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A Study of Inactivation of TSG and Cancer Therapy: An Evolutionary Game Theory Approach[1]

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***Abstract*— Inactivation of alleles in tumor suppressor genes (TSG) is one of the most important issues that results 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. Different combinations of the equilibrium points of the parameterized nonlinear system is studied and categorized to some cases. In each case, the interaction rates values are suggested in which, the equilibrium points are located in the appropriate location in the state space, such that, at least one of the desired equilibrium points are stable. Based on the suggested interaction rates, it is proved that the system doesn't have any interior equilibrium point and will converge to one of the boundary equilibrium points. In addition, the proposed conditions for interaction rates guarantees that, when a trajectory of the system reaches to the boundaries, then it will converge to a desired equilibrium point.**

Keywords- cancer; tumor supperessor genes; evolutionary game theory; convergency; equilibrium point; interaction rates

I. INTRODUCTION

The investigation of biological systems have been studied by complex nonlinear models [1] [2]. Many parameters of the system, usually leads to having multiple equilibrium points and this makes the stability analysis of such systems much more complicated [3]. 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], [5].

The use of complex mathematical approaches such as replicator dynamics is investigated to analyze population dynamics of complex evolutionary systems [6]. New techniques such as passivity notion are used in replicator equations and evolutionary dynamics [7], to study the global stability of the systems [8]. Replicator equations has been used in network extensions of zero-sum games for optimization in complex systems [9]. Evolutionary dynamics are also utilized for multi-agent learning that is not connected to equilibrium point concept or utility of single agents [10].

The evolution of cancerous cells is due to the growth of a distorted cell replica [11], and is commonly described by autonomous evolutionary dynamics [12]. Cancer development can be looked as a result of an evolutionary game between normal and offensive cells. Therefore, Instead of removing all of the cancer cells which has not been successful attempt till now, therapies have tried to reduce the fitness of offensive cells compared to the normal cells. This results in, providing the condition for natural selection for removal of the cancerous tumor [13]. The evolutionary game theory is also used to model the joint interactions among cancerous cells in order to study the dynamics of the reproduction growth and the effect of therapies [14], [15], [16] . The evolutionary game method is used also to model the interaction between cancerous plasma cells [17].

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 evolution of the cancer [18]. In this paper, the inactivation of TSG is considered as the most important reason for development of the cancer. In previous studies, the proposed evolutionary game model consists of just a few number of effective parameters [19], and some other studies just contain some therapeutic suggestion, which has some limitations regarding the changing of the parameters of the game model as treatment [13]. We assume evolution of the cancer as a dynamical system and apply evolutionary game theory together with replicator dynamics. In this study, we investigate almost all situations that can be happened among game parameters. The equilibrium points of the nonlinear dynamical system is derived in terms of parameters and the convergence of the system to those equilibrium points are studied. In addition, to provide the desired situation of the system [14], that results in removing the cancerous cells the design parameters of the system are suggested such that, the system has only desired stable equilibrium points.

The rest of the paper is organized as follows: Section II describes the evolutionary model of the cancer cells using replicator dynamics. The analysis of the equilibrium points of the model and convergence of the system is given in Section III. In this section, the proposed interaction rate parameters to provide the conditions of convergence to desired non-cancerous cells is given and finally the paper is concluded in Section IV.

II. MODELING

A. Game theoretic modeling

The inactivation of TSG is caused by two point mutations [20]. The first mutation inactivates one allele of TSG and the mutant cell becomes a cell with one lost allele. The second mutation which is more probable than the first one, inactivates the second allele of the cell. Although the first inactivation of

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the allele doesn't change the cell genotype, but inactivation of both alleles increases the cell proliferation rate and the affected cell tends to become a cancerous cell.

The evolutionary game theory is used in this paper, to model the interaction among the mentioned species. We want to analyze, in different condition, which cells going to be the evolutionary stable strategy and how this evolution can be controlled, such that the game converge to the desired cell type. The evolutionary game is defined with 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 included: 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 cells with two missing alleles (A^{--}), (i.e. s_3).

The payoffs of the matrix game is defined as follows:

$$P=\begin{array}{c c} & \begin{array}{ccc} s_1 & s_2 & s_3 \end{array} \\ \begin{array}{c} s_1 \\ s_2 \\ s_3 \end{array} & \begin{bmatrix} 1 & 1-\alpha & 1-\beta \\ 1+\alpha-\varepsilon & 1-\varepsilon & 1-\varepsilon-\gamma \\ 1+\beta-\eta & 1+\gamma-\eta & 1-\eta \end{bmatrix} \end{array} \quad (1)$$

Where, the parameter α stands for the damage on A^{++} cells, caused by A^{+-} cells and the benefit that A^{+-} cell gains in this interaction (since A^{+-} is a stronger species). β and γ are related to the same circumstance for interaction between A^{++} cell and A^{-}, and A^{+-} cell and A^{-}, respectively. The parameter ε stands for the cost of being A^{+-} cell, due to the damage caused by the immune system to these cells and the parameter η shows the same concept for A^{-} cells [20].

