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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.

Keywords: Tumor Suppressor Gene; Evolutionary Game Theory; Equilibrium point

I. Introduction

The evolution of cancerous cells is due to the growth of a distorted cell replica (Hanahan and Weinberg, 2011, Bozic et al., 2013), and is commonly described by autonomous evolutionary dynamics (Vogelstein and Kinzler, 2004, Gatenby et al., 2010, Lambert et al., 2011). The use of complex mathematical approaches such as replicator dynamics is investigated to analyze population dynamics of complex evolutionary systems (Liao and Tlsty, 2014, Roca et al., 2009). New techniques such as passivity notion are applied to replicator equations and evolutionary dynamics (Ramirez-Llanos and Quijano, 2010), to study the global stability of the system (Fox and Shamma, 2013). Replicator equations has been used in network extensions of zero-sum games for optimization in complex systems (Piliouras and Shamma, 2014). Also, evolutionary dynamics was utilized for multi-agent learning that is not connected to equilibrium point concept or utility of single agents (Piliouras et al., 2014).

The investigation of biological systems has been studied by complex nonlinear models (Mehrjerdi et al., 2013, Nguyen et al., 2013, Bologna et al., 2016). Differential equations are used to predict the possibility of disease elimination (Greenhalgh et al., 2015). Many parameters of the system, usually leads to having multiple equilibrium points and this makes the stability analysis of such systems much more complicated (Xiong and Zhou, 2013). 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 (August et al., 2012, Blanchini et al., 2012). Adaptive control model was used to personalized drug administration for cancer therapy (Babaei and Salamci, 2015).

Cancer development may be considered as a result of an evolutionary game between normal and offensive cells (Tomlinson and Bodmer, 1997, Archetti and Scheuring, 2011). 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 (Dingli et al., 2009). 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 (Archetti, 2013). Tomlinson (1997) proposed a model of a population dynamics including two cell types, one of them with a growth factor advantage to both cells (Tomlinson, 1997). Recent personalize research works have extended this model up to four cell types, (Basanta et al., 2011, Gerstung et al., 2011) considering stochastic and spatial effects (Bach* et al., 2003). Jorge M. Pacheco et al proposed an evolutionary game method to model the interaction between cancerous plasma cells (Pacheco et al., 2014).

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 (Hanahan and Weinberg, 2000). 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 (Hanahan and Weinberg, 2011). 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 (Nowak et al., 2004). In previous studies, the proposed evolutionary game models employed a few number of effective parameters (Bach et al., 2001). 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 (Dingli et al., 2009). 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 II 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 III. In this section, the proposed interaction rate parameters to provide the conditions of convergence to desired non-cancerous cells are given. Section IV demonstrates the Simulation results and finally the paper is concluded in Section V.

II. 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 (Nowak, 2006). 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 (Nowak, 2006). 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) (Nowak, 2006). 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).

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

Table 1. Payoff matrix of the game

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

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 (Basanta et al., 2012).

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 (Wodarz and Komarova, 2005). 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) (Wodarz and Komarova, 2005) (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.

A. Replicator equations

Our analysis is based on the replicator equation describing the frequency dependent evolutionary dynamics of three well-mixed cell population (Attal et al., 1996). Consider, x_1, x_2 and x_3 as the frequency of individuals adopting the strategies s_1, s_2 and s_3, respectively. Equation (1) represent the evolution of different cell types (strategies).

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

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 of x_i s are equal to zero (i.e. some species will be removed), or interior equilibrium point where all the species coexist with the same fitness (Cressman, 2003).

B. Non-uniform Interaction rates

In ordinary replicator dynamics, the probability of interaction between strategies completely depends on their proportion in environment. However, in real state condition, some other factors

affect the rate of interaction between strategies. 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 can be considered as the interaction rate parameters (Taylor and Nowak, 2006).

The interaction rates between different cell types is defined by the symmetric matrix R as shown in table 2.

Table 2. Non-Uniform interaction rates

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

Where the strategy s_i and s_j interact with each other by the reaction rate $r_{ij} = r_{ji}$ (and $r_{ij} \neq 0$). By taking into account the interaction rates, the payoffs of the matrix game is formulated as follows:

$$Q(x) = \left[q_{ij}(x) \right]_{3\times 3} \qquad (2)$$

Where: $q_{ij} = \dfrac{r_{ij}}{\sum_{k=1}^{3} r_{ik} x_k} p_{ij}$ (3)

It is obvious that the modified payoff matrix is not constant and depends on the frequencies of the strategies which makes the analysis of the replicator dynamics more complicated.

In our analysis, we consider the replicator dynamics (1) together with the effect of interaction rates which results:

$$f_i = q_i x$$

$$M = x^T Q(x) x$$

Where q_i is the i^{th} row of the matrix $Q(x)$.

III. Analysis

In this section equilibrium points and convergence of the system is investigated. The purpose is to converge the system to the desired region consisting the least number of cancerous cells. We represent the system's state space as a two- dimensional triangle with vertices at the three pure strategies (S_1, S_2, S_3) which means that on the vertices the frequency of two cell types are zero and the frequency of the other one is equal to one. On triangle's sides, frequency of one cell type is zero and the other ones are non-zero. Finally, in the interior points of the triangle, percentage of all cell types are non-zero.

We divide the interior part of the state space into three regions as follows and is illustrated in Figure (1).

Region 1 $x_3 < \sigma$

Region 2 $\sigma < x_3 < 1-\varepsilon$

Region 3 $1-\varepsilon < x_3 < 1$

Where σ and $\mathcal{E}$ are infinitesimal magnitudes depending on specific problem. In fact, we want the system converges to the region 1 if the system is initialized on any point in region 1 or 2 ($x_3 < 1-\varepsilon$). Since boundaries of the regions are arbitrary, they are determined based on the system's initial condition so that initial condition falls into region 1 or 2. Then, the system will converge to the desired point regardless of initial conditions.

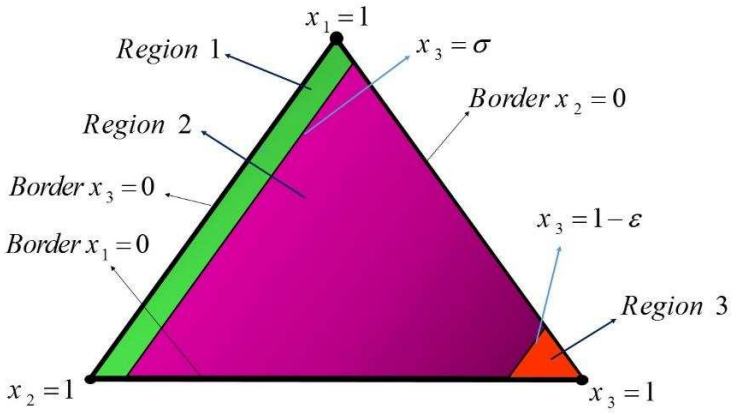


Figure 1. Dividing the system state space into three separated regions

The proposed method is discussed in following 4 steps:

First step: In this step the system is studied in $x_1 = 0$ and $x_2 = 0$ boundaries. Hence, the game will experience four various conditions depending on its parameters' value on aforementioned boundaries. For each situation we propose to embed all the equilibrium points on sections of $x_1 = 0$ and $x_2 = 0$ borders that lies in region 1 or 3 (to have no equilibrium point on the border located in region 2) and make the section of borders in region 2 an attraction manifold to an equilibrium point in region 1 .This means that in all points of these borders the game will converge to region 1 which is desirable. Thus, if a trajectory reaches the borders it will eventually converge to region 1.

