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Fuzzy Delay Tumor Growth With Quiescence Cells: Stability of Steady States

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Abstract—This paper presents a system of delay tumor growth that describes an interaction between the proliferating and quiescent cells tumor. This system is fuzzified by parametric form of α-cut representation of symmetric triangular fuzzy number. The steady state and linear stability of fuzzy tumor growth system with quiescence and without quiescence cells are determined and analyzed. Here, we show that the trivial steady state of the system with quiescence is stable for τ =0 by Routh Hurwitz conditions. For increasing delay the steady state is unstable by using Strum theorem.

Keywords—Delay tumor growth with quiescence, Steady States, Stability, Fuzzy delay tumor growth.

I. Introduction

PREDATOR-PREY interaction is the fundamental model in population dynamics. Understanding the dynamics of predator-prey models will be useful for investigating multiple species interaction. However, one of application of predator-prey interaction is tumor growth cells. Many researchers examined delay predator-prey type interaction in tumor studies where the immune or the quiescence cells play the role of predator and prey respectively [1].

Tumor cells can be divided into proliferating or cycling cells and nonproliferating or quiescent cells [2]. A cell is assumed cancerous when it has lost its ability to regulate cell growth and division (mitosis). Thus, cancer is a disease of rapid uncontrolled growth of malignant cells. In this paper the mathematical system proposed describes the delay tumor growth interaction between the proliferating and quiescent cells of two differential equations with one delay.

Yafia [3] develops a delay differential equation model for interaction of proliferating and quiescent tumor cells. However, this paper does not include immune cell nor the impact of the drugs. In fact, it may be important for cancer treatment to target the proliferating cells. Including quiescent cells in the model should be more realistic and could provide additional insight into complex system. In [4], the authors discuss the existence, uniqueness and non-negativity of solutions and they obtain that under an appropriate hypotheses and using Poincare-Bendixon theorem, the nontrivial steady state is globally asymptotically stable for the system with =0.

In real life, we have learned to accept that we are actually dealt with uncertainty. Modeling the real life problems in such cases, usually involves uncertainty or vagueness in some of the parameters including the tumor growth system. In this system, the condition of the patients and the tumor type can be considered as uncertain parameters. Meanwhile, the concept of fuzzy set and system was initially introduced by Zadeh [5] and has been used to model a dynamical system under possibility uncertainty [6]. Therefore, in this paper we used fuzzy concept to propose a system known as fuzzy delay tumor growth system. Specifically, the discussion on the theory and analysis of delay tumor growth system with uncertainty parameters is considered.

The organization of this paper is as follows. In Section II, tumor growth system without and with quiescent cells are given. Including dynamical analysis in a delayed system for tumor growth. In addition some definitions regarding the fuzzy number are briefly presented. In Section III, fuzzy tumor system without quiescent cells is introduced. In Section IV, two examples are given to demonstrate the results for the fuzzy delay tumor growth with quiescence cells. Finally the conclusion of the finding is given in Section V.

II. TUMOR GROWTH SYSTEM

In the absence of quiescent cells and the delay, the proliferating cells follow the logistic equation $\dot{P}(t) = bP(t)$ and the tumor becomes a malignant tumor for $b > 0$ and becomes benign for $b < 0$. In absence of proliferating cells the quiescent cells are normally absent.

A. Dynamics Analysis in a Delayed system for Tumor Growth with Quiescence

Consider the following system:

$$\begin{aligned} \frac{dP(t)}{dt} &= bP(t-\tau) - r_P(N(t))P(t) + r_Q(N(t))Q(t) \\ \frac{dQ(t)}{dt} &= r_P(N(t))P(t) - (\mu_Q + r_P(N(t)))Q(t) \end{aligned} \tag{1}$$

