{dI}{dt} &= r_I I(1 - \frac{I}{K_I}) - \frac{r_I \beta_{IT}}{K_I} IT + \xi IP \\
\frac{dP}{dt} &= r_P P(1 - \frac{P}{K_P}) - \frac{r_P \beta_{PI}}{K_P} PI
\end{aligned} \tag{2}$$

where I denotes the immune cell density combating the diseases, T denotes the tumor cells density and P the parasites density. K_I and K_T denote the maximal immune and tumor cell densities (i.e. minus tumor cell loss by apoptosis or necrosis) and K_P is the maximal parasites density. The coefficients r_I, r_T and r_p represent the maximum growth rates of the immune cells, the tumor cells, and the parasites, respectively. Hence, these parameters represent terms with the following biological significance at the complex biological system: β_{IT} represents the negative effects of the tumor on immune cells, such as tumor-induced extra-cellular matrix breakdown and micro-environmental changes. β_{TI} represents the host immune response against tumor cells. ξ represents the rate of immune response due to parasitic infections. By taking

$$\alpha_I = \frac{r_T \beta_{TI}}{K_T}$$
$$\alpha_T = \frac{r_I \beta_{IT}}{K_I}$$
$$\alpha_p = \frac{r_P \beta_{PI}}{K_P}$$

the system becomes:

$$\begin{aligned}
\frac{dT}{dt} &= r_T T(1 - \frac{T}{K_T}) - \alpha_I TI \\
\frac{dI}{dt} &= r_I I(1 - \frac{I}{K_I}) - \alpha_T IT + \xi IP \\
\frac{dP}{dt} &= r_P P(1 - \frac{P}{K_P}) - \alpha_p PI
\end{aligned} \tag{3}$$

where, in the absence of a tumor, the system reduces to an ecological competition between immune cells and parasites; while, in the absence of a parasite, the tumor growth is competing with immune cells only. In addition, we can see a form of the Gompertz equation, which shows that if $r_T T(1-\frac{T}{K_T}) - \alpha_I TI$ is $\leq$ than 0, the tumor cell population can be reduced.

2.2 Non-dimensionalization

To simplify calculations, the model is non-dimensionalized using the following change of variables:

$$\tau = r_T * t(M) = \frac{T}{k_T}, (N) = \frac{I}{k_I} and (P_r) = \frac{P}{k_P} \quad (4)$$

Thus, deriving over τ, the equations become:

$$\frac{dM}{d\tau} = M(1-M) - \beta_1 MN \quad (5)$$

$$\frac{dN}{d\tau} = \frac{r_I}{r_T} N(1-N) - \beta_2 NM + \xi NP_r$$

$$\frac{dP_r}{d\tau} = \frac{r_p}{r_I} P_r(1-P_r) - \beta_3 P_r N$$

The equilibria points of this system are derived simply by letting the 3X3 Jacobian matrix of equations (6) to be zero. This is achieved easily with the Mathematica software (the equilibria points are given in the appendix). For instance, we can mention (0,0,0) which corresponds to the mutual extinction of all the populations (which is not the realistic case as the immune cells are at their normal size), (0,1,0) referring to cancer and parasite-free biological system when the immune cells are at their carrying capacity and (0,0,1) corresponds to the existence of the parasitic cells while the tumor cells extinct and the immune cells are at their carrying capacities, etc. In our model the case (1,1,1) describes the co-existence of the three populations: the tumor cells, the immune cells, and the parasites. Technically, the stability analysis of system (6) depends on the rates: r_I, r_T, r_P, K_I, K_T, K_P, and ξ. The cancer growth scenario is a complex mechanism, and the mathematical approach to cell growth needs a more realistic framework based on in vivo observations. Thus, for a better understanding of our model, experimental data should be used to perform the stability analysis of the system.

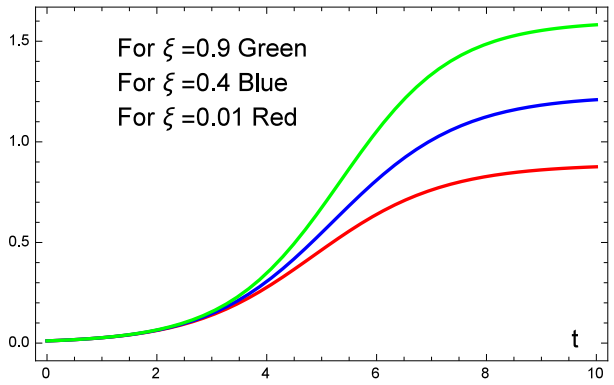
3 Analysis

3.1 Equal Initial Conditions

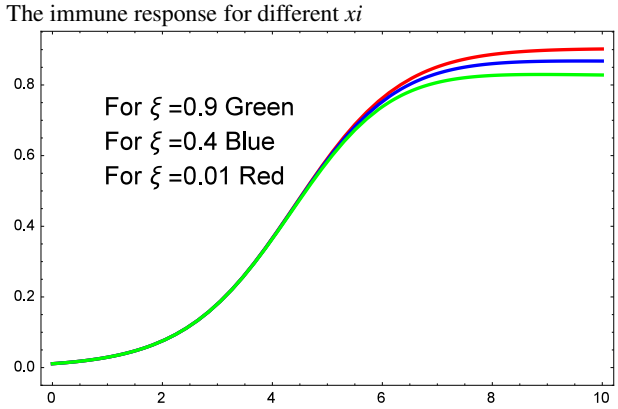
Figures (1a) and (1b) show the population density of immune cells and tumor cells, respectively. The cells of different populations increase and level out at the same time (t=8 in units of τ) with the greatest population size at ξ=0.9 for the immune cells. Introducing the parasite population to the system in association with the immune cells and cancer growth at ξ=0.01, figure (1c) shows a growth attained by all with the highest population size due to cancer population followed by the immune cells and parasite population, respectively. Interestingly, by increasing ξ to 0.9, the immune cell population size will be drastically increased to be higher than the tumor and parasite populations, respectively (fig. 1d).