Afterwards, a combination of different conditions on the aforementioned borders ($x_1 = 0$ and $x_2 = 0$) is considered, which results in 16 distinguished conditions for the whole game. Then we will state our proposal to achieve our goal in each case (placing all equilibrium points on sections of $x_1 = 0$ and $x_2 = 0$ borders that settles in region 1 or 3 and make the section of the border located in region 2 an attraction manifold to an equilibrium point in subspace 1).

Second step: In this step the equilibrium points in region 2 for all 16 game conditions are identified. The region 2 is divided into three separated sub-regions 2.1, 2.2 and 2.3 as shown in Figure (2). Suggestions are presented to eliminate the chance of having any equilibrium point in these regions. Consequently, there is no equilibrium point in region 2 for all game conditions. In other words, the game does not converge to interior equilibrium points where there is substantial amount of cancerous cells.

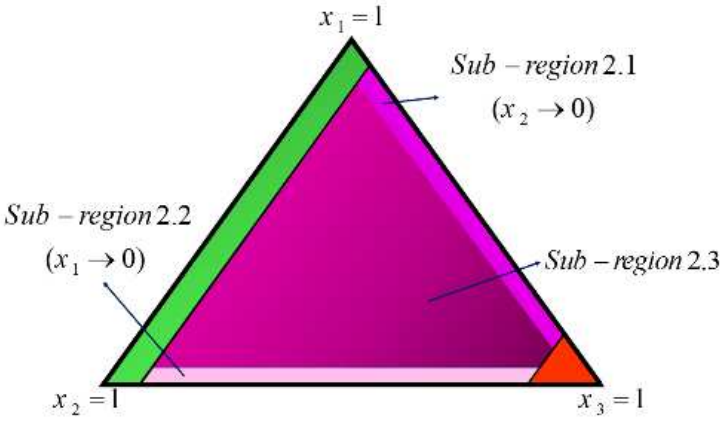


Figure 2. Dividing region 2 into three sub-regions

Third step: Conditions in which the system's trajectory cannot enter region 3 from region 2 in all of the game's determined situations are discussed.

Fourth step: the situation in which the system do not exit from region 1 in all of the game condition is investigated. Therefore, the system acts in domain of region 1 permanently, expressing a perfect condition.

This four-step method guarantee the convergence of system to region 1 where there is infinitesimal percentage of cancerous cells for any arbitrary initial condition inside the triangle. To precisely illustrate the phenomenon, two possible condition may happen as follows.

1- If the percentage of cancerous cells is low enough, it implies that the disease is progressed a little or has not happened yet and the purpose is cancer prevention. In this case, we assume that the system is in region 1 and applying the first and the fourth steps are adequate to fetter the system to stay in this region permanently.

2- If the percentage of cancerous cells is high, the regions are defined in a way that the system acts in region 2 and then the four steps are applied to converge the system to region 3. This is mainly because there is no limit cycle in region 2 (since there is no equilibrium point in this region). Moreover, the system is second-order and chaos cannot occur. As a result, the system can't stay in region 2 forever and inevitably there is no way for it except going to region 1. Henceforward, the system will stay in region 1 forever because it cannot exit from it.

Here we present the biological conception of our four step procedure:

In the first step we guarantee that by adjusting interaction rate parameters in a proper way, if there is not any "A^{++}" cells (healthy ones), in competition between two other types, "A^{+-}"invade "A^{--}" cells (cancerous cells); and if the system doesn't have any "type two" cells, the "type one" cells will annihilate cancerous cells.

In the second step we propose conditions to guarantee that starting from any initial fraction of three types of cells, at least one of the cell types will be extinct and invaded by two other types.

At the third step, our suggestions on the interaction rates for an already cancerous system at large, avoid the cancerous cells to invade two other cell types. It means that, we do not let the system to become entirely cancerous.

At the forth step, by applying our suggestions on the interaction rates, for the cancerous system at the beginning, we do not let cancerous cells to grow up more than a small specific percentage. In means that, we impede a healthy system to become cancerous or a cured one to relapse.

In fact, under these four step mechanism:

1- A healthy system cannot become cancerous;

2- A sick system is prevented to become completely cancerous (which means all of its cells become cancerous and we assume that such a system is cureless);

3- For an ill system, eventually one cell type will be destroyed (according to step two). If this extinct cell type is “type three”, then the system is cured. If it is “type one” or “two”, the population consists of two remaining cell types. Then, the cell “type three” will be eliminated by the other one and the system is cured again and after the remedy it cannot go back to the cancerous situation (step four again).

Based on different conditions on the boundaries of $x_1 = 0$ and $x_2 = 0$, 16 cases for the game is considered as presented in Table 3 and steps 1 to 4 of the proposed method is applied.

Table 3. Different cases on $x_1 = 0$ and $x_2 = 0$ boundaries

Border $x_1 = 0$		**Border $x_2 = 0$**	
Sub-Case A1	$p_{32} > p_{22} > p_{33} > p_{23}$	**Sub-Case B1**	$p_{31} > p_{11} > p_{33} > p_{13}$
Sub-Case A2	$p_{22} > p_{32} > p_{23} > p_{33}$	**Sub-Case B*2***	$p_{11} > p_{31} > p_{13} > p_{33}$
Sub-Case A3	$p_{22} > p_{32}, p_{33} > p_{23}$	**Sub-Case B*3***	$p_{11} > p_{31}, p_{33} > p_{13}$
Sub-Case A4	$p_{32} > p_{22}, p_{23} > p_{33}$	**Sub-Case B*4***	$p_{31} > p_{11}, p_{13} > p_{33}$

1. **Case A1B1**

Step 1:

Sub-Case A1: $p_{32} > p_{22} > p_{33} > p_{23}$

On the $x_1 = 0$ boundary, the payoff matrix and replicator dynamics is reduced as table 4:

Table 4. Reduced payoff matrix on the $x_1 = 0$ boundary

$$Q(x) = \begin{matrix} \\ s_2 \\ s_3 \end{matrix} \begin{matrix} \begin{matrix} s_2 & s_3 \end{matrix} \\ \begin{bmatrix} q_{22} & q_{23} \\ q_{32} & q_{33} \end{bmatrix} \end{matrix}$$

