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Inactivation of tumor suppressor genes and cancer therapy: An evolutionary game theory approach

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ABSTRACT

Inactivation of alleles in tumor suppressor genes (TSG) is one of the important issues resulting in evolution of cancerous cells. In this paper, the evolution of healthy, one and two missed allele cells is modeled using the concept of evolutionary game theory and replicator dynamics. The proposed model also takes into account the interaction rates of the cells as designing parameters of the system. Different combinations of the equilibrium points of the parameterized nonlinear system is studied and categorized into some cases. In each case, the interaction rates' values are suggested in a way that the equilibrium points of the replicator dynamics are located on an appropriate region of the state space. Based on the suggested interaction rates, it is proved that the system doesn't have any undesirable interior equilibrium point as well. Therefore, the system will converge to the desirable region, where there is a scanty level of cancerous cells. In addition, the proposed conditions for interaction rates guarantee that, when a trajectory of the system reaches the boundaries, then it will stay there forever which is a desirable property since the equilibrium points have been already located on the boundaries, appropriately. The simulation results show the effectiveness of the suggestions in the elimination of the cancerous cells in different scenarios.

1. Introduction

The evolution of cancerous cells is due to the growth of a distorted cell replica [11,19], and is commonly described by autonomous evolutionary dynamics [15,20,35]. The use of complex mathematical approaches such as replicator dynamics is investigated to analyze population dynamics of complex evolutionary systems [21,30]. New techniques such as passivity notion are applied to replicator equations and evolutionary dynamics [29], to study the global stability of the system [14]. Replicator equations has been used in network extensions of zero-sum games for optimization in complex systems [28]. Also, evolutionary dynamics was utilized for multi-agent learning that is not connected to equilibrium point concept or utility of single agents [27].

The investigation of biological systems has been studied by complex nonlinear models [10,22,23]. Differential equations are used to predict the possibility of disease elimination [17]. Many parameters of the system, usually leads to having multiple equilibrium points and this makes the stability analysis of such systems much more complicated [37]. There are several well-known control theoretic concepts like Lyapunov or Jacobian methods which are widely used in term of stability analysis of different equilibrium points of the biological systems [4,9]. Adaptive control model was used to personalized drug administration for cancer therapy [5].

Cancer development may be considered as a result of an evolutionary game between normal and offensive cells [2,34]. Therefore, instead of making effort to remove all of the cancer cells which has not been successful until now, therapies have tried to reduce the fitness of offensive cells compared to the normal ones. This approach results in providing the condition for natural selection to remove the cancerous tumor [13]. M.Archetti used evolutionary game theory to model the joint interactions among cancerous cells to study dynamics of the reproduction growth and the effect of therapies on reducing their quantity [1]. Tomlinson [33] proposed a model of a population dynamics including two cell types, one of them with a growth factor advantage to both cells [33]. Recent personalize research works have extended this model up to four cell types, [8,16] considering stochastic and spatial effects [3]. Jorge M. Pacheco et al proposed an evolutionary game method to model the interaction between cancerous plasma cells [26].

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Cancer is a collection of many diseases that have a common feature: over-proliferation. Cancerous cells has many key hallmarks such as: sustaining proliferative signal, evading growth suppressors, resisting cell death, inducing angiogenesis, enabling replicative immortality, activating invasion and metastasis and avoiding immune system signals [18]. It can be studied also from some key aspects such as: inactivation of tumor suppressor genes, activation of oncogenes, telomere erosion, contact inhibition, senescence and necrosis [19]. This work considers the cancer only as a result of inactivation of tumor suppressor genes and the other aspects of cancer are not modeled in this study.

Tumor suppressor genes (TSGs) protect against somatic evolution of cancer. Losing both alleles of a TSG in a single cell represents the suitable conditions for the evolution of cancer [25]. In previous studies, the proposed evolutionary game models employed a few number of effective parameters [6]. The therapeutic suggestions are also proposed which impose some limitations due to the change in the parameters of the game model to apply the treatment method [13]. In this paper also, the inactivation of TSG is studied as one of the momentous and significant causes of development of cancer. Nevertheless, in our research, the therapeutic suggestions are proposed in terms of interaction rates. In this way, the cancer therapy becomes closer to implementation, since the therapies are performed by changing the interaction rates rather than changing the game parameters that alters the natural reproduction ability of different cell types. Therefore, to achieve the desired state of the system where the cancerous cells are removed, interaction rates are suggested in a way that the system includes only favorable stable equilibrium points. To this aim, evolution of cancer is considered as a dynamical system and evolutionary game theory together with replicator dynamics is applied. Different feasible conditions based on the game's parameters are studied using the proposed method. The equilibrium points of the nonlinear dynamical system is derived in terms of parameters and interaction rates and the convergence of the system to those equilibrium points is investigated.