In biological terms, where $P(t)$ and $Q(t)$ represent the numbers of proliferating tumor cells and quiescent tumor cells respectively. $N(t)=P(t)+Q(t)$ is the total number of tumor cells at time t, $b=\beta-\mu_P>0$ the rate of the proliferating cells where ($\beta>0$) and the division rate of the proliferating cells, $\mu_P\geq 0$ the death rate of cells of the proliferating cells, $\mu_Q\geq 0$ is the mortality rate of the quiescent cells, $r_P(N)$ is the nonlinear transition rate from the proliferating class to the quiescent class and $r_Q(N)$ is the nonlinear transition rate from the quiescent class to the proliferating class . For this tumor population, we assume that $r_P(N)$ is non-decreasing and $r_Q(N)$ is non -increasing, both rates are Lipschitz continuous on bounded sets of N in R (see Gyllenberg and Webb [4]) and the constant is the time delay which the proliferating cells takes to divide.

Yafia [3] analyzed system (1) and concluded that it has a trivial and unique positive steady state. Dynamical study of the system is also presented in [3] in terms of local stability of the two steady states. Yafia consider the function $f:\mathbb{R}^+\to\mathbb{R}$ and $g:\mathbb{R}^+\to\mathbb{R}$ as

$$f(x)=\mu_Q r_P(x)-b(\mu_Q+r_Q(x))$$

and

$$g(x)=b-\mu_Q-r_P(x)-r_Q(x),$$

respectively.

Assuming the hypotheses:

(A_1) $f(0)<0$,

(NA_1) $f(0)>0$,

(A_2) $f(+\infty)>0$,

(A_3) $g(x)<0$ for all $x\geq 0$,

(NA_3) $g(x)>0$ for all $x\geq 0$.

Yafia's paper proved the next three theorems where the first theorem gives the stability result for the trivial steady state while the nontrivial is not exist.

Theorem 1

Assume the hypotheses (NA_1) and (A_3). Then the trivial steady state of the system (1) is asymptotically stable for all $\tau\geq 0$.

The next theorem gives a result of instability of the trivial steady state when the nontrivial steady state exists.

Theorem 2

Assume the hypotheses (A_1) and (NA_3). Then the trivial steady state of the system (1) is unstable for all >0.

The last theorem gives the result of change of stability of non trivial steady state.

Theorem 3

Assume the hypotheses (A_1)-(A_3) and the functions r_P (increasing function) and r_Q (decreasing function) are of class C^1. Then there exists a critical value τ_0 of the time delay, such that the nontrivial steady state is asymptotically stable, for $\in[0,\ \tau_0\ ]$ and unstable, for $>\tau_0$.

B. Fuzzy Theory

Definition 1 [5]

A fuzzy number is a function such as $u:\mathbb{R}\to[0,1]$ satisfies the following properties:

1) u is normal, i.e $\exists x_0\in\mathbb{R}$ with $u(x_0)=1$.

2) u is a convex fuzzy set i.e $u(\lambda x+(1-\lambda)y)\geq\min\{u(x),u(y)\}\forall x,y\in\mathbb{R},\lambda\in[0,1]$.

3) u is upper semi-continuous on $\mathbb{R}$.

4) $\overline{\{x\in\mathbb{R}:u(x)>0\}}$ is compact where $\overline{A}$ denotes the closure of A.

Definition 2 [6]

An α-cut, u_α is a crisp set which contains all the elements of universal set X that have a membership function greater or equal to α and can be expressed as $u_\alpha=\{x\in X:\mu_u(x)\geq\alpha\}$.

Definition 3 [7]

A fuzzy number u is completely determined by any pair $u=(\underline{u},\bar{u})$ of functions $\underline{u}(\alpha),\bar{u}(\alpha):[0,1]\to\mathbb{R}$ satisfies the three conditions:

1) $\underline{u}(\alpha),\bar{u}(\alpha)$ is a bounded, monotonic , (nondecreasing, nonincreasing) left-continuous function for all $\alpha\in(0,1]$ and right-continuous for $\alpha=0$.