Therefore, replicator equations is:

$$\begin{cases} \dot{x}_2 = x_2(f_2 - M) \\ \dot{x}_3 = x_3(f_3 - M) \end{cases} \qquad (4)$$

Since $x_2 + x_3 = 1$, after some algebraic calculations, equation 4 can be written as:

$$\dot{x}_2 = x_2(1-x_2)[(q_{22}-q_{23}-q_{32}+q_{33})x_2+q_{23}-q_{33}] \quad (5)$$

$x_2 = 0$ and $x_2 = 1$ are two trivial solutions of equation 5. Potentially, there are some interior equilibrium points between zero and one which are the feasible solutions of equation 6.

$$(q_{22}-q_{23}-q_{32}+q_{33})x_2+q_{23}-q_{33}=0 \quad (6)$$

The solutions of (6) are:

$$x_2 = \frac{y \pm \sqrt{s}}{2z} \quad (7)$$

Where:

$$\begin{cases} y = (p_{23}-p_{32})r_{23}^2+(p_{22}-p_{33})r_{22}r_{23}+2(p_{33}-p_{23})r_{23}r_{33} \\ s = (p_{22}-p_{33})^2 r_{22}^2 r_{33}^2+(p_{23}-p_{32})r_{23}^4+(4p_{22}p_{33}+4p_{23}p_{32} \\ -2p_{22}p_{23}-2p_{22}p_{32}-2p_{23}p_{33}-2p_{32}p_{33})r_{23}^2 r_{22}r_{33} \\ z = (p_{23}-p_{32})r_{23}^2+(p_{32}-p_{22})r_{22}r_{23}+(p_{22}-p_{33})r_{22}r_{33} \end{cases} \quad (8)$$

If $s = 0$,then bifurcation occurs in system (4) (Thompson and Stewart, 2002) and this is the case if $(r_{22}r_{33}/r_{23}^2) = k_1$, in which:

$$\begin{aligned} k_1 = {} & \frac{1}{(p_{22}-p_{33})^2}\left(p_{22}(p_{23}+p_{32}-2p_{33})+p_{23}(p_{33}-2p_{32})+p_{32}p_{33}\right) \\ & +\frac{1}{(p_{22}-p_{33})^2}\left((p_{22}-p_{23})(p_{22}-p_{32})(p_{23}-p_{33})(p_{32}-p_{33})\right)^{\frac{1}{2}} \end{aligned} \quad (9)$$

Therefore $r_{22}r_{33}/r_{23}^2$ can be defined as the system bifurcation parameter (Taylor and Nowak, 2006).

In case A1B1, after some algebraic manipulations location of equilibrium points and their attraction and repelling manifold on $x_1 = 0$ border for different values of bifurcation parameter is depicted in figure (3):

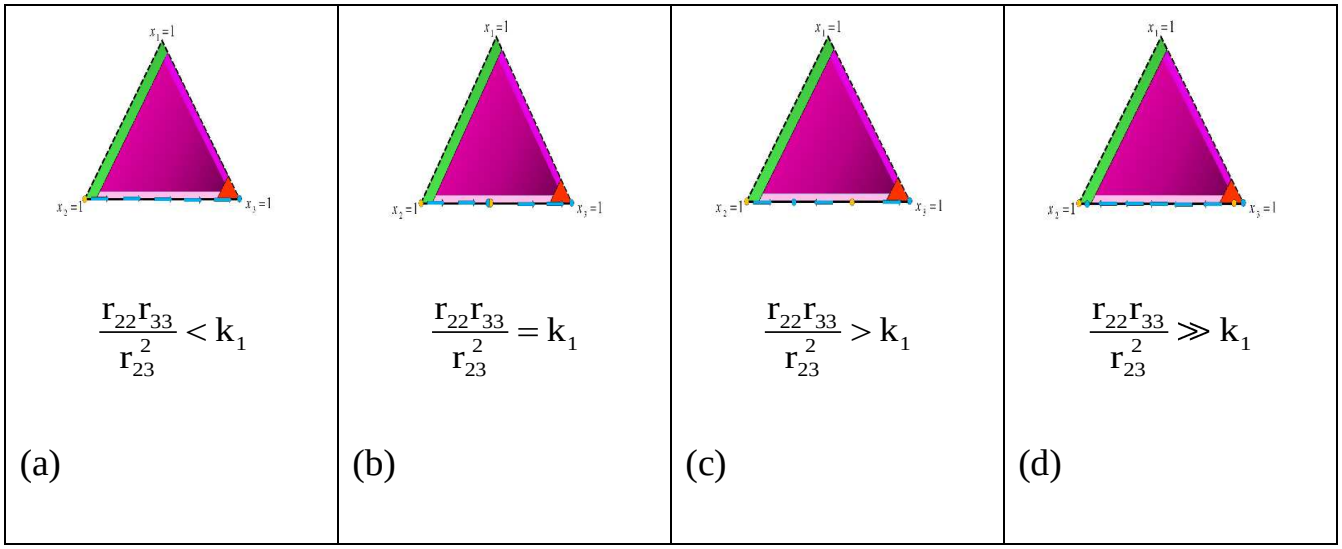


Figure 3. Location of the system equilibrium points on $x_1 = 0$ border for different values of bifurcation parameters in case A1

Figure 3(d) is the desired objective where all equilibrium points on this border are located region 1 and 3. Besides, the part of $x_1 = 0$ boundary that is lied in region 2, acts as an attraction manifold for an equilibrium point placed in region 1. Suggestions to achieve figure3(d) is described in equation 10:

$$(r_{22}r_{33}) / r_{23}^2 \gg k_1 \quad \text{Our suggestion is:} \begin{cases} r_{22}r_{33} \to \infty \\ r_{13} \to 0 \end{cases} \qquad (10)$$

Sub-Case B1: $p_{31} > p_{11} > p_{33} > p_{13}$

The location of equilibrium points on $x_2 = 0$ border for different amount of bifurcation parameter is given in figure (4).

