STIFF EQUATION WITH APPLICATION IN OVARIAN CANCER DISEASES

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Abstract

Cancer is characterised by an abnormal, uncontrolled growth that may destroy and invade adjacent healthy body tissues or elsewhere in the body. Ovarian carcinoma is the leading cause of death from gynaecological malignancies in the western world. Ovarian cancer is thought to result from an accumulation of genetic changes. We propose an original mathematical model with small parameter for the growth of cell-cycle dose limiting bone marrow in ovarian cancer. Both the equation of this system includes small parameter . We introduce the mathematical technique known as boundary function method for singular perturbation system. In this system, the small parameter is an asymptotic variable, different from the independent variable. We write solution of this system in a small parameter, and investigation of asymptotic solution for system. Using the program Matlab and numerical method Runge-Kutta, I did various simulations for different values of biological parameters presented in the model studied .

Keywords: *boundary function, cell-cycle, ovarian cancer, small parameter, asymptotic analyses*

ACM/AMS Classification: 92C42, 92C47, 34E05, 34E10, 34E20

1. Introduction

Ovarian cancer remains a highly lethal disease. Estimates indicate that 1 in 70 women will develop ovarian cancer in her lifetime. Ovarian cancer accounts for 3.3% of all new cases of cancer. Ovarian cancer is frequently

considered to be diseases of the cell cycle alterations in different families of cell cycle regulators cooperate in tumor development. Molecular analysis of human tumours has shown that cell cycle regulators are frequently mutated in human neoplasm's, which underscores how important the maintenances of cell cycle commitment is in the prevention of human cancer. Chemotherapy involves using drugs to destroy cancer cells. Many of these drugs destroy cancer cells by preventing them from growing and dividing rapidly. Unfortunately many normal cells also divide rapidly and are damaged by chemotherapy. Cell cycle specific chemotherapy drugs are a common type of drug used in treating ovarian cancer. The main action of these drugs works against cells in a specific phase of the cell cycle. The cell-cycle is a series of steps that both normal cells and cancer cells go through in order to form new cells. In this article consider only the active process of the cell cycle, is that there is reduced toxicity to the bone marrow when the drugs are administrated at integer multiplies of the bone marrow's mean cell-cycle length. In the process, the above regimens also destroy fewer cancer cells. Understating how these drugs work helps oncologists predict which drugs are likely to work well together. High-dose chemotherapy has been utilized in primary, salvage, consolidation therapy of ovarian cancer. Treatment has been reasonably tolerated with long-term follow-up available (Preziosi, 2003).

Resistance to a particular chemotherapeutic drug is dependent on a particular tumor within a patient whereby the drug is ineffective in controlling tumor growth without causing excessive toxicity . Resistance to therapy may be intrinsic or may emerge after initial successful treatment. Mechanisms for resistance include variations in cell cycle kinetics, biologic or biochemical phenomena, and pharmacologic or drug level. All living tissue is composed of cells. Cells grow and reproduce to replace cells lost due to injury or normal wear and tear. Chemotherapy can't guarantee that the cancer will not come back, but it can reduce the chance that it will. The risk of the cancer coming back varies according to each woman's situation. If the chance of your cancer coming back is small, chemotherapy may only slightly reduce the risk of the cancer coming back (Wheldon, 1988).

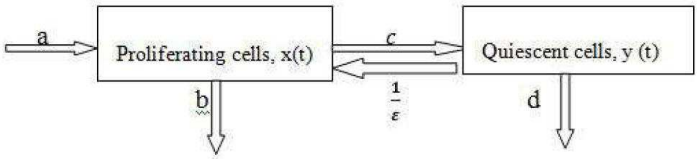

Figure 1. *The cell-cycle*

2. **Matherial and Methods**

In this article, we analyze an original singularly perturbed system of ordinary differential equations for the model discussed in (Panetta, 1997; Fister,

2000) with form:

$$(P_\varepsilon) \quad \begin{cases} \varepsilon \frac{dx}{dt} = (\varepsilon a - \varepsilon b - \varepsilon c)\, x + y \\ \varepsilon \frac{dy}{dt} = \varepsilon c x - (\varepsilon d + 1)\, y \end{cases} \tag{1}$$

With initial conditions:

$$x(0) = x_0, y(0) = y_0 \tag{2}$$

Where x is number a proliferating cells, y is number a quiescent cells mass in the bone marrow. The parameter are all considered constant, are defined as follows: a, is cycling cells growth; b, natural cell death; c, transition rate from proliferating; d, cell differentiation-mature bone marrow cell leaving the bone marrow and entering the blood stream as various types of blood cells. We work on the assumption that $1/\varepsilon$, transition rate from resting to proliferating is long, where ε is the small parameter. All the units for the parameters are $days^{-1}$. The use of a small parameter here is simply for definiteness. For example, a problem depending on a large parameter θ can be rewritten as one depending on a small parameter: $\varepsilon = 1/\theta$. Equation (P_ε) corresponds to the extended model.