2) For all $\alpha\in(0,1]$ we have : $\underline{u}(\alpha)\leq\bar{u}(\alpha)$.

3) For every $u=(\underline{u},\bar{u}),v=(\underline{v},\bar{v})$ and $k>0$,

$(\underline{u+v})(\alpha)=\underline{u}(\alpha)+\underline{v}(\alpha)$

$(\overline{u+v})(\alpha)=\bar{u}(\alpha)+\bar{v}(\alpha)$

$(\underline{ku})(\alpha)=k\underline{u}(\alpha),(\overline{ku})(\alpha)=k\bar{u}(\alpha)$

Fuzzy set is a mapping from a universal set into [0,1]. Conversely, every function $\mu:X\to[0,1]$ can be represented as a fuzzy set ([5]). We can define a set $F_1=\{x\in\mathbb{R}:xisabouta_2\}$ with triangular membership function as below:

Definition 4 [5]

$$\mu_{F_1}=\begin{cases}\dfrac{x-a_1}{a_2-a_1}\,x\in[a_1,a_2)\\ 1x=a_2\\ \dfrac{-x+a_3}{a_3-a_2}\,x\in(a_2,a_3]\end{cases}$$

So the fuzzy set F can be written as any ordinary function $F=\{(x,\mu_F(x)):x\in X\}$.

III. Fuzzy Tumor Growth

Consider the following differential tumor equation without quiescent cells:

$$\dot{P}(t)=bP(t)\,. \qquad (2)$$

We fuzzy the equation by parametric representation of α-cut as follows: let

$$b=[b-(1-\alpha)\sigma_1,b+(1-\alpha)\sigma_1],\alpha\in[0,1]$$

and

$$b_1=(1-\mu)(b-(1-\alpha)\sigma_1)+\mu(b+(1-\alpha)\sigma_1)\,,\ \mu\in[0,1]\,.$$

Then the fuzzy system of (2) is

$$\begin{aligned}\dot{\underline{P}}&=b_1\underline{P}(t),\\ \dot{\overline{P}}&=b_1\overline{P}(t).\end{aligned} \qquad (3)$$

The fuzzy tumor system (3) has trivial steady states with the characteristic equation $(b_1-\lambda)^2=0$ and, hence the root of characteristic equation is b_1. Then if b_1 is positive the steady state is unstable and the tumor will be malignant. Otherwise the steady state is stable and the tumor will be benign.

A. Fuzzy Delay Tumor Growth System with Quiescent Cells

Now consider System (1) with assuming that there are uncertainty parameters. Here again, we fuzzify the system and let $P(t),Q(t),\mathrm{r}_P(t),r_Q(t)$ be non-negative fuzzy functions and

$$\tilde{b}=[b-(1-\alpha)\sigma_1,b+(1-\alpha)\sigma_1],$$

$$\mu_Q=[\mu_Q-(1-\alpha)\sigma_2,\mu_Q+(1-\alpha)\sigma_2],$$

where

$$b_1=(1-\mu)(b-(1-\alpha)\sigma_1)+\mu(b+(1-\alpha)\sigma_1),$$

$$b_2=(1-\mu)(\mu_Q-(1-\alpha)\sigma_2)+\mu(\mu_Q+(1-\alpha)\sigma_2).$$

By using parametric representation of α-cut (see [8]) we write the system in matrix form as follows:

$$\begin{bmatrix}\dot{\underline{P}}_\alpha(t)\\ \dot{\overline{P}}_\alpha(t)\\ \dot{\underline{Q}}_\alpha(t)\\ \dot{\overline{Q}}_\alpha(t)\end{bmatrix}=\begin{bmatrix}0&0&0&0\\0&0&0&0\\0&0&0&-b_2\\0&0&-b_2&0\end{bmatrix}\begin{bmatrix}\underline{p}_\alpha\\ \overline{P}_\alpha\\ \underline{Q}_\alpha\\ \overline{Q}_\alpha\end{bmatrix}+$$