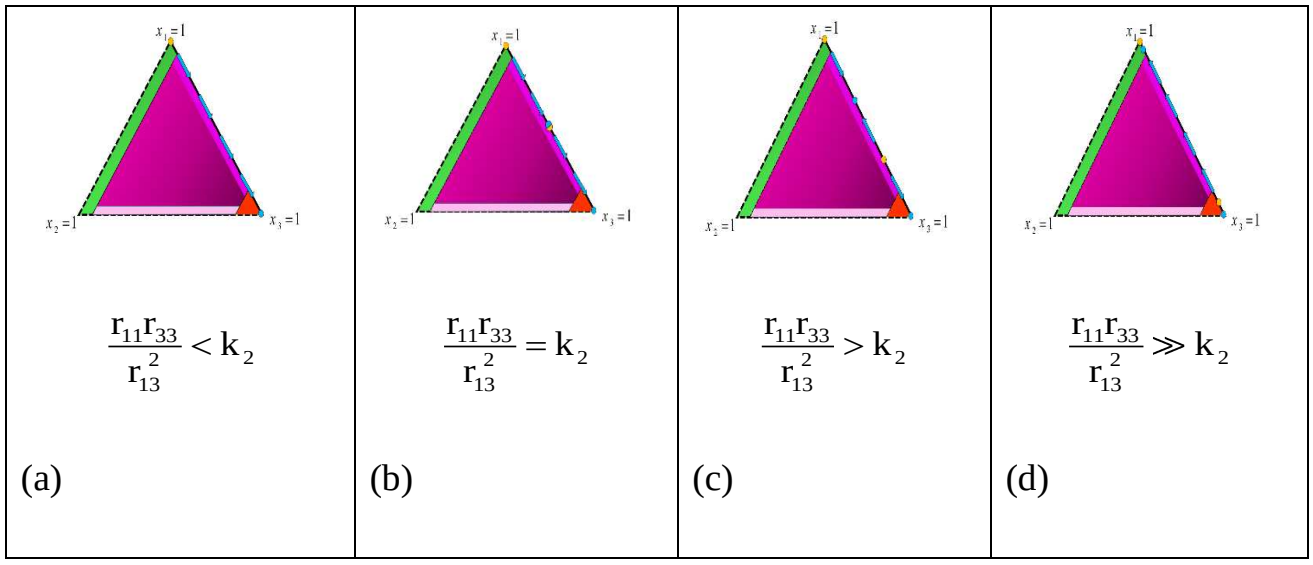


Figure 4. Location of the system equilibrium points on $x_1 = 0$ border for different values of bifurcation parameter in case B1

Similarly, figure 4(d) is the ideal situation and the requisite to create this condition is:

$$(r_{11}r_{33}) / r_{13}^2 \gg k_2 \quad \text{Our suggestion is:} \begin{cases} r_{11}r_{33} \to \infty \\ r_{13} \to 0 \end{cases} \qquad (11)$$

Taking into account the previous discussions, the following expressions for case A1B1 in first step is represented:

$$\begin{cases} r_{22}r_{33} \to \infty \\ r_{23} \to 0 \end{cases} \quad \text{and} \quad \begin{cases} r_{11}r_{33} \to \infty \\ r_{13} \to 0 \end{cases} \qquad (12)$$

Step 2:

In this step, first, calculations of the first step is applied to the system to identify any equilibrium point located in region 2 and then solutions are proposed to exclude region 2 from equilibrium points. Region 2 would be divided into 3 different sub-regions and each sub-region is studied.

Sub-region 2.1:

In this sub-region we may write:

$$\begin{cases} r_{12}x_2 \to 0 \quad , \quad r_{13}x_3 \to 0 \\ r_{22}x_2 \to 0 \quad , \quad r_{23}x_3 \to 0 \\ r_{31}x_1 \to 0 \quad , \quad r_{32}x_2 \to 0 \end{cases} \quad \text{Then :} \quad \begin{cases} f_1 \to p_{11} \\ f_2 \to p_{21} \\ f_3 \to p_{33} \end{cases} \qquad (13)$$

It is clear that for interior equilibrium points $f_1 = f_2 = f_3 = M$. On the other hand, in Eq.13, $f_1 > f_3$ and consequently there are no equilibrium point in sub-region 2.1 in this case.

Sub-region 2.2:

In this sub-region, $x_1 \to 0$, the following conditions are applied.

$$\begin{cases} r_{11}x_1 \to 0 \quad , \quad r_{13}x_3 \to 0 \\ r_{21}x_1 \to 0 \quad , \quad r_{23}x_3 \to 0 \\ r_{31}x_1 \to 0 \quad , \quad r_{32}x_2 \to 0 \end{cases} \quad \text{Then :} \quad \begin{cases} f_1 \to p_{12} \\ f_2 \to p_{22} \\ f_3 \to p_{33} \end{cases} \qquad (14)$$

Since $f_2 > f_3$ (as mentioned before), there is no equilibrium point in this sub-region as well.

Sub-region 2.3:

In this sub-region, for case 1, equations are:

$$\begin{cases} r_{13}x_3 \to 0 \quad , \quad r_{23}x_3 \to 0 \\ r_{31}x_1 \to 0 \quad , \quad r_{32}x_2 \to 0 \end{cases} \quad \text{Then :} \quad \begin{cases} f_1 \to \dfrac{r_{11}x_1p_{11} + r_{12}x_2p_{12}}{r_{11}x_1 + r_{12}x_2} \\ f_2 \to \dfrac{r_{21}x_1p_{21} + r_{22}x_2p_{22}}{r_{21}x_1 + r_{22}x_2} \\ f_3 \to p_{33} \end{cases} \qquad (15)$$

Considering the fact that $f_2 \in (p_{22}, p_{21})$ and $f_2 > f_3$ (because in this case $p_{33} < p_{22}$ and $p_{33} < p_{21}$) , there is no equilibrium point in this sub-region.

So, no proposal is required for step 2 and the objective is achieved by applying the procedures described in step 1.

Step 3:

In this step recommendations are provided so that $\dot{x}_3 < 0$ where $x_3 = 1 - \varepsilon$.

$$\begin{cases} x_3 = 1-\varepsilon \\ x_1 + x_2 = \varepsilon \end{cases} \dot{x}_3 < 0 \quad \text{Then : } f_3 < M \quad \text{then : } \quad f_3 < x_1f_1 + x_2f_2 + x_3f_3 \qquad \text{Then : } \qquad \varepsilon f_3 < x_1f_1 + x_2f_2 \quad (16)$$

The purpose is to make equation 16 active in sub-regions.

Sub-region 2.1:

In this sub-region:

$$\begin{cases} x_1 \to \varepsilon \quad , \quad f_1 \to p_{11} \\ x_2 \to 0 \quad , \quad f_2 \to p_{21} \\ x_3 = 1-\varepsilon \quad , \quad f_3 \to p_{33} \end{cases} \quad \text{Then :} \begin{cases} x_1f_1 + x_2f_2 \to \varepsilon p_{11} \\ \varepsilon f_3 \to \varepsilon p_{33} \end{cases} \quad \text{Then : } \varepsilon f_3 < x_1f_1 + x_2f_2 \qquad (17)$$

It is obvious that using the above constraints make the equation active and there is no need for further analysis.

Sub-region 2.2:

In this sub-region:

$$\begin{cases} x_1 \to 0 & , \quad f_1 \to p_{12} \\ x_2 \to \varepsilon & , \quad f_2 \to p_{22} \\ x_3 = 1-\varepsilon & , \quad f_3 \to p_{33} \end{cases} \quad \text{Then}: \begin{cases} x_1 f_1 + x_2 f_2 \to \varepsilon p_{22} \\ \varepsilon f_3 \to \varepsilon p_{33} \end{cases} \quad \text{Then}: \varepsilon f_3 < x_1 f_1 + x_2 f_2 \quad (18)$$

Similar to the previous case, the equation is active in this sub-region.