B. Replicator equations

Our analysis is based on the replicator equation describing the frequency dependent evolutionary dynamics of three well-mixed cell population [21]. Consider, x_1, x_2 and x_3 as the frequency of individuals adopting the strategies s_1, s_2 and s_3, respectively. The following replicator dynamics represent the evolution of different cell types (strategies) within the tissue.

$$\begin{cases} \dot{x}_1 = x_1(p_1^T x - x^T P x) \\ \dot{x}_2 = x_2(p_2^T x - x^T P x) \\ \dot{x}_3 = x_3(p_3^T x - x^T P x) \end{cases} \quad (2)$$

Where $x^T=[x_1,x_2,x_3]$, p_i^T, $i=1,2,3$ is the i^{th} row of the matrix P, $p_i^T x$, $i=1,2,3$ is the average fitness of s_i (f_i) and $x^T P x$ is the average fitness of all strategies (M). Clearly we have $x_1+x_2+x_3=1$ and it can be easily verified that this condition is always preserved by replicator dynamics (2). The replicator dynamics shows that the frequency of the spices with more fitness then the average fitness will increase, while, those with the fitness lower than the average will decrease. The final population consists of the spices (one or many) that could earn more fitness than the other ones, during the time. In this way, the replicator dynamics can converge to different equilibrium points, including the boundary equilibrium points, where some of x_i are equal to zero (i.e. some of the species will be removed), or interior equilibrium point, where, all the spices coexist with the same fitness [22].

c. Interaction rates

In the ordinary replicator dynamics, the probability of interaction between strategies depends uniformly on their proportion in environment. However, in reality, some other factors affect the interaction probability between strategies. For example, according to effect of chemical reactions on the cells, some species has more tendency to interact with some special species. This fact naturally results in more interaction between some species rather than other ones. These factors are usually considered as the interaction rate parameters [23]. The interaction rates of different cell types is defined by the symmetric matrix R.

$$R=\begin{array}{c c} & \begin{array}{ccc} s_1 & s_2 & s_3 \end{array} \\ \begin{array}{c} s_1 \\ s_2 \\ s_3 \end{array} & \begin{bmatrix} r_{11} & r_{12} & r_{13} \\ r_{21} & r_{22} & r_{23} \\ r_{31} & r_{32} & r_{33} \end{bmatrix} \end{array} \quad (3)$$

Where, the strategy s_i interacts with s_j, by the reaction rate $r_{ij}=r_{ji}$. Without loss of generality, we consider one of the interaction rates equal to one (i.e. r_{22}). By taking into account the interaction rates, the payoffs of the matrix game would be as follows:

$$Q(x)=\left[q_{ij}(x)\right]_{3\times 3}, where: q_{ij}=\frac{r_{ij}}{r_{i1}x_1+r_{i2}x_2+r_{i3}x_3}p_{ij} \quad (4)$$

Therefore, the modified payoff matrix of the game is not constant and is dependent on the frequencies of the strategies and this makes the analysis of the replicator dynamics more complicated.

In our analysis, we consider the replicator dynamics (2) together with the effect of interaction rates which results in the following dynamic equations:

$$\begin{cases} \dot{x}_1 = x_1(q_1^T x - x^T Q(x) x) \\ \dot{x}_2 = x_2(q_2^T x - x^T Q(x) x) \\ \dot{x}_3 = x_3(q_3^T x - x^T Q(x) x) \end{cases} \quad (5)$$

Where, q_i, $i=1,2,3$ is the i^{th} row of the matrix $Q(x)$.

III. ANALYSIS

In this section, different equilibrium points of the dynamic system (5) is achieved and convergence of the system to those equilibrium points is analyzed. The final goal of this study is to provide the conditions such that the system converges to a *desired* equilibrium point(s) (i.e. non-cancerous). For this purpose, different situations of the system is investigated, based on different conditions on the system's parameters. Then, the stability of boundary equilibrium points are studied on the boundaries. Because our desired equilibrium points are within the boundary ones (i.e. the cancerous type is equal to zero).

