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Nonlinear Coupled Differential Equations Modeling of Drug Resistance in Conjoint Normal and Tumor Cells.

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ABSTRACT

In this paper, we investigate conjoint tumor model in order to make a distinction between tumor cells that are responsive to chemotherapy and those that may show resistance. The model is based on nonlinear coupled differential equations arising in conjoint normal tumor cells containing non-linear terms related to normal and tumor cells. The results provide us with a deeper understanding of the possible evolution of normal, drug responsive, and drug-resistant tumor cells during the cancer progression, which may contribute to improving the therapeutic strategies. A mathematical modeling drug resistance in a conjoint normal-tumor setting is discussed. A good agreement with available limiting case results is noticed. This work aims to contribute to a deeper understanding of drug resistance effects on cancer progression through the analysis of a new mathematical model and the analytical expression with the computational simulation for a coupled tumor-normal cell framework. To simulate the population evolution of our model, we have used Mathematical software MATLABR2007B.

Keywords: Cancer modeling, Cellular aging, conjoint cell growth, Non-linear differential equation.

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INTRODUCTION

Non-linear phenomena play a very important role in physics, chemistry and biology [1,2](heat and mass transfer, filtration if liquids, diffusion in chemical reactions, etc.) in particular in physics, non-linear waves are encountered in numerous domains such as fluid mechanics [3], solid-state physics [4], plasma physics [5] and chemical physics [6]. New names like solitons, kinks, breathers, etc. are now commonly used in the vast literature [7] dealing with this subject. Unfortunately these topics are treated only in advanced courses and can rarely be found on an introductory level. Therefore, simple techniques and methods are needed to investigate these phenomena and to make them accessible for undergraduate study.

Construction of particular exact solutions for the non-linear equations remains an important problem. Finding exact solutions that have a physical, chemical or biological interpretation is of fundamental importance. Linear superposition principal cannot be applied to find the solution non-linear differential equations. Thus, the standard methods are not applicable for solving non-linear differential equations. A key step in investigating these problems is the derivation of traveling-waves from the associated wave equations. However, in contrast with linear wave theory where one can make use of the basic techniques, a variety of methods and often involving complex mathematical technique is used for the solution of non-linear problems. The aim of this chapter is to propose a unifying method that leads to straight forward solutions.

Assessing the evolution of cancer, in the presence of surrounding normal cells, is the subject of many biomedical studies. Recently reported evidence strongly indicates that the dynamics of tumor cells and the surrounding normal cells are not independent of each other and may be mutually tuned [8]. Examination of the coupled population dynamics of tumor and normal cell populations can potentially provide substantial knowledge that may contribute to the identification of more effective therapeutic interventions, particularly in aging populations. The interaction of tumor and normal cells is not the exclusive factor causing different dynamical patterns during cancer progression, the interaction of cells with the host immune system, therapeutic agents such as chemotherapy, immune therapy, or any other therapeutic interactions are additional factors which can influence the evolution patterns of the cell populations [9-15]. While researchers continuously improve cancer treatment strategies, one of the most serious obstacles in cancer treatment are related to drug resistance, where the chemotherapeutic treatments do not lead to the hoped for outcome. The issues related to the drug resistance have been broadly studied from a variety of different perspectives [16-24]. Model parameters values are estimated based on values previously introduced in the literature and are given in Table 1 of this paper. We conclude and examine future research directions.

MATERIALS AND METHODS

Feizabadi & Witten [22] extended the earlier work of Witten [16] proposing the following generalized model to describe the inter-connection between normal and tumor cells. The core model equation system is given by[23]:

$$\frac{dT(t)}{dt} = r_T T\left(1-\frac{T}{K_T}\right) - \beta\left(\frac{\rho_0 N}{\rho_1 + N}\right);\ T(0) = T_0 \tag{1}$$

$$\frac{dN(t)}{dt} = r_N N\left(1-\frac{N}{K_N}\right) + \kappa T\left(1-\frac{T}{T^*}\right);\ N(0) = N_0 \tag{2}$$

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Table 1: Table of parameters: parameters used in simulations have been estimated based on the values introduced in following sources