Sub-region 2.3:

In this sub-region:

$$\begin{cases} f_1 \to \dfrac{r_{11} x_1 p_{11} + r_{12}(\varepsilon - x_1) p_{12}}{r_{11} x_1 + r_{12}(\varepsilon - x_1)} \\ f_2 \to \dfrac{r_{21} x_1 p_{21} + r_{22} x_2 p_{22}}{r_{21} x_1 + r_{22}(\varepsilon - x_1)} \\ f_3 \to p_{33} \end{cases} \quad (19)$$

If: $x_1 f_1 + x_2 f_2 > \varepsilon f_3 \Rightarrow r_{11} x_1 (x_1 p_{11} - M_1) > r_{12}(\varepsilon - x_1)(M_1 - x_1 p_{12})$ (20)

Where: $M_1 = \varepsilon f_3 - x_2 f_2$ (21)

If $M_1 < x_1 p_{11}$ the following situation is our proposal to make (20) active:

$$r_{11} > \frac{r_{12}(\varepsilon - x_1)(M_1 - x_1 p_{12})}{x_1 (x_1 p_{11} - M_1)} \quad (22)$$

Also, we check if the following equation is active:

$$M_1 < x_1 p_{11} \quad (23)$$

$$M_1 - x_1 p_{11} = \varepsilon i - (\varepsilon - x_1)\left(\frac{r_{21}x_1 p_{21} + r_{22}(\varepsilon - x_1)p_{22}}{r_{12}x_1 + r_{22}(\varepsilon - x_1)}\right) - x_1 p_{11}$$

$$= \frac{r_{12}x_1(\varepsilon p_{33} - (\varepsilon - x_1)p_{21} - x_1 p_{11}) - r_{22}(\varepsilon - x_1)(x_1 p_{11} + (\varepsilon - x_1)p_{22} - \varepsilon p_{33})}{r_{12}x_1 + r_{22}(\varepsilon - x_1)} \quad (24)$$

And: $\begin{cases}(\varepsilon p_{33} - (\varepsilon - x_1)p_{21} - x_1 p_{11}) < 0 \\ (x_1 p_1 + (\varepsilon - x_1)p_2 - \varepsilon p_{33}) > 0\end{cases}$ Then : $M_1 - x_1 p_{11} < 0$ Then : $M_1 < x_1 p_{11}$ (25)

Therefore, equation 20 is always active and there is no need to alter the situation.

Step 4:

In this step we propose $\dot{x}_3 < 0$ and $x_3 = \sigma$. The only difference with the step 3 is replacing $1-\varepsilon$ with σ in equations.

$$\begin{cases} f_1 \to \dfrac{r_{11}x_1 p_{11} + r_{12}(\varepsilon - x_1)p_{12}}{r_{11}x_1 + r_{12}(1-\sigma - x_1)} \\ f_2 \to \dfrac{r_{21}x_1 p_{21} + r_{22}x_2 p_{22}}{r_{21}x_1 + r_{22}(1-\sigma - x_1)} \\ f_3 \to p_{33} \end{cases} \quad (26)$$

Our suggestion: $r_{11} > \dfrac{r_{12}(1-\sigma - x_1)(N_1 - x_1 p_{12})}{x_1(x_1 p_{11} - N_1)}$ (27)

Where: $N_1 = (1-\sigma)f_3 - x_2 f_2$ (28)

By applying our proposed four steps the location of equilibrium point in this case is demonstrated in figure 5:

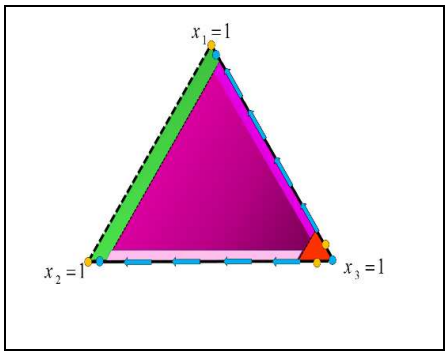


Figure 5. The location of system equilibrium points in case A1B1 on the boundaries of $x_1=0$ and $x_2=0$ using the four steps for case 1

Proposed solutions for the remaining cases are presented in table 4. More detailed calculations are available in supplementary of the paper.

Also, it is discussed in the supplementary that there is no need to consider extra suggestions for the remaining 15 cases in step 2 and by applying the first step, no equilibrium point is located in region 2. Therefore, there is no necessity to present the details of step 2.

Table 5. the proposed approach for different cases in different steps

Case	Step 1	Step 3	Step 4
A1B2	$\begin{cases} r_{22}r_{33}\to\infty \\ r_{23}\to 0 \end{cases}$ $\frac{r_{11}r_{33}}{r_{13}^2}>k_2$	$r_{11}>\frac{r_{12}(\varepsilon-x_1)(M_2-x_1p_{12})}{x_1(x_1p_{11}-M_2)}$ $M_2=\varepsilon f_3-x_2f_2$	$r_{11}>\frac{r_{12}(1-\sigma-x_1)(N_2-x_1p_{12})}{x_1(x_1p_{11}-N_2)}$ $N_2=(1-\sigma)f_3-x_2f_2$
A1B3	$\begin{cases} r_{22}r_{33}\to\infty \\ r_{23}\to 0 \end{cases}$ $r_{11}\to\infty$	$r_{22}>\frac{r_{12}x_1(M_3-(\varepsilon-x_1)p_{21})}{(\varepsilon-x_1)((\varepsilon-x_1)p_{22}-M_3)}$ $r_{33}>\frac{r_{31}x_1(\varepsilon p_{31}-x_1p_{11}-(\varepsilon-x_1)p_{21})}{\varepsilon((\varepsilon-x_1)p_{21}+x_1p_{11}-\varepsilon p_{33})}$ $M=\varepsilon f_3-x_1f_1$	$r_{22}>\frac{r_{12}x_1(N_3-(1-\sigma-x_1)p_{21})}{(1-\sigma-x_1)((1-\sigma-x_1)p_{22}-N_3)}$ $r_{33}>\frac{r_{31}x_1((1-\sigma)p_{31}-x_1p_{11}-(1-\sigma-x_1)p_{21})}{(1-\sigma)((1-\sigma-x_1)p_{21}+x_1p_{11}-(1-\sigma)p_{33})}$ $N_3=(1-\sigma)f_3-x_2f_2$
A1B4	$\begin{cases} r_{22}r_{33}\to\infty \\ r_{23}\to 0 \end{cases}$ $r_{33}\to\infty$	$r_{11}>\frac{r_{12}(\varepsilon-x_1)(M_4-x_1p_{12})+r_{13}(1-\varepsilon)(M_4-x_1p_{13})}{x_1(x_1p_{11}-M_4)}$ $M_4=\varepsilon f_3-x_2f_2$	$r_{11}>\frac{r_{12}(1-\sigma-x_1)(N_4-x_1p_{12})+r_{13}\sigma(N_4-x_1p_{13})}{x_1(x_1p_{11}-N_4)}$ $N_4=(1-\sigma)f_3-x_2f_2$
A2B1	$\frac{r_{22}r_{33}}{r_{23}^2}>k_1$ $\begin{cases} r_{11}r_{33}\to\infty \\ r_{13}\to 0 \end{cases}$	$r_{11}>\frac{r_{12}(\varepsilon-x_1)(M_5-x_1p_{12})}{x_1(x_1p_{11}-M_5)}$ $M_5=\varepsilon f_3-x_2f_2$	$r_{11}>\frac{r_{12}(1-\sigma-x_1)(N_5-x_1p_{12})}{x_1(x_1p_{11}-N_5)}$ $N_5=(1-\sigma)f_3-x_2f_2$