$$\begin{bmatrix}b_1&0&0&0\\0&b_1&0&0\\0&0&0&0\\0&0&0&0\end{bmatrix}\begin{bmatrix}\underline{P}_{\alpha t}\\ \overline{P}_{\alpha t}\\ \underline{Q}_{\alpha t}\\ \overline{Q}_{\alpha t}\end{bmatrix}+\begin{bmatrix}-\bar{r}_P\overline{P}+\underline{r}_Q\underline{Q}\\ -\underline{r}_P\underline{P}+\bar{r}_Q\overline{Q}\\ \underline{r}_P\underline{P}-\bar{r}_Q\overline{Q}\\ \bar{r}_P\overline{p}-\underline{r}_Q\underline{Q}\end{bmatrix}\,. \qquad (4)$$

Where $\underline{P}_{\alpha t}=\underline{P}_\alpha(t-\tau),\overline{P}_{\alpha t}=\overline{P}_\alpha(t-\tau)$ similarly for Q. So, the system (4) is known as fuzzy delay tumor growth system.

The system (4) has trivial steady state. And the characteristic equation is :

$$\lambda^4+C\lambda^2+E+e^{-\lambda\tau}(A\lambda^3+D\lambda)+e^{-2\lambda\tau}(B\lambda^2+F)=0\,. \qquad (5)$$

Where

$$\begin{aligned}&A=-2b_1,\\ &B=b_1^2,\\ &C=-b_2^2-\underline{r}_P(0)\bar{\mathrm{r}}_P(0)-\mathrm{b}_2\bar{r}_Q(0)-\mathrm{b}_2\underline{r}_Q(0)-\underline{r}_Q(0)\bar{r}_Q(0)\\ &-\bar{r}_P(0)\bar{r}_Q(0)-\underline{r}_P(0)\underline{r}_Q(0),\\ &D=2b_2^2b_1+2b_2b_1\bar{r}_Q(0)+2b_2b_1\underline{r}_Q(0)+2b_1\underline{r}_Q(0)\bar{r}_Q(0)\\ &+\mathrm{b}_1\bar{r}_P(0)\bar{r}_Q(0)+\mathrm{b}_1\underline{r}_P(0)\underline{r}_Q(0),\\ &\mathrm{E}=\mathrm{b}_2^2\underline{r}_P(0)\bar{r}_P(0),\\ &\mathrm{F}=-b_2^2b_1^2-b_2b_1^2\bar{r}_Q(0)-\mathrm{b}_2b_1^2\underline{r}_Q(0)-\mathrm{b}_1^2\underline{r}_Q(0)\bar{\mathrm{r}}_Q(0).\end{aligned} \qquad (6)$$

In absence of delay the steady state is stable if the roots of $\lambda^4+(B+C)\lambda^2+D\lambda+(E+F)=0$ have negative real part. By Routh-Hurwitz conditions this occurs if $A>0,D>0,(E+F)>0,\mathrm{A(B+C)D}>\mathrm{D}^2+A^2(E+F)$. Now for increasing , $\tau\neq0$, we assume that the root of the characteristic equation (5) is $\lambda=i\mu$ and $\mu>0$. Substitute $\lambda=i\mu$ in (5) we obtain,

$$\mu^4-C\mu^2+E(\cos(\mu\tau)-i\sin(\mu\tau))(-iA\mu^3+iD\mu)+$$

$$(\cos(2\mu\tau)-i\sin(2\mu\tau))(-B\mu^2+F)=0.$$

Separating the real and imaginary parts, we get

$$\begin{aligned}&\mu^4-C\mu^2+E=-(-A\mu^3+D\mu)\sin(\mu\tau)-\\ &(-B\mu^2+F)\cos(2\mu\tau),\\ &(-A\mu^3+D\mu)\cos(\mu\tau)-(-B\mu^2+F)\cos(2\mu\tau)=0\end{aligned} \qquad (7)$$