3. **Asymptotic Solution**

As we see, both part of (P_ε)contains the small parameter multiplying the derivate. We use the notation $x(t, \varepsilon), y(t, \varepsilon)$ for the solution of (1)and (2). The choice of a small parameter is connected with the order of the solution and the asymptotic sequence which describes the behaviour of the solution as $\varepsilon \to 0$. Setting $\varepsilon = 0$ in (P_ε) , we obtain:

$$(P_0) \quad \begin{cases} \tilde{y}^0 = 0 \\ \breve{x}^0 = F(a, b, c, d, t) \end{cases} \tag{3}$$

Equation (P_0) might be a simplified model of this process. We started out with two differential equations, and ended up saying that one of the differential equations degenerates to an algebraic equation. A system of two differential equations is quite different from a single differential equation with an algebraic constraint. The system (3) his is called the degenerate system. Not know the shape function F, and that does not help at all to justify the asymptotic solution.

The overall procedure (Vasil'eva, 1995) for work is :

• Develop an appropriate scaling for the equations. Identify the small parameter.

• Writting regular series.

• Writting boundary function series.

• Match up the two solutions in an intermediate time range.

We will seek the asymptotic expansions for the solution of (1), (2) in a format that is quite typical for singularly perturbed problems:

$$\begin{cases} x(t,\varepsilon) = \sum_{i=0}^{2} \left(x^i + \pi_i x\right) \varepsilon^i + O(\varepsilon^3) \\ y(t,\varepsilon) = \sum_{i=0}^{2} \left(y^i + \pi_i y\right) \varepsilon^i + O(\varepsilon^3) \end{cases} \tag{4}$$

Where:

$$\begin{cases} \tau = \frac{t}{\varepsilon} \text{ , deals with system with clear separation of time} - \text{scale} \\ \sum_{i=0}^{2} x^i \varepsilon^i \quad \text{is regular series} \\ \sum_{i=0}^{2} \pi_i x \varepsilon^i \quad \text{is boundary function series} \end{cases} \tag{5}$$

Substituting the series (4) into system (1), we obtain the equalities for terms of regular part of the asymptotic:

$$\varepsilon^0 : \quad y^0 = 0 \tag{6}$$

$$\varepsilon^1 : \quad \begin{cases} \frac{dx^0}{dt} = (a-b-c)\, x^0 + y^1 \\ \frac{dy^0}{dt} = -cx^0 - dy^0 - y^1 \end{cases} \tag{7}$$

$$\varepsilon^2 : \begin{cases} \frac{dx^1}{dt} = ax^1 - bx^1 - cx^1 + y^2 \\ \frac{dy^1}{dt} = cx^1 - dy^1 - y^2 \end{cases} \tag{8}$$

Solving systems (6), (7), (8), we obtain:

$$\begin{cases} y^0(t) = 0 \\ x^0(t) = e^{(a-b)t} \\ x^1(t) = (cb - ac - dc)\, te^{(a-b)t} \\ y^1(t) = ce^{(a-b)t} \\ y^2(t) = e^{(a-b)t}[cb - ac - dc + t(a-b) - (a-b-c)(cb-ac-dc)t] \end{cases} \tag{9}$$

Of relationship (6), (7), (8) note that we cannot determine function $x_2(t)$. Therefore, we consider:

$$x_2(t) \in O(\varepsilon^3) \tag{10}$$

Substituting expansions (4) into conditions (2) we obtain:

$$\begin{cases} x^0(0) + \pi_0 x(0) = x_0 \\ y^0(0) + \pi_0 y(0) = y_0 \end{cases} \tag{11}$$

$$\begin{cases} x^1(0) + \pi_1 x(0) = 0 \\ y^1(0) + \pi_1 y(0) = 0 \end{cases} \tag{12}$$

$$\begin{cases} x^2(0) + \pi_2 x(0) = 0 \\ y^2(0) + \pi_2 y(0) = 0 \end{cases} \tag{13}$$

Recall that the functions $\pi_0 x, \pi_1 x, \pi_0 y, \pi_1 y, \pi_2 x, \pi_2 y$ should be boundary functions, they should approach zero as $\tau \to \infty$. The function $y(t,\varepsilon)$ does not have a boundary layer in the zero-order approximation.