A2B2	$\frac{r_{22}r_{33}}{r_{23}^2} > k_1$ $\frac{r_{11}r_{33}}{r_{13}^2} > k_2$	$r_{11} > \frac{r_{12}(\varepsilon - x_1)(M_6 - x_1p_{12}) + r_{13}(1-\varepsilon)(M_6 - x_1p_{13})}{x_1(x_1p_{11} - M_6)}$ $M_6 = \varepsilon f_3 - x_2 f_2$	$r_{11} > \frac{r_{12}(1-\sigma-x_1)(N_6 - x_1p_{12}) + r_{13}\sigma(N_6 - x_1p_{13})}{x_1(x_1p_{11} - N_6)}$ $N_6 = (1-\sigma)f_3 - x_2 f_2$
A2B3	$\frac{r_{22}r_{33}}{r_{23}^2} > k_1$ $r_{11} \to \infty$	$r_{22} > \frac{r_{21}x_1(M_7 - (\varepsilon - x_1)p_{21})}{(\varepsilon - x_1)((\varepsilon - x_1)p_{22} - M_7)}$ $r_{33} > \frac{r_{13}x_1(\varepsilon p_{31} - x_1p_{11} - (\varepsilon - x_1)p_{21})}{(1-\varepsilon)((\varepsilon - x_1)p_{21} + x_1p_{11} - \varepsilon p_{33})}$ $M_7 = (1-\sigma)f_3 - x_1 f_1$	$r_{22} > \frac{r_{21}x_1(N_7 - (1-\sigma-x_1)p_{21})}{(1-\sigma-x_1)((1-\sigma-x_1)p_{22} - N_7)}$ $r_{33} > \frac{r_{13}x_1((1-\sigma)p_{31} - x_1p_{11} - (1-\sigma-x_1)p_{21})}{\sigma((1-\sigma-x_1)p_{21} + x_1p_{11} - (1-\sigma)p_{33})}$ $N_7 = (1-\sigma)f_3 - x_1 f_1$
A2B4	$\frac{r_{22}r_{33}}{r_{23}^2} > k_1$ $r_{33} \to \infty$	$r_{11} > \frac{r_{12}(\varepsilon - x_1)(M_8 - x_1p_{12}) + r_{13}(1-\varepsilon)(M_8 - x_1p_{13})}{x_1(x_1p_{11} - M_8)}$ $M_8 = \varepsilon f_3 - x_2 f_2$	$r_{11} > \frac{r_{12}(1-\sigma-x_1)(N_8 - x_1p_{12}) + r_{13}\sigma(N_8 - x_1p_{13})}{x_1(x_1p_{11} - N_8)}$ $N_8 = (1-\sigma)f_3 - x_2 f_2$
A3B1	$r_{22} \to \infty$ $\begin{cases} r_{11}r_{33} \to \infty \\ r_{13} \to 0 \end{cases}$	$r_{11} > \frac{r_{12}(\varepsilon - x_1)(M_9 - x_1p_{12})}{x_1(x_1p_{11} - M_9)}$ $r_{23} > \frac{r_{33}(1-\varepsilon)(\varepsilon p_{31} - (\varepsilon - x_1)p_{22} + x_1p_{11})}{(\varepsilon - x_1)(\varepsilon p_{32} - (\varepsilon - x_1)p_{22} - x_1p_{11})}$ $M_9 = \varepsilon f_3 - x_2 f_2$	$r_{11} > \frac{r_{12}(1-\sigma-x_1)(N_9 - x_1p_{12})}{x_1(x_1p_{11} - N_9)}$ $r_{23} > \frac{r_{33}\sigma((1-\sigma)p_{31} - ((1-\sigma)-x_1)p_{22} + x_1p_{11})}{(1-\sigma-x_1)((1-\sigma)p_{32} - (1-\sigma-x_1)p_{22} - x_1p_{11})}$ $N_9 = (1-\sigma)f_3 - x_2 f_2$
A3B2	$r_{22} \to \infty$ $\frac{r_{11}r_{33}}{r_{13}^2} > k_2$	$r_{11} > \frac{r_{12}(\varepsilon - x_1)(M_{10} - x_1p_{12})}{x_1(x_1p_{11} - M_{10})}$ $r_{23} > \frac{r_{33}(1-\varepsilon)(\varepsilon p_{31} - (\varepsilon - x_1)p_{22} + x_1p_{11})}{(\varepsilon - x_1)(\varepsilon p_{32} - (\varepsilon - x_1)p_{22} - x_1p_{11})}$ $M_{10} = \varepsilon f_3 - x_2 f_2$	$r_{11} > \frac{r_{12}(1-\sigma-x_1)(N_{10} - x_1p_{12})}{x_1(x_1p_{11} - N_{10})}$ $r_{23} > \frac{r_{33}\sigma(\varepsilon p_{31} - (1-\sigma-x_1)p_{22} + x_1p_{11})}{\sigma(\varepsilon p_{32} - (1-\sigma-x_1)p_{22} - x_1p_{11})}$ $N_{10} = (1-\sigma)f_3 - x_2 f_2$
A3B3	$r_{22} \to \infty$ $r_{11} \to \infty$	$r_{11} > \frac{r_{12}(\varepsilon - x_1)(M_{11} - x_1p_{12}) + r_{13}(1-\varepsilon)(M_{11} - x_1p_{13})}{x_1(x_1p_{11} - M_{11})}$ $M_{11} = \varepsilon f_3 - x_2 f_2$	$r_{11} > \frac{r_{12}(1-\sigma-x_1)(N_{11} - x_1p_{12}) + r_{13}\sigma(N_{11} - x_1p_{13})}{x_1(x_1p_{11} - N_{11})}$ $N_{11} = \varepsilon f_3 - x_2 f_2$
A3B4	$r_{22} \to \infty$ $r_{33} \to \infty$	$r_{11} > \frac{r_{12}(\varepsilon - x_1)(M_{12} - x_1p_{12}) + r_{13}(1-\varepsilon)(M_{12} - x_1p_{13})}{x_1(x_1p_{11} - M_{12})}$ $M_{12} = \varepsilon f_3 - x_2 f_2$	$r_{11} > \frac{r_{12}(1-\sigma-x_1)(N_{12} - x_1p_{12}) + r_{13}\sigma(N_{12} - x_1p_{13})}{x_1(x_1p_{11} - N_{12})}$ $N_{12} = \varepsilon f_3 - x_2 f_2$
A4B1	$r_{33} \to \infty$ $\begin{cases} r_{11}r_{33} \to \infty \\ r_{13} \to 0 \end{cases}$	$r_{11} > \frac{r_{12}(\varepsilon - x_1)(M_{13} - x_1p_{12})}{x_1(x_1p_{11} - M_{13})}$ $M_{13} = (1-\sigma)f_3 - x_2 f_2$	$r_{11} > \frac{r_{12}(1-\sigma-x_1)(N_{13} - x_1p_{12})}{x_1(x_1p_{11} - N_{13})}$ $N_{13} = (1-\sigma)f_3 - x_2 f_2$
A4B2	$r_{33} \to \infty$ $\frac{r_{11}r_{33}}{r_{13}^2} > k_2$	$r_{11} > \frac{r_{12}(\varepsilon - x_1)(M_{14} - x_1p_{12}) + r_{13}(1-\varepsilon)(M_{14} - x_1p_{13})}{x_1(x_1p_{11} - M_{14})}$ $M_{14} = \varepsilon f_3 - x_2 f_2$	$r_{11} > \frac{r_{12}(1-\sigma-x_1)(N_{14} - x_1p_{12}) + r_{13}\sigma(N_{14} - x_1p_{13})}{x_1(x_1p_{11} - N_{14})}$ $N_{14} = (1-\sigma)f_3 - x_2 f_2$
A4B3	$r_{33} \to \infty$ $r_{11} \to \infty$	Free	Free