Squaring and adding both sides of (7) gives the polynomial of degree eight as follows:

$$(\mu^4 - C\mu^2 + E)^2 - (-A\mu^3 + D\mu)^2 - (-B\mu^2 + F)^2 + 2(-A\mu^3 + D\mu)(-B\mu^2 + F)\sin(-\mu\tau) = 0. \quad (8)$$

If $\tau = \frac{n\pi}{\mu}$ then $\sin(2\mu\tau)$ =0 and let $\gamma = \mu^2$ the equation (8) can be written in terms of γ as follows:

$$\gamma^4 + (-2C - A^2)\gamma^3 + (2E + C^2 + 2AD - B^2)\gamma^2 + (-2CE - D^2 + 2BF)\gamma + (E^2 - F^2) = 0. \quad (9)$$

We look for the case when the lead coefficient of (9) is positive so, there are two cases for a positive real root can obtain. The first and simplest is ($E^2 - F^2$) < 0. Now assume ($E^2 - F^2$) >0. Since the polynomial is even, there are four roots we are focusing for these roots to be real (four of them positive or two positive and two negative or four of them negative). If four of the roots are negative we suppose to take the strum chain of polynomial (9) denoted P_0, P_1, P_2, P_3, P_4.

Let

$$P_0 = \gamma^4 - (A^2 + 2C)\gamma^3 + (2E + C^2 + 2AD - B^2)\gamma^2 + (-2CE - D^2 + 2BF)\gamma + (E^2 - F^2) = 0$$

and

$$P_1 = 4\gamma^3 - 3(A^2 + 2C)\gamma^2 + 2(2E + C^2 + 2AD - B^2)\gamma + (-2CE - D^2 + 2BF) = 0$$

The bifurcation occurs in the case ($E^2 - F^2$) >0 if and only if the lead coefficient P_2, P_3 and P_4 are positive.

Hence by division algorithm the lead coefficient of P_2, P_3, P_4 is positive which are

,,

$$\left(\frac{1}{2}(2E + C^2 + 2AD - B^2) - \frac{3}{16}(-2C - A^2)^2 > 0,\right.$$

$$-(A_2 - A_3) > 0,$$

$$-\left((E^2 - F^2) - \frac{1}{16}(-2C - A^2)(-2CE - D^2 + 2BF) - \frac{A_5}{A_2 - A_3}\left((-2CE - D^2 + 2BF) - \frac{A_1\left((E^2 - F^2) - \frac{1}{16}(-2C - A^2)(-2CE - D^2 + 2BD)\right)}{\frac{1}{2}(CE + C^2 + 2AD - B^2) - \frac{3}{16}(2C - A^2)^2}\right) > 0, \quad (10)$$

Where

$$A_1 = 3(-2C - A^2) - \frac{3(-2CE - D^2 + 2BF)}{\frac{1}{2}(2E + C^2 + 2AD - B^2) - \frac{3}{16}(2C - A^2)^2} - \frac{\frac{1}{2}(-2C - A^2)(2E + C^2 + 2AD - B^2)}{\frac{1}{2}(2E + C^2 + 2AD - B^2) - \frac{3}{16}(2C - A^2)^2},$$

$$A_2 = 2(2E + C^2 + 2AD - B^2) - \frac{4(E^2 - F^2)}{\frac{1}{2}(2E + C^2 + 2AD - B^2) - \frac{3}{16}(2C - A^2)^2} \frac{\frac{1}{16}(-2C - A^2)(-2EC - D^2 + 2BF)}{\frac{1}{2}(2E + C^2 + 2AD - B^2) - \frac{3}{16}(2C - A^2)^2},$$

$$A_3 = \frac{A_1\left(\frac{3}{4}(-2CE - D^2 + 2BF)\right)}{\frac{1}{2}(2E + C^2 + 2AD - B^2) - \frac{3}{16}(2C - A^2)^2} - \frac{\frac{1}{8}(-2C - A^2)(2E + C^2 + 2AD - B^2))}{\frac{1}{2}(2E + C^2 + 2AD - B^2) - \frac{3}{16}(2C - A^2)^2},$$