A. Analysis of equilibrium points on the border of $x_2 = 0$

In this case, the replicator dynamics (5) is reduced as:

$$\begin{cases} \dot{x}_1 = x_1(q_1^T x_1 - x^T Q(x)x) \\ \dot{x}_3 = x_3(q_3^T x_3 - x^T Q(x)x) \end{cases} \quad (6)$$

Since, $x_1 + x_3 = 1$, after some algebra, (6) can be written as the following one state equation:

$$\dot{x}_1 = x_1(1-x_1)[(q_{11} - q_{13} - q_{31} + q_{33})x_1 + q_{13} - q_{33}] \quad (7)$$

Where:

$$q_{ij} = \frac{r_{ij}}{r_{i1}x_1 + r_{i3}(1-x_1)} p_{ij} \quad (8)$$

$x_1 = 0, x_1 = 1$, are two trivial equilibrium points of (7). Potentially, there are some interior point(s), which are the feasible solution(s) of the following equation (i.e. those are between zero and one):

$$(q_{11} - q_{13} - q_{31} + q_{33})x_1 + q_{13} - q_{33} = 0 \quad (9)$$

The solutions of (9) are:

$$x_1 = \frac{y \pm \sqrt{s}}{2z} \quad (10)$$

Where:

$$\begin{cases} y = (p_{13} - p_{31})r_{13}^2 + (p_{11} - p_{33})r_{11}r_{13} + 2(p_{33} - p_{13})r_{13}r_{33} \\ s = (p_{11} - p_{33})^2 r_{11}^2 r_{33}^2 + (p_{13} - p_{31})r_{13}^4 + (4p_{11}p_{33} + 4p_{13}p_{31} \\ -2p_{11}p_{13} - 2p_{11}p_{31} - 2p_{13}p_{33} - 2p_{31}p_{33})r_{13}^2 r_{11} r_{33} \\ z = (p_{13} - p_{31})r_{13}^2 + (p_{31} - p_{11})r_{11}r_{13} + (p_{11} - p_{33})r_{11}r_{33} \end{cases} \quad (11)$$

If $s = 0$,then bifurcation occurs in system (7) [24] and this is the case if $(r_{11}r_{33}/r_{13}^2) = k_1$, in which:

$$k_1 = \frac{1}{(p_{11} - p_{33})^2}(p_{11}(p_{13} + p_{31} - 2p_{33}) + p_{13}(p_{33} - 2p_{31}) + p_{31}p_{33}) \\ + \frac{1}{(p_{11} - p_{33})^2}((p_{11} - p_{13})(p_{11} - p_{31})(p_{13} - p_{33})(p_{31} - p_{33}))^{\frac{1}{2}} \quad (12)$$

Therefore $r_{11}r_{33}/r_{13}^2$ can be defined as the system's bifurcation parameter [23].

Based on the different system's parameters conditions, the stability of the system is studied in the following cases: [19].

1. $p_{11} > p_{31}, p_{33} > p_{13}$: This case can be divided into 3 different subcases:

1.1. $p_{11} > p_{33}$: In this condition, if $(r_{11}r_{33}/r_{13}^2) > k_1$, then both solutions of the (8) lay in [0 1].

1.2. $p_{13} > p_{31}$: In this scenario, if $(r_{11}r_{33}/r_{13}^2) < k_1$, both solutions of the (8) will be in [0 1].

1.3. If conditions in the cases 1.1 and 1.2 are not met, then the solutions of the (8) will never lay in the range of [0 1].

2. $p_{11} < p_{31}, p_{33} < p_{13}$: This is a desired situation and as a result, it is enough to provide the conditions such that the solutions of the (9) lay out of the range [0 1]. This situation can be divided into three cases:

2.1. $p_{31} > p_{13}$: In this case if $(r_{11}r_{33}/r_{13}^2) > k_1$, then the solutions of (8) are not in the range [0 1].

2.2. $p_{33} > p_{11}$: In this case if $(r_{11}r_{33}/r_{13}^2) < k_1$, then the solutions of (8) are not in the range [0 1].

2.3. If conditions in 2.1 and 2.2 are not met, then the answer of the (8) will never lay in [0 1].

3. $p_{11} > p_{31}, p_{33} > p_{13}$: In this scenario, one of the solutions of (8) is in the range of [0 1].

4. $p_{31} > p_{11}, p_{13} > p_{33}$: In this case, one of the solutions of (8) is in the range of [0 1].

Proposition 1: In the dynamical system presented by (7) and (8), the equilibrium point at $x_1 = 0$ ($x_3 = 1$) has an attraction manifold (distraction manifold) on boundary of $x_2 = 0$, if $p_{33} > p_{13}$ ($p_{33} < p_{13}$). This condition is hold for the equilibrium point at $x_1 = 1$ ($x_3 = 0$), if $p_{11} > p_{31}$ ($p_{11} < p_{31}$).