The functions $\pi_0(\tau)$, $\pi_1(\tau)$ decay exponentially as τ increases. Therefore they are important only in a small vicinity of the initial point $t = 0$. For $\tau \gg \theta$, where θ is an arbitrarily small, $\pi_k(\tau) \to 0$ as $\varepsilon \to 0$ faster any power of ε. Let is try to construct an asymptotic expansions of the solution of (1), (2)in the form of power series in the power of ε. Series (4) satisfies formally the differential system (1), but it does not in general satisfy the initial condition (2).

$$\frac{d\pi x}{dt} = \frac{d\pi x}{d\tau}\ \frac{d\tau}{dt} = \frac{1}{\varepsilon}\ \frac{d\pi x}{d\tau} \tag{14}$$

Equation (11) contains four unknowns. Similar case takes place in (12), (13). It is clear that by using only (11), it is impossible to define these four unknowns. Equation (6) is not differential, and therefore we need not impose any condition on $x^0(0)$. Thus we need not treat $x^0(0)$ in (6) as an unknown. The same is true for the quantities: $x^0(0)$, $x^1(0)$, $x^2(0)$. Substituting the series (4) into system (1), we obtain the equalities for terms of the boundary functions part of the asymptotic:

$$\varepsilon^0: \qquad \begin{cases} \frac{d\pi_0 x}{d\tau} = \pi_0 y \\ \frac{d\pi_0 y}{d\tau} = -\pi_0 y \end{cases} \tag{15}$$

$$\varepsilon^1: \qquad \begin{cases} \frac{d\pi_1 x}{d\tau} = a\pi_0 x - b\pi_0 x - c\pi_0 x + \pi_1 y \\ \frac{d\pi_1 y}{d\tau} = c\pi_0 x - d\pi_0 y - \pi_1 y \end{cases} \tag{16}$$

$$\varepsilon^2: \begin{cases} \frac{d\pi_2 x}{d\tau} = (a-b-c)\,\pi_1 x + \pi_2 y \\ \frac{d\pi_2 y}{d\tau} = (c-d)\,\pi_1 y - \pi_2 y \end{cases} \tag{17}$$

Solving systems (15), (16), (17), we obtain:

$$\begin{cases} \pi_0 x = -e^{-\tau} \\ \pi_0 y = e^{-\tau} \\ \pi_1 x = e^{-\tau}\left(a - b - c + c\tau + c + d\tau + d\right) \\ \pi_1 y = (-c-d)\,\tau e^{-\tau} \\ \pi_2 y = \left(ac - bc + \tau c^2 + \tau cd + 2dc + d^2\right)\tau e^{-\tau} \\ \pi_2 x = Me^{-\tau} - N\left(\tau + 1\right)e^{-\tau} \end{cases} \tag{18}$$

Where constants are M,N are given:

$$\begin{cases} M = (b + c - a)\,(a - b - c + \tau c + \tau d + d) \\ N = (ac - bc + \tau c^2 + \tau cd + 2dc + d^2) \end{cases} \tag{19}$$

The relations (11)-(18) we find:

$$\begin{cases} \pi_0 y\,(0) = y_0 \\ \pi_k x\,(\infty) = 0, k = 0, 1, 2. \\ \|\pi_k x(\tau)\| \le u e^{-v\tau} \end{cases} \tag{20}$$

Here we will use m,p to represent appropriate positive number, which are, generally speaking in different inequalities (Ilea,2006).

Let us now give some formal explications: the terms containing small parameter ε are called perturbations. The extended model (P_ε) is then called perturbed, and the simplified model (3) is called unperturbed. In this article, the model is formulated in terms of differential equations with small parameter multiplying the highest derivates.

