HOPF BIFURCATIONS FOR A TIME-DELAYED CANCER CELL POPULATION MODEL

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Abstract

The paper investigates the structural stability of a cancer cell population time-delayed flow, establishing the critical value of the delay parameter that produces Hopf bifurcation. The model is investigated for three sets of values of the parameters. Numerical results are obtained using the software Maple 11.

Keywords: *dynamical system, time-delay, stationary point, Hopf bifurcation, quiescent cell population, proliferating cell population*

AMS Classification: 34K18, 34K60, 37N25

1. Introduction

The understanding of the cancer mechanism has a significant impact on cancer treatment strategies. Recent research in cancer progression and treatment indicates that many forms of cancer arise from one abnormal cell or a small subpopulation of abnormal cells ([9]). These cells, which support cancer growth and spread are called *cancer stem cells* (CSCs). Moreover, they have the capacity of initiating new tumors after long periods of remission ([3]). Because these CSCs display many of the same characteristics as healthy stem cells, finding methods to target them (without killing the healthy stem cells) is an essential objective.

It is well known that cancer cell populations consist of a combination of *proliferating, quiescent (resting)* and *dead cells* that determine tumor growth or cancer spread ([4], [7]).

In 2006, Garner et al. introduces in [6] a mathematical non-dimensionalized model of cancer cell population consisting of a 2-dimensional system of ordinary differential equations (SODE) with 4 parameters. Based on applicative biological aspects, we considered in this paper a time-delay for one of the state variable of the system. Of course, the time-delayed flow could induce structural instability and Hopf bifurcation.

The model introduced by Garner is based on the dynamical system proposed by Solyanik et al. ([11]), and estimates the behavior of the two types

of cancer cell population (proliferating and quiescent) based on approximately 10 measurements of the total cell population over one week [11]. Its main assumptions are as follows:

- the cancer cell population consists of proliferating and quiescent (resting) cells;
- the cells can lose their ability to divide under certain conditions and then transit from the proliferating to the resting state;
- resting cells can either return to the proliferating state, or die.

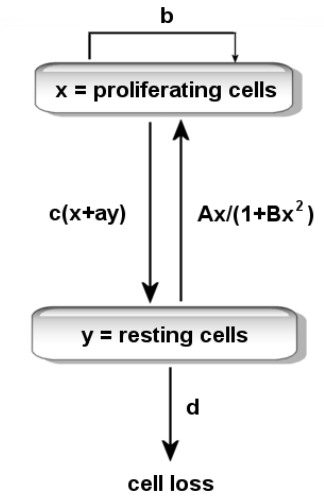

Figure 1. *Cancer cell population evolution*

Figure 1 presents a block diagram of the system. We note that Solyanik's model utilizes two coupled, nonlinear differential equations with the final cell behavior dependent upon initial total cell number and the ratio between proliferating and quiescent cells. The state variables are

- x - the number of proliferating cells, and
- y - the number of resting (quiescent) cells.

Their dynamics in time is described by the following differential equations introduced by Solyanik et al. [11]:

$$\begin{cases} x' = bx - Px + Qy \\ y' = -dy + Px - Qy, \end{cases}$$

where the parameters involved have the following meaning:

- b is the rate of cell division of the proliferating cells;

- d is the rate of cell death of the resting cells (per day);
- Q and P describe the intensity of cell transition from the quiescent to proliferating cells and vice versa (per day).

Based on the experimental observation that cancer cells multiply in the presence of sufficient biological and physical factors, they assumed that P must depend on the number of cells present and, in the simplest form, can be written as $P = c(x + ay)$, where:

- a is a dimensionless constant that measures the relative nutrient uptake by resting vs. proliferating cancerous cells;
- c depends on the intensity of consumption by proliferating cells and gives the magnitude of the rate of cell transition from the proliferating stage to the resting stage in per cell per day.