Proof:

We can write (7) and (9) in this form:

$$\begin{cases} \dot{x}_1 = x_1(f_1 - M) \\ \dot{x}_3 = x_3(f_3 - M) \end{cases}, where: \begin{cases} f_1 = x_1 q_{11} + x_3 q_{13} \\ f_3 = x_1 q_{31} + x_3 q_{33} \\ M = x_1 f_1 + x_3 f_3 \end{cases} \quad (13)$$

Then we have:

$$\begin{cases} \frac{\partial \dot{x}_1}{\partial x_1} = f_1 - M + x_1(\frac{\partial f_1}{\partial x_1} - \frac{\partial M}{\partial x_1}) \\ \frac{\partial \dot{x}_3}{\partial x_3} = f_3 - M + x_3(\frac{\partial f_3}{\partial x_3} - \frac{\partial M}{\partial x_3}) \end{cases} \rightarrow \begin{cases} x_1 = 0 \Rightarrow \frac{\partial \dot{x}_1}{\partial x_1} = f_1 - M = p_{13} - p_{33} \\ x_3 = 0 \Rightarrow \frac{\partial \dot{x}_3}{\partial x_3} = f_3 - M = p_{31} - p_{11} \end{cases}$$

Therefore if $p_{13} - p_{33} < 0$ ($p_{13} - p_{33} > 0$), then $x_1 = 0$ has attraction manifold (distraction manifold) on $x_2 = 0$, and if $p_{31} - p_{11} < 0$ ($p_{31} - p_{11} > 0$), then $x_1 = 1$ has attraction manifold (distraction manifold) on $x_2 = 0$ border and the proof is completed. ■

To ensure the convergence of the system to desired equilibrium point (i.e. $x_1 = 1$ on boundary of $x_2 = 0$), we propose conditions such that the attraction manifold of the equilibrium point that is located close to $x_1 = 1$ becomes almost entire boundary of $x_2 = 0$, in all cases. To this end, system bifurcation parameter is adjusted such that the solution(s) of (9) lay in our desired place on the boundary. The adjustment of bifurcation parameter for just two dimensional system is given in [23], similarly we expressed our suggestion.

The summery of the analysis is given in second column of Table 1.

In all of the pictures, the red points indicate the unstable equilibrium points on each boundary (can be saddle point due to the instability in another boundary). The green points are the stable equilibrium points on the boundaries (they are either stable or saddle) and blue points are the saddle point equilibriums on the boundaries.

Proposition 2: In the case 1.1, if $(r_{11}r_{33}/r_{13}^2) > k_1$ both solutions of (9) are in the range [0 1]. The solution which is close to 0 is unstable and the other one is stable (in the boundary of $x_2 = 0$).

Proof: Assume that:

$$h(x_1) = \dot{x}_1 = x_1(1 - x_1)[(q_{11} - q_{13} - q_{31} + q_{33})x_1 + q_{13} - q_{33}]$$

From proposition 1 we know that $x_1 = 0$ is stable and $x_1 = 1$ is unstable on the boundary of $x_2 = 0$. Therefore:

$$x_1 = 0 \Rightarrow \frac{\partial h(x_1)}{\partial x_1} < 0, x_1 = 1 \Rightarrow \frac{\partial h(x_1)}{\partial x_1} > 0$$

According to Bolzano theorem [25], it can be easily proofed for two other equilibrium points those are solutions of (9) we have:

$$x_1 = \frac{y - \sqrt{s}}{2z} \Rightarrow \frac{\partial h(x_1)}{\partial x_1} > 0, x_1 = \frac{y + \sqrt{s}}{2z} \Rightarrow \frac{\partial h(x_1)}{\partial x_1} < 0$$

Therefore, the solution of (9) that is nearer to $x_1 = 0$ is unstable on boundary of $x_2 = 0$ and other solution of (9) is stable on this boundary. ■

The proof of other cases are in the same way and is not given here due to the lack of space.

B. Analysis of equilibrium points on the border of $x_1 = 0$

In this scenario, the general idea of finding different equilibrium points of the system and stability analysis is similar to the last section (Section A). But, in this case we define the bifurcation parameter as $r_{33}/(r_{23})^2$ and k_2 instead of k_1 as follows:

$$k_2 = \frac{1}{(p_{22}-p_{33})^2}\left(p_{22}(p_{23}+p_{32}-2p_{33})+p_{23}(p_{33}-2p_{32})+p_{32}p_{33}\right) + \frac{1}{(p_{22}-p_{33})^2}\left(4(p_{22}-p_{23})(p_{22}-p_{32})(p_{23}-p_{33})(p_{32}-p_{33})\right)^{\frac{1}{2}}$$

In addition, similar to Section *A*, the suggested values of the interaction rates are given in Table 1. The purpose of these conditions is to ensure that almost entire boundary of $x_1 = 0$ is an attraction manifold for the equilibrium point that is located close to $x_2 = 1$, which is our desired equilibrium point. The summery of the results is given in second column of Table 1.