S No.	Parameter	Description	Estimated value	Reference
1	r_T	Growth rate for the drug sensitive tumor cells	0.3 $Time^{-1}$	[23]
2	K_T	Carrying capacity of tumor cells	1.2×10^6 Cells	[23]
3	B	Normal-tumor cell interaction rate	1 $Time^{-1}$	[23]
4	ρ_0	Interaction clearance term	1 Cells	[23]
5	ρ_1	Half-saturation for interaction	1000 Cells	[23]
6	r_N	Growth rate for the normal cells	0.4 $Time^{-1}$	[23]
7	K_N	Carrying capacity of normal cells	106 Cells	[23]
8	K	Tumor-normal cell interaction rate	0–0.028 $Time^{-1}$	[23]
9	T*	Critical size of tumor	3×10^5 Cells	[23]

where T(t), N(t), K_T, K_N, r_T, r_N are respectively the total number of tumor cells at time t the total number of normal cells at time t, the carrying capacity for the tumor cells, the carrying capacity for the normal cells, and the per capita growth rate for the tumor and normal cells, andare the functional rules relating normal-to-tumor and tumor-to-normal interaction respectively. Witten and Feizabadi [23] have shown that one possible set of coupled, nonlinear equations for the tumor-normal cell system may be expressed follows:

$$\frac{dT(t)}{dt} = r_T T\left(1-\frac{T}{K_T}\right) - \beta\left(\frac{\rho_0 N}{\rho_1 + N}\right);\ T(0) = T_0 \quad (3)$$

$$\frac{dN(t)}{dt} = r_N N\left(1-\frac{N}{K_N}\right) + \kappa T\left(1-\frac{T}{T^*}\right);\ N(0) = N_0 \quad (4)$$

Where T, N, K_T, K_N, r_T, r_N are previously defined. In each equation, the second terms represent the interaction between tumor and normal cells. Here, β and κ have the units of 1/time. Also, for consistency, ρ0 and ρ1 have units of cells. T* is the critical size of the tumor and as the size of tumor exceeds the critical size, the normal cells growth rate decreases.

COMPARISON OF RESULTS

In this Fig. 1 the blue curve illustrates the evolution of the normal cell population and the red curve illustrates the evolution of tumor cell population.

In this figure (a), the normal and the tumor cells grow, uncoupled following a Gompertzian law; r_T = 0.4; r_N = 0.5; $K_t = 1.2\times10^6$; $K_N = 1\times10^6$; β = 1; ρ_0 = 1; $\rho_1 = 1\times10^3$; κ = 0.040; $T^* = 3\times10^5$;

(b) In this figure, the normal and the tumor cells grow conjointly using the following parameter values r_T = 0.5; r_N = 0.6; $K_t = 1.2\times10^6$; $K_N = 1\times10^6$; β = 1; ρ_0 = 1; $\rho_1 = 1\times10^3$; κ = 0.060; $T^* = 3\times10^5$;. In this case, the tumor cells can contain the growth of normal cells. The population of the normal cells declines as the population magnitude of the tumor cells passes the critical value of $T^* = 3\times10^5$. The inhibition time in which the normal cells begin to decrease is approximately time t = 100 days;

(c) In this role of normal cells on the growth of tumor cells is increased. As the growth of tumor cells starts with a delay. As compared with the Figure (b), the decrease starts at almost time t = 100. Therefore, the normal cells continue a higher population for a longer time.

(d) It status the evolution of normal and tumor cells when κ =0.1, β = 1. This time, the interaction effect of tumor cells on normal cells is increased. Under this set of simulation conditions, the population of normal cells goes to minimum value and they die out of system.