We will call the terms $\pi_k(\tau)$ boundary functions. If we accept approximate solution, where the approximation is based on the inherently small modelling parameter ε, we do have the possibility to gradually increase the complexity of a model, and study small but significant effects in the most efficient way. The exact solutions to (1) depend on the parameter $\varepsilon > 0$. We use $x_\varepsilon(t,\varepsilon), y_\varepsilon(t,\varepsilon)$ for exact solution of (1), (2). In general, it is not possible to find an exact solution of this problem. If the specimen, we derive an exact solution, her form is quite complicated.

$$\begin{cases} x_\varepsilon(t) = Ue^{r_+t} + Ve^{r_-t} \\ y_\varepsilon(t) = e^{r_+t}(\varepsilon r_+ U - \varepsilon aU + \varepsilon bU + \varepsilon cU) + e^{r_-t}(\varepsilon r_- V - \varepsilon aV + \varepsilon bV + \varepsilon cV) \\ r_{+,-} = \frac{\varepsilon^2(a-b-c+d)+\varepsilon \pm \sqrt{W}}{2\varepsilon} \\ W = (\varepsilon^2 a - \varepsilon^2 b - \varepsilon^2 c + \varepsilon^2 d + \varepsilon)^2 + 4\varepsilon(\varepsilon^2 ad - \varepsilon^2 db - \varepsilon^2 dc + \varepsilon a - \varepsilon b) \end{cases} \tag{21}$$

Where constants U, V are of form:

$$\begin{cases} U = \frac{x_0(2\varepsilon r_+ - \varepsilon r_- + \varepsilon a + \varepsilon b + \varepsilon c) - y_0}{\varepsilon(r_+ - r_-)} \\ V = \frac{y_0 - x_0(\varepsilon r_+ - \varepsilon a + \varepsilon b + \varepsilon c)}{\varepsilon(r_+ - r_-)} \end{cases} \tag{22}$$

For $\Omega \subseteq R^2$, be a convex domain, $h = \begin{pmatrix} (a-b-c)x + \frac{1}{\varepsilon}y \\ cx - \left(d + \frac{1}{\varepsilon}\right)y \end{pmatrix} \in C^1(\Omega, R^2)$, $p = \begin{pmatrix} x \\ y \end{pmatrix} \in R^2$, consider the following problem for ordinary differential (1):

$$\begin{cases} \frac{dp}{dt} = h(p,\varepsilon), p \in R^2 \\ p(0) = p^0 \end{cases} \tag{23}$$

4. **Phase Portrait**

The focus of this chapter is on behaviour of solutions differential system (1) in the phase plane,that is, considering y as a function of x. The qualitative behaviour of solutions is revealed by the phase portrait.Also in the 2D case, a slope field can be used, the procedure is as follows.

Let $(x(t,\varepsilon), y(t,\varepsilon))$ be a solution curve of an autonomous differential system (1). For each point of time t, the ODE system yields the corresponding tangent vector. Each point (x, y) is assigned to a vector. Thereby, a rough overview about the behaviour of $(x(t,\varepsilon), y(t,\varepsilon))$ is given. In this case, isoclines are very useful:

The curve with $\frac{dx}{dt} = 0$ is called x-Nullisocline (the vectors are vertical): $y_1(x) = (-\varepsilon a + \varepsilon b + \varepsilon c)x$.

The curve with $\frac{dy}{dt}=0$ is called y-Nullisocline (the vectors are horizontal): $y_2(x)=\frac{\varepsilon cx}{\varepsilon d+1}$. Observe that:

$$\begin{cases} \lim_{x\to\infty} y_1(x) = \lim_{x\to\infty} y_2(x) = \infty \\ y_1(0) = y_2(0) = 0 \end{cases} \tag{24}$$

Since both y_1 and y_2 are strictly increasing and $y_1(x) > y_2(x)$ for all $x > 0$. Let be region between the isoclines: $\triangle := \{(x,y) : x > 0, y_2(x) < y_1(x)\}$.

Theorem 1. Let $(x_\varepsilon(t,\varepsilon), y_\varepsilon(t,\varepsilon))$ be a solution to differential system (1). Then, there exists a $t_0 > 0$ such that:

$$(x_\varepsilon(t,\varepsilon), y_\varepsilon(t,\varepsilon)) \in \triangle, \forall t \geq t_0. \tag{25}$$

We show that solutions can enter $\triangle$ but not leave it and solutions outside $\triangle$ eventually enter $\triangle$.We will also work with the one-dimensional version of differential system (1) given by:

$$\begin{cases} \frac{dy}{dx} = u(x,y) \\ u(x,y) = \frac{cx-\left(d+\frac{1}{\varepsilon}\right)y}{(a-b-c)x+\frac{1}{\varepsilon}y} \end{cases} \tag{26}$$