Similarly, the other cases on this border that is mentioned in Table 1, are as:

1.1: $p_{32} > p_{22} > p_{33} > p_{23}$, 1.2: $p_{33} > p_{23} > p_{32} > p_{22}$

2.1: $p_{22} > p_{32} > p_{23} > p_{33}$, 2.2: $p_{23} > p_{33} > p_{22} > p_{32}$

3: $p_{22} > p_{32}, p_{33} > p_{23}$, 4: $p_{32} > p_{22}, p_{23} > p_{33}$

C. *Investigating the equilibrium points on $x_3 = 0$ boundary*

The equilibrium points on boundary of $x_3 = 0$ are not investigated, since, there is no cancerous cells type in all the cases on this boundary. Therefore, the convergence to any of those equilibrium points is considered as a desired condition.

D. Interior equilibrium point

Due to the fact that any interior point includes some proportion of cancerous cells, this kind of equilibrium points are not desired and as hence it is important to provide the conditions to prevent the system to have such an equilibrium point.

For this purpose, we consider different combinations of equilibrium points on the boundaries of $x_2 = 0$ and $x_1 = 0$ simultaneously. Then in each case, the conditions of "*not having any interior equilibrium point*" is given.

The second column of Table 1 gives some sufficient conditions in which, the stable equilibrium points on the boundaries are placed in the desired locations and third column includes the sufficient conditions such that the replicator dynamics (5) doesn't have any interior equilibrium point.

Proposition 3: In the case (1.1-1.1) (Table 1) by applying the conditions proposed in third column, (i.e. $r_{11} \to \infty$ and $p_{11} \neq p_{33}$) the replicator dynamics (5) has no interior equilibrium point.

Proof: From (2) in the interior equilibrium point the average fitness of all strategies are the same. Hence we have: $f_1 = f_2 = f_3$. According to the condition (1.1-1.1) in Tables 1, to ensure the appropriate locations for the equilibrium points we have (second column):

$$\begin{cases} r_{11}r_{33} \to \infty \\ r_{13} \to 0 \end{cases} \text{and} \begin{cases} r_{33} \to \infty \\ r_{23} \to 0 \end{cases}$$

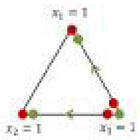
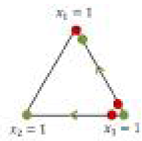
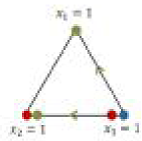
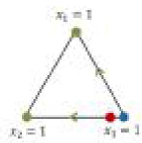
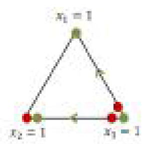
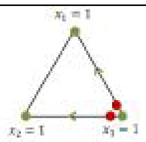
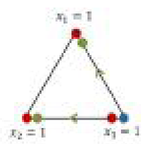
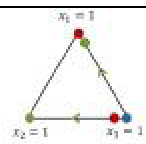
if $r_{11} \to \infty$, then: $\begin{cases} f_1 = p_{11} \\ f_3 = p_{33} \end{cases} \Rightarrow if : p_{11} \neq p_{33} \Rightarrow f_1 \neq f_3$

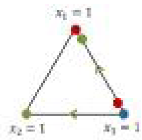
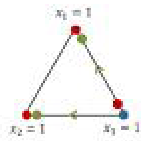
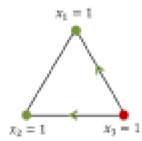
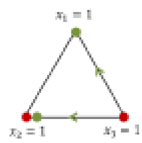
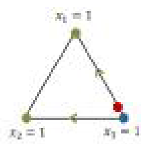
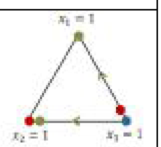
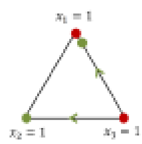
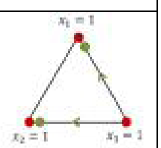
But since $p_{11} \neq p_{33}$ we have $f_1 \neq f_3$ and hence, there is no interior equilibrium point in this case (i.e. $r_{11} \to \infty$ and $p_{11} \neq p_{33}$). In the other cases, in a similar way, it can be proved that the proposed suggestion for interaction rates and system's parameters (in Tables 1) are the sufficient conditions to have no interior equilibrium point in each case. But the proofs are omitted for sake of brevity. ■

E. *Convergence of the evolutionary game*

Based on the proposed conditions provided in Table 1, in each case, the system doesn't have any interior equilibrium point. In addition, all of the stable equilibrium points (green points on the figures) are in non-cancerous ones and the system always converges to one of the green points.