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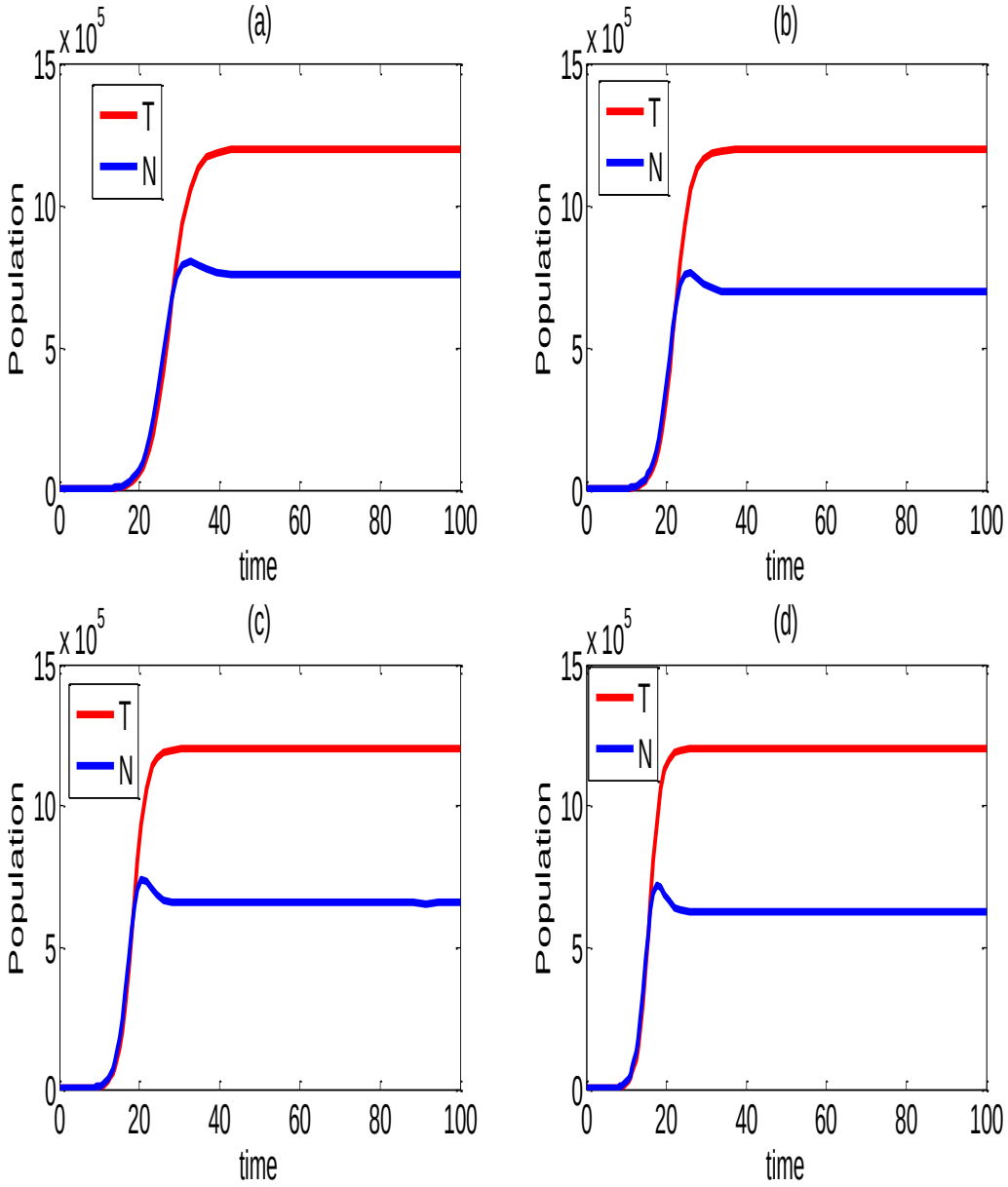

Fig 1: Evolution of normal cells and tumor cells for 100 days.

DISCUSSION

In briefly the normal-tumor cell is to discuss the conjoint model. In Conjoint core model in a chemo-resistance, we derive the coupled nonlinear differential equation for the drug resistance assumptions and numerical method to make a distinction between tumor-responsive and tumor-resistant cells. In Chemo-treatment strategies in a resistance, we include the effects of numerical solution to the modified conjoint model and discuss the dynamics of the system.

In this paper, the normal and tumor of the cells are two other important factors that can potentially cause different numerical method [24]. Another factor that plays a significant role in the system dynamics is the dosage of the anti-tumor drugs. It is more probable that a better response is achieved by increasing the drug dosage. However, since a majority of the chemotherapeutic drugs are toxic to normal cells and the host

immune system, consequently, the dosage and the level of toxicity must be carefully considered in order to minimize the potential damage to normal cells and to the patient. A combination therapy is considered a more effective treatment strategy with cancers that show resistance to some of the chemotherapeutic agents. In this mode of intervention, while the tumor is treated by the recommended chemotherapeutic drug protocol, other chemotherapeutic drugs are also used in order to target those tumor cells that have developed defense mechanisms against the first type of chemotherapeutic agent.

In Fig. 1 illustrate the dynamics of the system under a normal and tumor cells growth. In this simulation, both drugs are administered at the same time, t = 100. A lower dosage and therefore lower toxicity is considered for the anti-resistant tumor cell population. This mode of intervention was chosen due to the fact that, at the start of chemotherapy, drug responsive tumor cells have a higher population. Therefore, a higher drug dosage was considered for the non-resistant population.

CONCLUSION

The numerical expression for the total number of normal cell and the tumor cell are derived using MATLAB codes. This method is an extremely simple method and it is also a promising method to solve other non-linear equations. The extension of procedure to other cases such as conjoint core model in a chemo-resistance setting and chemo-treatment strategies in a resistance setting seems possible.

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