Let $y(x)$ the corresponding one-dimensional solution. If $y(x)$ is below the horizontal isoclines $y_2(x)$, then:

$$-\infty < \frac{dy}{dx} < \varepsilon^{-1} \tag{27}$$

And so y must intersect $y_2(x)$ for a higher value of x . Similarly,if $y(x)$ is above the orizontal isocline $y_1(x)$,

$$-\varepsilon^{-1} < \frac{dy}{dx} < \infty \tag{28}$$

And so y must intersect $y_2(x)$ for a lower value of x. Behaviour of solutions differential system (1) near the origin,is governed by matrix:

$$A = \frac{\partial h}{\partial x}(0) = \begin{pmatrix} a-b-c & \frac{1}{\varepsilon} \\ c & -d-\frac{1}{\varepsilon} \end{pmatrix} \tag{29}$$

The qualitative dynamic behaviour (of the solution curves) depends on the eigenvalues. The eigenvalues of A are given by:

$$\begin{cases} \det(A-\lambda I_2) = 0 \to \lambda^2 - \lambda\left(a-b-c-d-\frac{1}{\varepsilon}\right) + (a-b)\left(-d-\frac{1}{\varepsilon}\right) + cd = 0 \\ \lambda_{1,2} = \frac{\left(a-b-c-d-\frac{1}{\varepsilon}\right) \pm \sqrt{\left(a-b-c-d-\frac{1}{\varepsilon}\right)^2 - 4\left[(a-b)\left(-d-\frac{1}{\varepsilon}\right)+cd\right]}}{2} \end{cases} \tag{30}$$

Let $\varepsilon = 0.1$. Then $\lambda_1 > 0$, $\lambda_2 < 0$, $\det(A) < 0$, $tr(A) < 0$. We can see that:

$$\lambda_2 < 0 < \lambda_1 < 1 \tag{31}$$

Corresponding eigenvectors are:

$$\begin{cases} v_1 = \begin{pmatrix} \frac{1}{\varepsilon} \\ \lambda_1 - a + b + c \end{pmatrix} \\ v_2 = \begin{pmatrix} \frac{1}{\varepsilon} \\ \lambda_2 - a + b + c \end{pmatrix} \end{cases} \tag{32}$$

Since the eigenvalues are real-valued and distinct, the initial value problem (23) has solution of the form:

$$p\left(t\right) = m_1 e^{\lambda_1 t} v_1 + m_2 e^{\lambda_2 t} v_2 \tag{33}$$

The matrix A is cooperative $(a_{ij} \geq 0,\ i \neq j)$. If A is cooperative, then the system (23) leaves the cone $C = R_+^2$ positively invariant. In more detail, for $x\left(t, \varepsilon\right)$ and $y(t, \varepsilon)$ being trajectories, the implication is holds:

$$x_0 \leq y_0 \rightarrow x\left(t, \varepsilon\right) \leq y(t, \varepsilon),\ \ for\ \ t \geq 0 \tag{34}$$

In this case: $y \geq x \sim (y - x) \in R_+^2$. The ODE (32) is called quasimonotone,because A is cooperative.

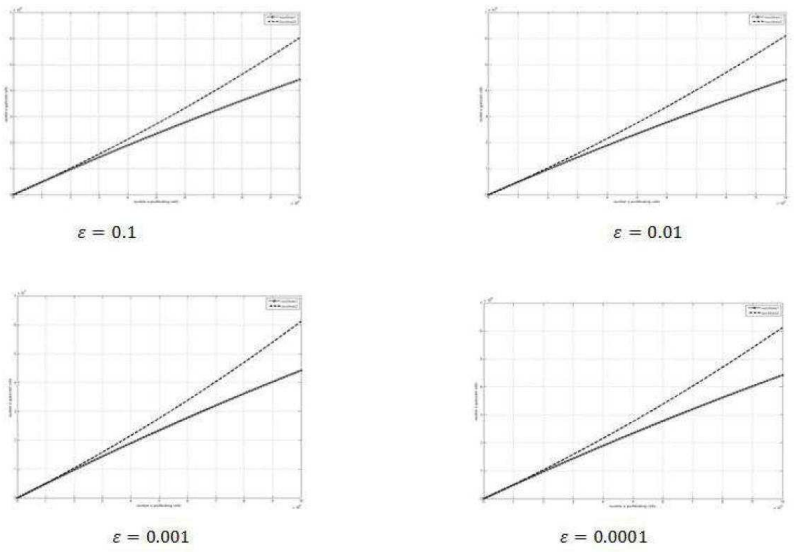

Figure 2. *A phase portrait for ordinary differential system for ε parameter values*