Table 1. Results of analysis and proposed conditions to have appropriate stable equilibrium point(s) and have no interior equilibrium point

Case	conditions to have appropriate equilibrium points	Sufficient condition to have not interior equilibrium point	Equilibrium points
1.1 -1.1	$r_{11}r_{33} \to \infty, r_{13} \to 0$ $r_{33} \to \infty, r_{23} \to 0$	$r_{11} \to \infty, p_{11} \neq p_{33}$	
1.1 -1.2	$r_{11}r_{33} \to \infty, r_{13} \to 0$ $r_{33} \to 0, r_{23} \to \infty$	$p_{11} \neq p_{23}$	
1.2 -1.1	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $r_{33} \to \infty, r_{23} \to 0$	$r_{12} \to 0, p_{13} \neq p_{22}$	
1.2 -1.2	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $r_{33} \to 0, r_{23} \to \infty$	$p_{13} \neq p_{23}$	
1.1-3	$r_{11}r_{33} \to \infty, r_{13} \to 0$ $r_{33} \to 0, r_{23} \to \infty$	$p_{11} \neq p_{32}$	
1.2-3	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $r_{33} \to 0, r_{23} \to \infty$	$p_{23} \neq p_{32}$	
2.1-1.1	$(r_{11}r_{33} / r_{13}^2) > k_1$ $r_{33} \to \infty, r_{23} \to 0$	$r_{11} \to \infty, p_{11} \neq p_{33}$	
2.1-1.2	$(r_{11}r_{33} / r_{13}^2) > k_1$ $r_{33} \to 0, r_{23} \to \infty$	$p_{23} \neq p_{32}$	
2.2-1.1	$(r_{11}r_{33} / r_{13}^2) < k_1$ $r_{33} \to \infty, r_{23} \to 0$	$r_{13} \to \infty, p_{13} \neq p_{33}$	
2.2-1.2	$(r_{11}r_{33} / r_{13}^2) < k_1$ $r_{33} \to 0, r_{23} \to \infty$	$p_{23} \neq p_{32}$	
2.1-3	$(r_{11}r_{33} / r_{13}^2) > k_1$ $r_{33} \to 0, r_{23} \to \infty$	$p_{22} \neq p_{32}$	
2.2-3	$(r_{11}r_{33} / r_{13}^2) < k_1$ $r_{33} \to 0, r_{23} \to \infty$	$p_{22} \neq p_{32}$	
3-1.1	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $r_{33} \to \infty, r_{23} \to 0$	$r_{12} \to 0, p_{13} \neq p_{22}$	
3-1.2	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $r_{33} \to 0, r_{23} \to \infty$	$p_{13} \neq p_{23}$	
3 -3	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $r_{33} \to 0, r_{23} \to \infty$	$p_{13} \neq p_{23}$	
4 -1.1	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $r_{33} \to \infty, r_{23} \to 0$	$p_{13} \neq p_{22}$	
4-1.2	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $r_{33} \to 0, r_{23} \to \infty$	$p_{13} \neq p_{23}$	
4-3	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $r_{33} \to 0, r_{23} \to \infty$	$p_{13} \neq p_{23}$	