$$A_4 = \left(\frac{\frac{1}{2}(2E + C^2 + 2AD - B^2) - \frac{3}{16}(2C - A^2)^2}{A_2 - A_3}\right)$$

$$\left((-2CE - D^2 + 2BF) - \frac{A_1\left((E^2 - F^2) - \frac{1}{16}(-2C - A^2)\right.}{\frac{1}{2}(2E + C^2 + 2AD - B^2) - \frac{3}{16}(2C - A^2)^2}\right) \quad (11)$$

$$\left(\frac{A_1(-2CE - D^2 + 2BD))}{\frac{1}{2}(2E + C^2 + 2AD - B^2) - \frac{3}{16}(2C - A^2)^2}\right),$$

$$A_5 = \frac{3}{5}(-2CE - D^2 + 2BF) - \frac{1}{8}(-2C - A^2)(2E + C^2 + 2AD - B^2) - A_4$$

Proposition 1

A steady state with characteristic equation (5) is stable in the absence of delay, and become unstable with increasing delay if and only if

1) $A>0, D>0, (E+F)>0$ and
$A(B+C)>D^2+A^2(E+F)$

2) $-(\frac{1}{2}(2E+C^2+2AD-B^2)-\frac{3}{16}(-2C-A^2)^2)>0,$

$-(A_2-A_3)>0,$

$-((E^2-F^2)-\frac{1}{16}(-2C-A^2)(-2CE-D^2+2BF)-$

$\frac{A_5}{A_2-A_3}((-2CE-D^2+2BF)-$

$\frac{A_2((E^2-F^2)-\frac{3}{16}(-2C-A^2)(-2CE-D^2+2BD))}{\frac{1}{2}(CE+C^2+2AD-B^2)-\frac{3}{16}(2C-A^2)^2}>0$

Where $A, B, C, D, E, F, A_1, A_2, A_3, A_4, A_5$ are given in (6), (11).

IV. Examples

Example 1

Consider the fuzzy delay tumor system (4) with the following conditions $\mu=1, b=1, \mu_Q=1, r_P=2, r_Q=1, \sigma_1=1.2$
$\sigma_2=0.1, \sigma_4=0.2, \sigma_5=0.5$

And the initial conditions is

$(\underline{P}(0), \overline{P}(0))=(4-(1-\alpha)\sigma_4, 4+(1-\alpha)\sigma_4),$

$(\underline{Q}(0), \overline{Q}(0))=(3-(1-\alpha)\sigma_5, 3+(1-\alpha)\sigma_5).$

As can be seen in Fig. 1, the behavior of the trivial steady state is unstable since the solution does not converge to the trivial steady state. It means the conditions of Proposition 1 are satisfied.

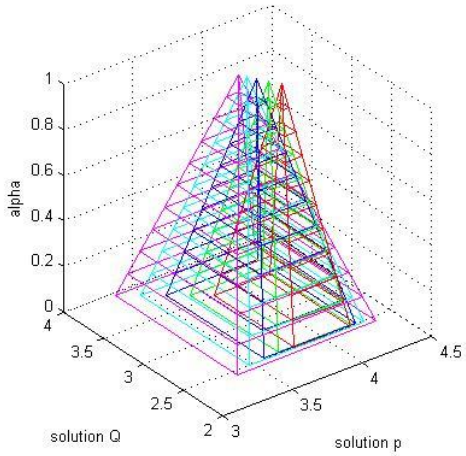

Figure 1: $\tau=20$

Example 2

We fixed all parameters as in Example 1 except for b, b is now equal to two. The solution does not converge to the trivial steady state (as in Figure 2). If b =4, the trivial steady state is also unstable (as in Figure 3).