4. **Numerical Results**

The simulation of a single set of equation can be performed on a single workstation because the numerical integration of a system (P_ε) not very time

consuming. The parameter values have highs impact on the accuracy of the model in representing real biological systems but these values are difficult to estimate experimentally. The simulation of the cell cycle pathway allows a better understanding of cell cycle control in normal and transformed cells which is useful to put on a more rational basis the discovery of anticancer drugs. Generally the estimation of the kinetic parameters is performed by fitting the experimental by computing a number of ordinary differential equations systems with different parameters and verifying the best solution. This model is essentially based on differential equations and they can describe abundances kinetics and binding affinities of pathway components and their interactions. The complexity of this biological process is revealed every time a mathematical simulation of the processes is carried out. The parameter ε estimation process usually implies time-consuming computations due to algorithms of linear regression and stochastic methods. Parameter estimation adjusts the model to reproduce the experimental results in the best possible way for a set of experimental data. When using an implicit Runge-Kutta method for solving a differential system, (P_ε) the order of the error can be reduced compared to what the classical theory predicts (Gerald,1992). Runge-Kutta methods have to advantage of being one-step methods, possibly having high order and good stability properties. The Runge-Kutta method for solving differential equations is fairly difficult to understand and rather involved algebraically to derive. The main point of the method is to approximate the tangent to the curve not with a single secant, which is done in the Euler method, but with a weighted average of some small number of secants. For simulations in MATLAB, we used values of biological parameters in the following table:

mean	*unit*
$a \in (0.066,\ 2)$	$days^{-1}$
$b \in (0.1,\ 0.3)$	$days^{-1}$
$c \in (4.92,\ 6.12)$	$days^{-1}$
$d = 0.164$	$days^{-1}$

Table 1. *Biological bone marrow parameters*

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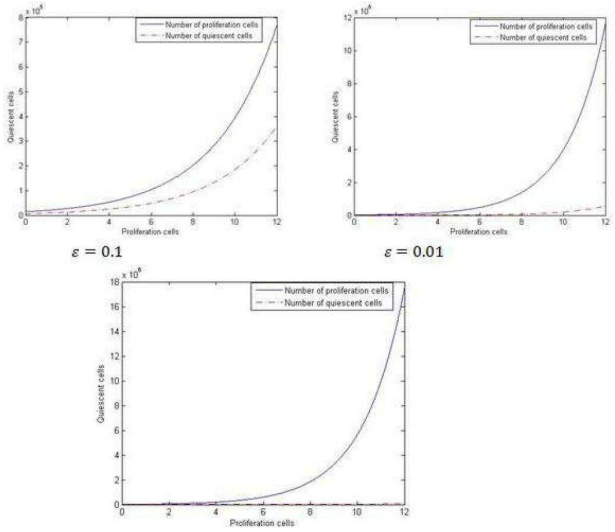

Figure 3. *Asymptotic solution to the perturbed problem for parameters value: a=0.667,b=0.1,c=4.92, d=0.164. Note that for long transition rate from resting to proliferating, more dynamic proliferating cells (blue) compared with number quiescent cells (red).*

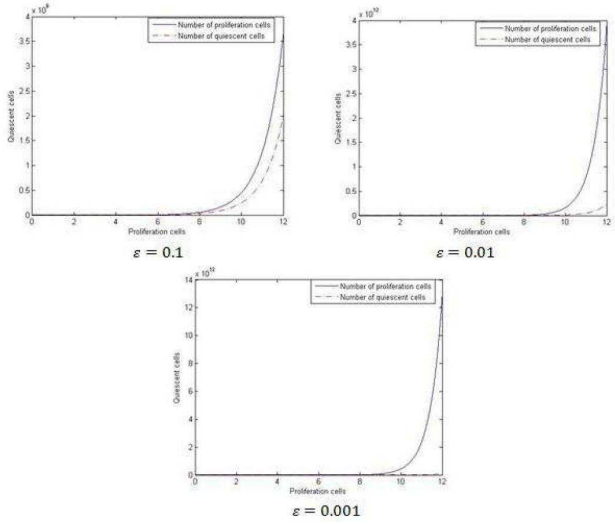

Figure 4. *Asymptotic solution to the perturbed problem for parameters value: a=2,b=0.3,c=6.12, d=0.164. Note that for long transition rate from resting to proliferating, more dynamic a proliferation cells (blue) compared with number a quiescent cells (red).*