Case	conditions to have appropriate equilibrium points	Sufficient condition to have not interior equilibrium point	Equilibrium points
1.1-2.1	$r_{11}r_{33} \to \infty, r_{13} \to 0$ $(r_{33} / (r_{23})^2) > k_2$	$r_{11}, r_{13} \to \infty, p_{11} \neq p_{33}$	
1.1-2.2	$r_{11}r_{33} \to \infty, r_{13} \to 0$ $(r_{33} / (r_{23})^2) < k_2$	$r_{11}, r_{23} \to \infty, p_{11} \neq p_{23}$	
1.2-2.1	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $(r_{33} / (r_{23})^2) > k_2$	$p_{13} \neq p_{31}$	
1.2-2.2	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $(r_{33} / (r_{23})^2) < k_2$	$p_{13} \neq p_{31}$	
1.1-4	$r_{11}r_{33} \to \infty, r_{13} \to 0$ $r_{33} \to 0, r_{23} \to \infty$	$p_{11} \neq p_{32}$	
1.2-4	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $r_{33} \to 0, r_{23} \to \infty$	$p_{23} \neq p_{32}$	
2.1-2.1	$(r_{11}r_{33} / r_{13}^2) > k_1$ $(r_{33} / (r_{23})^2) > k_2$	$r_{11}, r_{33} \to \infty, p_{11} \neq p_{33}$	
2.1-2.2	$(r_{11}r_{33} / r_{13}^2) > k_1$ $(r_{33} / (r_{23})^2) < k_2$	$r_{11}, r_{23} \to \infty, p_{11} \neq p_{22}$	
2.2-2.1	$(r_{11}r_{33} / r_{13}^2) < k_1$ $(r_{33} / (r_{23})^2) > k_2$	$r_{33} \to \infty, r_{11}, r_{12} \to 0$ $p_{13} \neq p_{33}$	
2.2-2.2	$(r_{11}r_{33} / r_{13}^2) < k_1$ $(r_{33} / (r_{23})^2) < k_2$	$r_{13} \to \infty, p_{13} \neq p_{31}$	
2.1-4	$(r_{11}r_{33} / r_{13}^2) > k_1$ $r_{33} \to 0, r_{23} \to \infty$	$p_{22} \neq p_{32}$	
2.2-4	$(r_{11}r_{33} / r_{13}^2) < k_1$ $r_{33} \to 0, r_{23} \to \infty$	$p_{22} \neq p_{32}$	
3-2.1	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $(r_{33} / (r_{23})^2) > k_2$	$p_{13} \neq p_{31}$	
3-2.2	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $(r_{33} / (r_{23})^2) < k_2$	$p_{13} \neq p_{31}$	
3-4	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $r_{33} \to 0, r_{23} \to \infty$	$p_{13} \neq p_{23}$	
4-2.1	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $(r_{33} / (r_{23})^2) > k_2$	$p_{13} \neq p_{31}$	
4-2.2	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $(r_{33} / (r_{23})^2) < k_2$	$p_{13} \neq p_{31}$	
4-4	$r_{11}r_{33} \to 0, r_{13} \to \infty$ $r_{33} \to 0, r_{23} \to \infty$	$p_{13} \neq p_{23}$	

Proposition 4: If the replicator dynamics (5) has no interior equilibrium point, then the system converges to one of the desired equilibrium point(s) on the boundaries.

Proof: It is well-known that without any interior equilibrium point, our system doesn't have any limit cycle in the triangle state space [26]. Moreover, according to Poincare-Bendixon theory [27], if the dynamical system starts from an initial condition inside the triangle space, then the trajectory converges to the boundaries in limited time. Therefore in our case, the system (5) converges to one of the green points in Table I. Because if a trajectory goes to any point of a boundary, then it will converge to a stable point in a boundary. Since we designed the equilibrium points of each boundary such that, the entire boundary is an attraction manifold for our desired equilibrium point, replicator dynamics (5) converge to a desired (green) equilibrium point on the boundaries.

IV. Conclusion

Our therapeutic suggestion to prevent cell population to become cancerous is to change the interaction parameters as given in Table 1 by medical approaches. We suggest detachment between different cell types in tissue, that can changes cells interaction rate. In this way, with natural selection, cancerous cells will remove and cell population will converge to non-cancerous cells. The suggested parameters of interaction rates in Table 1, are sufficient conditions for convergence of the game to appropriate equilibrium points for each initial condition. Although our proposes in Table 1 are not mild conditions and in reality it's not possible to achieve these conditions (it is most foible of modeling with evolutionary games), but if we changes parameters in direction of this proposes (for example if our propose is $r_{11} \to \infty$, we apply limited increasing on this parameter) finally, system will converge to appropriate equilibrium points with mild conditions in interaction rate parameters. ■

References

[1] T. Nguyen, A. Khosravi, D. Creighton, and S. Nahavandi, "Epidemiological dynamics modeling by fusion of soft computing techniques," in *Neural Networks (IJCNN), The 2013 International Joint Conference on*, 2013, pp. 1-8.

[2] M. Z. Mehrjerdi, G. Amoabediny, B. Moshiri, A. Ashktorab, and B. N. Araabi, "Model free predictive control for a nonlinear biological system with intelligent optimization approach," in *Control and Decision Conference (CCDC), 2013 25th Chinese*, 2013, pp. 2288-2293.

[3] J. Xiong and T. Zhou, "Parameter identification for nonlinear state-space models of a biological network via linearization and robust state estimation," in *Control Conference (CCC), 2013 32nd Chinese*, 2013, pp. 8235-8240.

[4] F. Blanchini, E. Franco, and G. Giordano, "Determining the structural properties of a class of biological models," in *CDC*, 2012, pp. 5505-5510.