A4B4	$r_{33} \to \infty$	$r_{11} > \frac{r_{12}(\varepsilon - x_1)(M_{16} - x_1 p_{12}) + r_{13}(1-\varepsilon)(M_{16} - x_1 p_{13})}{x_1(x_1 p_{11} - M_{16})}$ $M_{16} = \varepsilon f_3 - x_2 f_2$	$r_{11} > \frac{r_{12}(1-\sigma - x_1)(N_{16} - x_1 p_{12}) + r_{13}\sigma(N_{16} - x_1 p_{13})}{x_1(x_1 p_{11} - N_{16})}$ $N_{16} = (1-\sigma) f_3 - x_2 f_2$

IV. **Simulations**

In this section the results of simulation are presented in two parts.

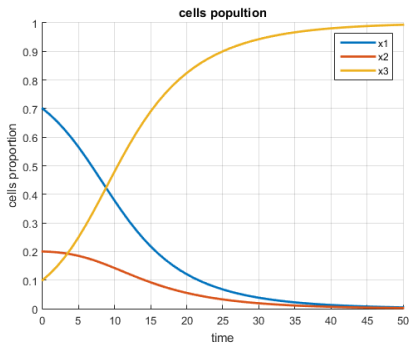
A. Part 1

Despite the fact that the proposed methods demands ideal condition (for example $r_{11} \to \infty$ that is unlikely to happen in real condition), by changing the parameters in proposed direction (for instance, increasing r_{11} to a sufficiently higher value), the system will converge to equilibrium points.

We suppose the game's parameters are assumed as follows:

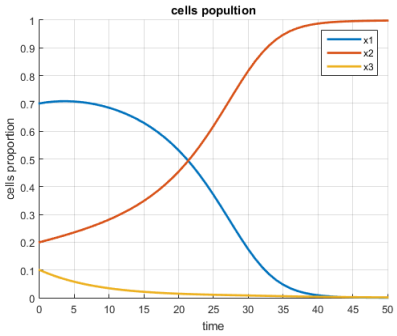
$$\alpha = 1, \gamma = 1.4, \lambda = 0.6, \xi = 0.3, \xi' = 0.4, \beta = 1.2, \eta = 0.3, \theta = 0.2, \theta' = 0.3, \delta = 0.4, \delta' = 0.05$$

This represents the case A1B1 in analysis. Convergence of the system with and without the proposed method using an initial condition is depicted in fig.6(a) and fig.6(b), respectively.



Uniform interaction rates (all equal 1)

(a)



$r_{13} = 0.01, r_{23} = 0.1, r_{33} = 100$ and others ones are 1

(b)

Figure 6. System convergence with a specific initial condition without and with (left and right pictures respectively) applying our proposals for case 1

It is clear that using the proposed method yields desirable results where there is no cancerous cells.

B. Part 2

In this part we present the results of game convergence considering non-cancerous and cancerous initial conditions for different values of interaction rates. The purpose is to find an optimum condition to eliminate cancerous cells with least changes in interaction rate parameters. The proposed method provided merely sufficient but not necessarily essential conditions and there might be other methods with lower cost in terms of optimization.

Due to high number of parameters, some of them are shown in figures 7 and 8 while the rest of the parameters are presented in table 5.

Figure 7 and 8 show 25 black border squares. In each one of the black border squares there are 4 brown border squares consisting 16 arrays. The value of r_{11} and r_{33} are presented in this figure. The parameter r_{22} is constant and equal to 1. The remaining parameters are provided in table 6.

Table 6. The value of interaction rate parameters in figures 7 and 8

Brown squares in each black square	r_{13}	Columns of each brown square (left to right direction)	r_{13}	Rows of each brown square (up to down direction)	r_{23}
lower-left	0.1	First	0.1	First	0.1
lower-right	1	Second	1	Second	1
Upper-left	10	Third	10	Third	10
Upper-right	100	Fourth	100	Fourth	100

Each specific color indicates the result of game convergence. For instance, blue means there are A^{++} and A^{--} cells in converged point which implies an equilibrium point on $x_2 = 0$ boundary (there is no A^{+-} cells or negligible number of them). Magenta, cyan or yellow represent the game convergence to points without cancerous cells or with a very scanty level of it that is desirable. Each color corresponds to a specific condition that is shown by legends in the figure. Besides, parameters ε and σ are set as 0.03 in the simulations presented in this part.

The model parameters of the game in both figures are assumed as follows:

$$\alpha = 1, \gamma = 1.4, \lambda = 0.8, \xi = 0.6, \xi' = 0.6, \beta = 1.2, \eta = 0.4, \theta = 0.4, \theta' = 0.4, \delta = 0.4, \delta' = 0.4$$

Figure 7 depicts the game convergence results with non-cancerous initial conditions ($x_1 = 0.98$, $x_2 = 0.01$ and $x_3 = 0.01$) for different values of interaction rate. It can be understood that by adjustment of interaction parameters, the system may converge to non-cancerous equilibrium

points (desired colors).