Also, another increase of b =5 we see the trivial steady state is unstable (as in Figure 4).

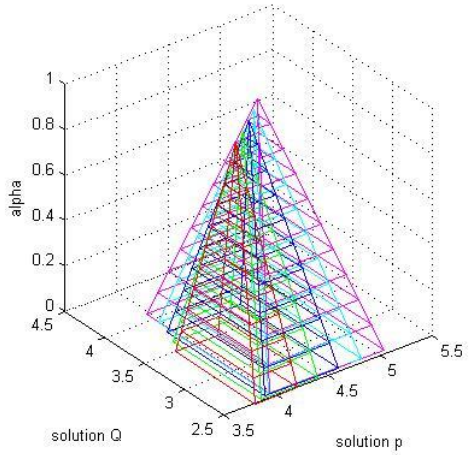

Figure 2: $\tau=20$

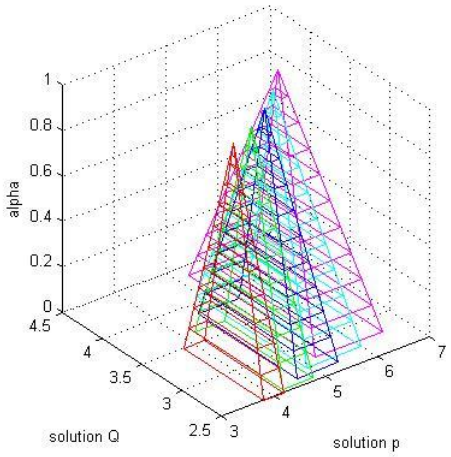

Figure 3: $\tau=20$

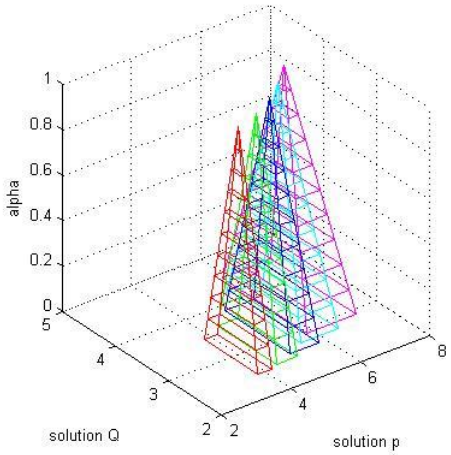

Figure 4: $\tau=20$

From above examples, physiologically it means that the fuzzy delay tumor system has stable trivial steady state when $\tau = 0$ and hence the growth of tumor is stopped by medical cure.
After extension of influence of medical cure (increasing the parameter) the stability of steady state is lost and the tumor starts to oscillate. The oscillations means either the tumor disappears or the patient is overcome.
If the delay is greater than zero, the tumor may experience a temporary appear and the trivial steady state is unstable. The tumor proliferates and it turns into necrotic mass. An increase in cell proliferation leads to an increase the concentration of many growth factors. However, it takes time for cell to up-regulate rate of growth. It means for large value of delay the fuzzy system showed irregular pattern for each cell population. And with increasing time delay in proliferation we observed periodic behavior of the number of cancerous cells. This behavior may explain periodic tumors growth and it's uncorrelated with the chemotherapy.

V. Conclusions

In this paper, we proposed a system of fuzzy delay tumor growth system by using symmetric triangular fuzzy number. The crisp tumor growth system of (2×2) system is extended to a fuzzy tumor growth of (4×4) system by using parametric form of α-cut. The fuzzy tumor growth with and without quiescence cells has trivial steady states. The fuzzy system proposed leads to the difficulty of locating the roots of the characteristic equation since the system becomes larger compare with the crisp system. Generally, the situation is more complex to arrive at general conditions on the coefficient of characteristic equation in order to describe a stability of trivial steady state. The trivial steady state for the system with quiescent cells is stable in absence of delay and increasing delay it is unstable. The applicability of the results is demonstrated by examples.

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