[5] E. August, G. Craciun, and H. Koeppl, "Finding invariant sets for biological systems using monomial domination," in *CDC*, 2012, pp. 3001-3006.

[6] D. Liao and T. D. Tlsty, "Evolutionary game theory for physical and biological scientists. II. Population dynamics equations can be associated with interpretations," *Interface focus,* vol. 4, p. 20140038, 2014.

[7] E. Ramírez-Llanos and N. Quijano, "A population dynamics approach for the water distribution problem," *International Journal of Control,* vol. 83, pp. 1947-1964, 2010.

[8] M. J. Fox and J. S. Shamma, "Population games, stable games, and passivity," *Games,* vol. 4, pp. 561-583, 2013.

[9] G. Piliouras and J. S. Shamma, "Optimization despite chaos: Convex relaxations to complex limit sets via Poincaré recurrence," in *Proceedings of the Twenty-Fifth Annual ACM-SIAM Symposium on Discrete Algorithms*, 2014, pp. 861-873.

[10] G. Piliouras, C. Nieto-Granda, H. I. Christensen, and J. S. Shamma, "Persistent patterns: multi-agent learning beyond equilibrium and utility," in *Proceedings of the 2014 international conference on Autonomous agents and multi-agent systems*, 2014, pp. 181-188.

[11] D. Hanahan and R. A. Weinberg, "Hallmarks of cancer: the next generation," *cell,* vol. 144, pp. 646-674, 2011.

[12] B. Vogelstein and K. W. Kinzler, "Cancer genes and the pathways they control," *Nature medicine,* vol. 10, pp. 789-799, 2004.

[13] D. Dingli, F. Chalub, F. Santos, S. Van Segbroeck, and J. Pacheco, "Cancer phenotype as the outcome of an evolutionary game between normal and malignant cells," *British journal of cancer,* vol. 101, pp. 1130-1136, 2009.

[14] M. Archetti, "Evolutionary game theory of growth factor production: implications for tumour heterogeneity and resistance to therapies," *British journal of cancer,* vol. 109, pp. 1056-1062, 2013.

[15] D. Basanta, J. G. Scott, R. Rockne, K. R. Swanson, and A. R. Anderson, "The role of IDH1 mutated tumour cells in secondary glioblastomas: an evolutionary game theoretical view," *Physical biology,* vol. 8, p. 015016, 2011.

[16] M. Gerstung, H. Nakhoul, and N. Beerenwinkel, "Evolutionary games with affine fitness functions: applications to cancer," *Dynamic Games and Applications,* vol. 1, pp. 370-385, 2011.

[17] J. M. Pacheco, F. C. Santos, and D. Dingli, "The ecology of cancer from an evolutionary game theory perspective," *Interface focus,* vol. 4, p. 20140019, 2014.

[18] M. A. Nowak, F. Michor, N. L. Komarova, and Y. Iwasa, "Evolutionary dynamics of tumor suppressor gene inactivation," *Proceedings of the National Academy of Sciences of the United States of America,* vol. 101, pp. 10635-10638, 2004.

[19] L. A. Bach, S. Bentzen, J. Alsner, and F. B. Christiansen, "An evolutionary-game model of tumour–cell interactions: possible relevance to gene therapy," *European Journal of Cancer,* vol. 37, pp. 2116-2120, 2001.

[20] D. Basanta, J. G. Scott, M. N. Fishman, G. Ayala, S. W. Hayward, and A. R. Anderson, "Investigating prostate cancer tumour–stroma interactions: clinical and biological insights from an evolutionary game," *British journal of cancer,* vol. 106, pp. 174-181, 2012.

[21] M. Attal, J.-L. Harousseau, A.-M. Stoppa, J.-J. Sotto, J.-G. Fuzibet, J.-F. Rossi, *et al.*, "A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma," *New England Journal of Medicine,* vol. 335, pp. 91-97, 1996.

[22] R. Cressman, *Evolutionary dynamics and extensive form games* vol. 5: MIT Press, 2003.

[23] C. Taylor and M. A. Nowak, "Evolutionary game dynamics with non-uniform interaction rates," *Theoretical population biology,* vol. 69, pp. 243-252, 2006.

[24] J. M. T. Thompson and H. B. Stewart, *Nonlinear dynamics and chaos*: John Wiley & Sons, 2002.

[25] D. F. Belding and K. J. Mitchell, *Foundations of Analysis*: Courier Corporation, 2008.

[26] E. M. Izhikevich, *Dynamical systems in neuroscience*: MIT press, 2007.

[27] G. Teschl, *Ordinary differential equations and dynamical systems* vol. 140: American Mathematical Soc., 2012.