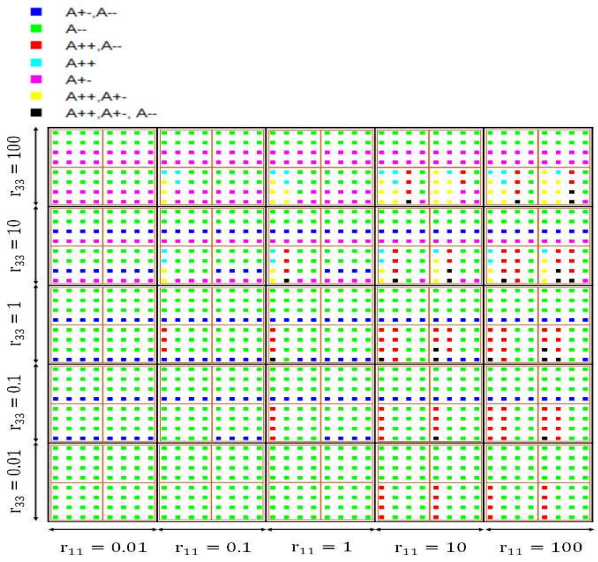


Figure 7. Convergence of the game with non-cancerous initial condition and model parameters: $\alpha = 1, \gamma = 1.4, \lambda = 0.8, \xi = 0.6, \xi' = 0.6, \beta = 1.2, \eta = 0.4, \theta = 0.4, \theta' = 0.4, \delta = 0.4, \delta' = 0.4$ **, for different values of interaction rate parameters**

Among the possible ways to prevent generating cancerous cells that can be interpreted from figure 7, an effective way to converge to a proper equilibrium point which is colored in cyan is to set $r_{23} = 0.1, r_{33} = 10$ and the other parameters to be 1.

Figure 8 indicates that with the same game parameters in the case shown in figure 7, setting the initial condition to be: $x_1 = 0.02$, $x_2 = 0.03$ and $x_3 = 0.95$ (almost all the cells are cancerous) and adapting the interaction rates, the game converges to equilibrium points (desired colors).

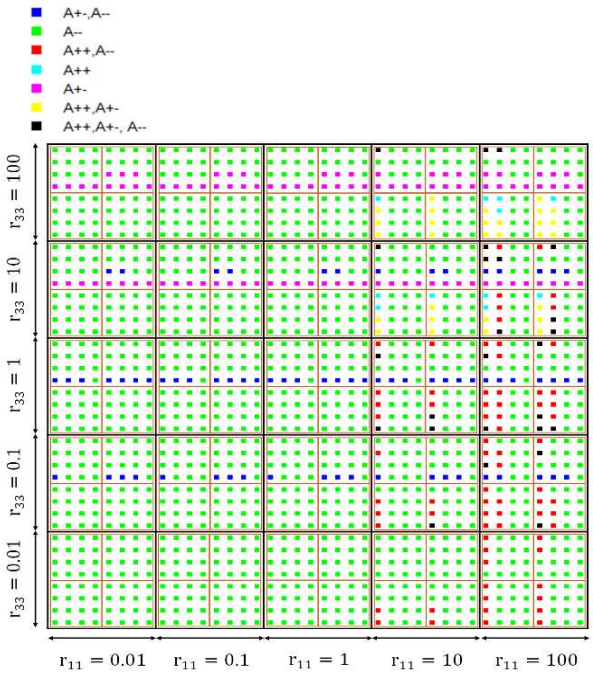


Figure 8. Convergence of the game with cancerous initial condition and model parameters: $\alpha=1,\gamma=1.4,\lambda=0.8,\xi=0.6,\xi'=0.6,\beta=1.2,\eta=0.4,\theta=0.4,\theta'=0.4,\delta=0.4,\delta'=0.4$ **, for different values of interaction rate parameters**

Regarding the results illustrated in figure 8, an efficient way to eradicate the cancerous cells is to choose $r_{12}=10, r_{23}=0.1, r_{33}=10$ and other interaction rate parameters to be 1.

V. Conclusion

The proposed therapeutic method in this paper based on changing the interaction parameters was to eliminate cancerous cells or prevent cell population to become cancerous, .

It was shown in Figure 7 that $r_{33}=10$ and $r_{23}=.01$ could be an appropriate strategy, since by placing A^{--}cells close to each other, the interaction rate increases and $r_{33}=10$ is obtained. On the other hand, separating A^{++} and A^{+-} cells reduces the interaction rate and $r_{23}=.01$ is attained.

Using the proposed method, with natural selection, cancerous cells are eliminated and cell population will converge to non-cancerous point. The suggested interaction rates in the analysis

section, gave some sufficient conditions for the convergence of the game to the desired equilibrium points. Nevertheless, as it was understood from the Simulation results, the desired convergence can be achieved by applying less conservative conditions on the interaction rates.

VI. Future works

In the light of our studies, it is an idea that the medical technology could be designed to change the interaction rate of cancerous cells. A clue on this is to separate the cell types in demarcated boundaries to change the interaction rate. For instance, conducting a population of cells through a filter or using an especial drug could separate them regarding the fact that cells' sizes are different. Therefore, the interaction rates among different cell's type could be changed. Another clue to change the interaction rate parameters could be utilizing the chemicals. For example, one can soak each cell types with specific chemicals through target therapy approaches which can lead to non-uniform interaction rates among different cell types. Another avenue for future work is to develop a more realistic model compared to what was presented in this work by building a more comprehensive model which incorporates more aspects of cancer. For example, researchers can consider the impact of current therapies such as chemotherapy, surgery or radiation instead or in tandem with the immune suppression.

Appendix

Here we prove the dynamics in border the of $x_2 = 0$ is given by (5).

From (4):

$$\dot{x}_2 = x_2(f_2 - M)$$

$$\dot{x}_2 = x_2(q_2 x - x^T Q(x) x)$$

On border of $x_2 = 0$, we have $x_2 = 0$ and $x_3 = 1 - x_1$, therefore:

$$\dot{x}_2 = x_2\left(\begin{bmatrix} q_{21} & q_{22} & q_{13} \end{bmatrix} \begin{bmatrix} 0 \\ x_2 \\ 1-x_2 \end{bmatrix} - \begin{bmatrix} 0 & x_2 & 1-x_2 \end{bmatrix} \begin{bmatrix} q_{11} & q_{12} & q_{13} \\ q_{21} & q_{22} & q_{23} \\ q_{31} & q_{32} & q_{33} \end{bmatrix} \begin{bmatrix} 0 \\ x_2 \\ 1-x_2 \end{bmatrix} \right)$$

$$\dot{x}_2 = x_2[q_{22}x_2 + q_{23}(1-x_2) - x_2(q_{22}x_2 + q_{23}(1-x_2)) - (1-x_2)(q_{32}x_2 + q_{33}(1-x_2))]$$

$$\dot{x}_2 = x_2[q_{22}(1-x_2)x_2 + q_{23}(1-x_2)^2 - q_{32}(1-x_2)x_2 - q_{33}(1-x_2)^2]$$

$$\dot{x}_2 = x_2(1-x_2)[(q_{22} - q_{23} - q_{32} + q_{33})x_2 + q_{23} - q_{33}]$$

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