3.2 Non-equal initial conditions

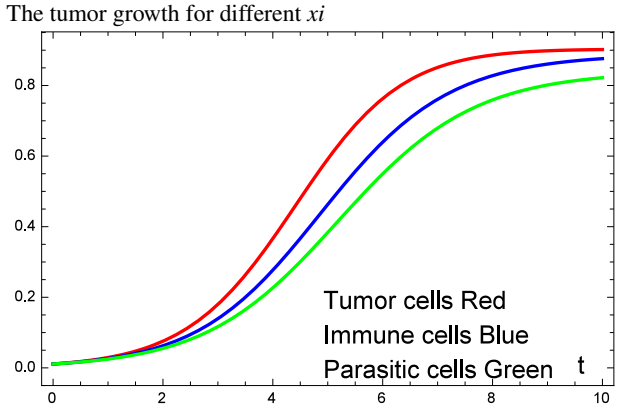
In figure (2), we investigate the case where the system has non-equal initial conditions in the biological system. The immune cells increase at a faster rate reaching bigger size than the tumor cells (fig. 2a) and parasite populations (fig. 2b). Interestingly, with a larger initial parasite population size (fig. 2b), the immune cell population reaches its carrying capacity and the steady level earlier than its counterpart when tumor cells population was initially bigger (fig. 2a).



The immune response for different *xi*



The tumor growth for different *xi*



The cells dynamics for a $\xi = 0.01$

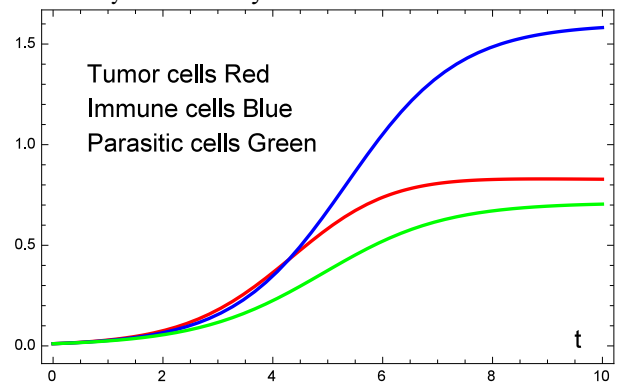
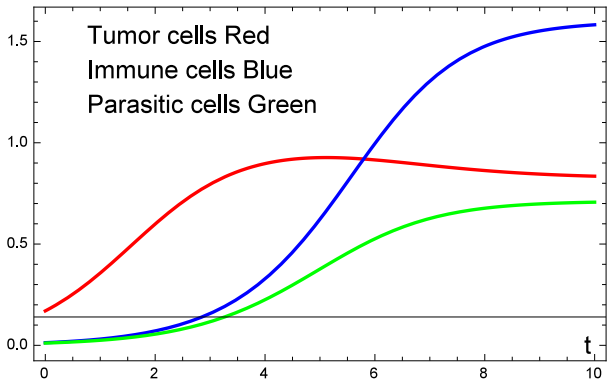
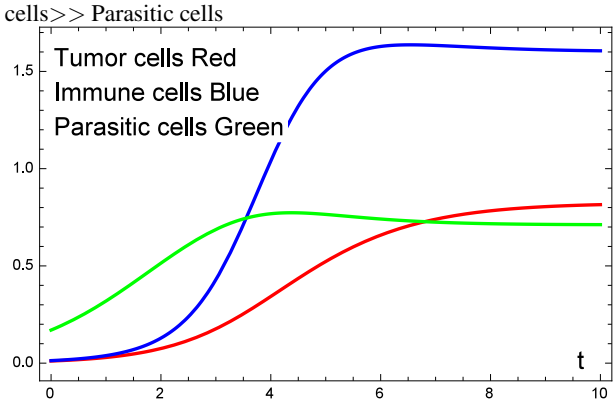


Fig. 1: The cells dynamics for a $\xi = 0.9$



The cell's dynamic for different ξ: tumour cells>> Immune cells>> Parasitic cells



The cell's dynamic for different ξ: parasitic cells >>Immune cells >> tumor cell

Fig. 2: The cells dynamics for different parasitic excitations

4 Conclusion

In this paper, we have employed the Voltera-Lotka model to investigate the regulation of cancer growth by the parasite-induced immune cells. Our model shows that the immune cells population augment due the parasitic infection. For non-equal initial conditions, a larger initial parasite population size induce a faster growth of the immune cells enabling them to compete with cancer. Similarly, at equal initial conditions, the response of the immune cells acts due to the large regulation size of parasites. A further development of the model is under investigation considering specific immunoregulatory cells, which are shared between some intestinal parasites and cancer. The authors are grateful to the anonymous referee for a careful checking of the details and for helpful comments that improved this paper.

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