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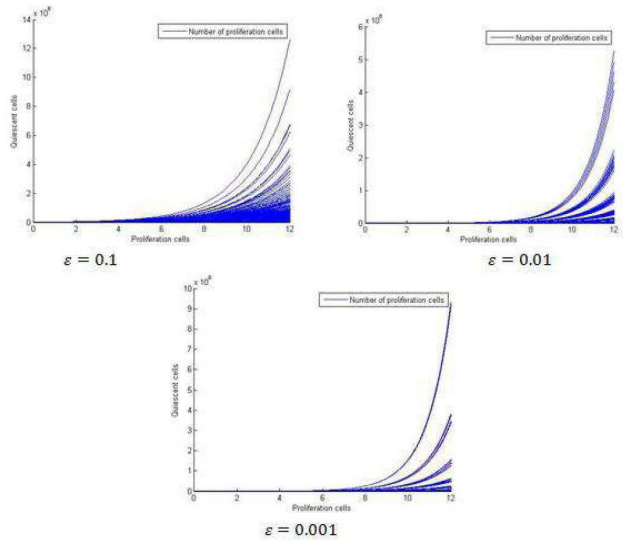

Figure 5. *Asymptotic solution to the perturbed problem for parameters value:* $a \in (0.0667, 2)$, $b \in (0.1, 0.3)$, $c \in (4.92, 6.12)$,*d=0.164.*

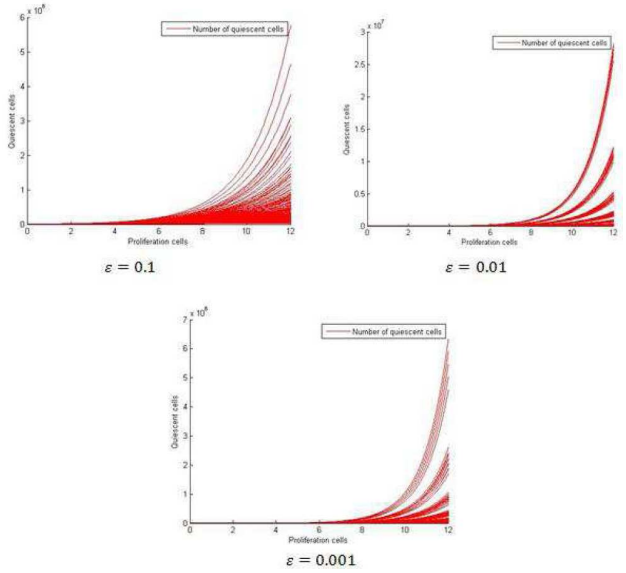

Figure 6. *Asymptotic solution to the perturbed problem for parameters value:* $a \in (0.0667, 2)$, $b \in (0.1, 0.3)$, $c \in (4.92, 6.12)$,*d=0.164.*

In initial value approach of the perturbed ODE system (P_ε), initial guesses for equation's parameters are chosen and the dynamical equations are solved numerically. As a matter of fact, our concept of the perturbation search method was inspired by the prospect of basic perturbation theory. The

principle of perturbation theory is to study dynamical systems that are small perturbation of integrable perturbed system. For this system,solutions can change on a time scale that is very short compared to the interval of integration, but the solution of interes changes on a much longer time scale.

4. **Conclusions**

Perturbation methods have their use as a natural step in the process of systematic modelling, the insight it provides in the nature of singularities occurring in the problem and typical parameter dependencies. Singularly perturbed differential equations are typically characterized by a small parameter multiplying some or all of the highest order terms in the differential equation. In general, the solutions of such equations exhibit multiscale phenomena. We call these thin regions of rapid change, boundary or interior layers, as appropriate. For small values of ε, an analytical approximation to the exact solution can be generated using the techniques of matched asymptotic expansions. Such asymptotic approximations identify the fundamental nature of the solution across the different scales. Matlab simulations obtained for transition rate from resting to proliferating is long, we show a similar asymptotic behaviour for two solutions of the perturbed problem. Interpret these results to be a permanent collaboration between maths and medical oncologists. Should mention this model system differential equations with small parameter are experimental and must be validated in future theoretical results.

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