The rest of the paper is organized as follows: Section 2 describes the evolutionary model of the tumor suppressor gene using replicator dynamics. The analysis of the equilibrium points of the model and convergence of the system is given in Section 3. In this section, the proposed interaction rate parameters to provide the conditions of convergence to desired non-cancerous cells are given. Section 4 demonstrates the Simulation results and finally the paper is concluded in Section 5.

2. Modeling

In the proposed model, we will investigate the development of the cancer cells due to inactivation of tumor suppressor genes (TSGs). Although cancers can arise through various mechanisms, in this work we will only focus on cancers that are a consequence of inactivation of TSGs. A TSG can typically be inactivated by any mutation that disrupts the functionality of the genes [24]. The inactivation of TSG is caused by two point mutations. The first mutation inactivates one allele of TSG and the mutant cell becomes a cell with a lost allele. The second mutation which is more probable than the first one, inactivates the second allele of the TSG [24]. Although the first inactivation of the allele doesn't change the cell genotype, it may increase the cell proliferation rate and the affected cell tends to become a cancerous cell (cell with two lost alleles) [24]. In our model each types of these cells are a specific species.

In present study, each one of three different types of cells are a specific species in our model and the evolutionary game theory is employed to model the interaction between them. The purpose is to identify which cell(s) are going to be the evolutionary stable strategy (ESS) and control the evolution in a way that game converges to the desired situation where there is a scanty amount of cancerous cells. The evolutionary game is defined by a set of species (strategies) and the corresponding payoff matrix. We have a set of three strategies $S = \{s_1, s_2, s_3\}$ and the corresponding payoff matrix defined by P. The species in this game are the healthy cells (A^{++}) (i.e. s_1), the cells with one missing (due to the first mutation) allele (A^{+-}), (i.e. s_2), and the cancerous cells which are cells with two missing alleles (A^{--}), (i.e. s_3).

Table 1
Payoff matrix of the game.

$$P = \begin{array}{c} \\ s_1 \\ s_2 \\ s_3 \end{array} \begin{array}{c} \begin{array}{ccc} s_1 & s_2 & s_3 \end{array} \\ \begin{bmatrix} \alpha & \alpha-\delta & \alpha-\xi \\ \beta-\eta+\delta' & \beta-\eta & \beta-\eta-\theta \\ \gamma-\lambda+\xi' & \gamma-\lambda+\theta' & \gamma-\lambda \end{bmatrix} \end{array}$$

The payoffs of the matrix game is defined in Table 1:

Where, the parameter α is sheer payoff that A^{++} cells earn in competition with each other. The parameters β and γ have the same definition as α for A^{+-} and A^{--} cells, respectively. The parameter δ stands for the damage to A^{++} cell, caused by A^{+-} cell and δ' is the benefit that A^{+-} cell gains in this interaction (since A^{+-} is a stronger specie). Identically, the parameters θ, θ' represent the damage caused by A^{+-} and the benefit gained by A^{+-} in interaction between A^{++} and A^{+-}. Also, the parameters ξ and ξ' imply the same meaning as θ, θ' for interaction between A^{+-} and A^{--} cells, respectively. Parameter η stands for the cost of being A^{+-} cell, due to the damage by the immune system to these cells and the parameter λ shows the same concept for A^{--} cells [7].

Although it is possible that parameters δ and δ' be negative, which means that A^{+-} cells are affected by A^{++} cells, it this paper we investigate the case which these parameters are positive [36]. Nevertheless, following the same procedure, it is straightforward to adjust parameters shown in Table 1 to reach the corresponding scenarios, similar to Table 3, when the aforementioned parameters be considered negative. Beside, in a real immune system, in some cases the immune system can help cancerous cells in competition with healthy cells (De Visser et al., 2006) [36] (which means parameters η and λ could be negative here). However, the immune system referred in this research is an abstract idea of what an immune system should do.

2.1. Replicator equations

Our analysis is based on the replicator equation describing the frequency dependent evolutionary dynamics of three well-mixed cell population [3]. Consider, x_1, x_2 and x_3 as the frequency of individuals adopting the strategies s_1, s_2 and s_3, respectively. Eq. (1) represent the evolution of different cell types (strategies).

$$\dot{x}_i = x_i(f_i - M), \qquad i = 1, 2, 3 \tag{1}$$

Where, $f_i = p_i x$ is the average fitness of s_i(p_i is the i^{th} row of the matrix P and $x = [x_1, x_2, x_3]^T$) and M is the average fitness of all strategies as follows:

$$M = Fx$$

Where $F = [\ F_1 \quad F_2 \quad F_3\ ]$. Clearly, $x_1 + x_2 + x_3 = 1$ and it can be easily verified that this condition is always preserved by replicator dynamics define by Eq. (1). The replicator dynamics show that the percentage of the species with fitness more than the average (M) will increase while those with the fitness lower than the average will decrease. The final population consists of the species (one or many) that gained more fitness than the other ones. In this way, the replicator dynamics may converge to different equilibrium points, including the boundary equilibrium points where some