Solyanik et al. pointed out that transition from the quiescent to the proliferating state was more complex. One can easily guess that increasing the number of proliferating cells would decrease the intensity of this transition; however, a decrease in the number of proliferating cells can also have the same effect ([13], [14]). Based on these remarks, one can assume that Q is non-monotonous with respect to x (the number of proliferating cells) so that it increases with increasing x up to a certain point, and then decreases as x becomes very large. Accordingly, Q has the form $Q = Ax/(1 + Bx^2)$, where:

- A is the initial rate of increase in Q at small x;
- A/B represents the rate of decrease in Q when x becomes larger.

In their paper, Solyanik et al. studied the resulting steady states and stability, assuming that the transition rate Q is zero ([11]).

In order to simplify the notations and reduce the number of parameters, Garner et al. introduced in their paper [6] (2005) the following dimensionless parameters:

$$\bar{x} = xc/b, \quad \bar{y} = yca/b, \quad \bar{t} = bt.$$

After dropping bars for notational convenience, the non-dimensional system rewrites

$$\begin{cases} x' = x - x(x + y) + \dfrac{hxy}{1 + kx^2} \\ y' = -ry + ax(x + y) - \dfrac{hxy}{1 + kx^2}, \end{cases} \tag{1}$$

where:

- $r = d/b$ is the ratio of the death rate of quiescent cells to the birth rate of proliferating cells;
- $h = A \cdot (ac)^{-1}$ represents a growth factor that preferentially shifts cells from the quiescent to proliferating state;

- $k = B \cdot (b/c)^2$ represents a slightly moderating effect.

Garner et al. analyzed the non-dimensional model of cancer cell population in order to estimate long-term behavior of quiescent and proliferating cells. For simplicity, they set $k = 1$ and vary h to represent changes in the effects of these growth factors.

2. **Dirac time-delayed evolution**

In the following, we focus our attention on the study of the biological flow, when one variable coordinate is subject to time-delay.

It is well known that in the living world the physiological processes did not occur simultaneously. We outlined in the previous section that Q, the rate of the cell transition from the quiescent to the proliferating state has the form $\dfrac{Ax}{1+Bx^2}$, because it increases with increasing x up to a certain point, and then decreases as x becomes very large. In fact, the rate Q is always low (negligible cf. Solyanik [11]), being extremely low when x becomes large. Consequently, if the proliferating cell population is very large at a certain time t_1, then the cell transition process from the quiescent to the proliferating state is very slow, controlling the number of proliferating cell population at another time $t_2 = t_1 + \tau$. This is the reason for the rate Q to become

$$Q(x(t), x(t-\tau)) = \frac{Ax(t)}{1+Bx^2(t-\tau)}.$$

In order to obtain the dynamical system with delayed argument, we recollect that for any probability density $f : \mathbf{R} \to \mathbf{R}_+$ obeying $\displaystyle\int_0^\infty f(s)ds = 1$, the transformation (perturbation) of the state variable $x(t) \in \mathbf{R}$ dependent on f is the new variable $\tilde{x}(t)$ defined by

$$\tilde{x}(t) = \int_0^\infty x(t-s)f(s)ds = \int_{-\infty}^t x(s)f(t-s)ds \tag{2}$$

Particularly, when f is the Dirac distribution of $\tau \geq 0$, i.e.,

$$f(s) = \delta_\tau(s) = \begin{cases} 1, & s = \tau \\ 0, & s \neq \tau, \end{cases}$$

then the transform $\tilde{x}(t) = x(t-\tau)$ denotes the variable x with delayed argument. After the time-delay process applied to x, the system (1) becomes

$$\begin{cases} x'(t) = x(t) - x(t)[x(t)+y(t)] + \dfrac{hx(t)y(t)}{1+kx^2(t-\tau)} \\ y'(t) = -ry(t) + ax(t)[x(t)+y(t)] - \dfrac{hx(t)y(t)}{1+kx^2(t-\tau)}, \end{cases} \tag{3}$$

with

$$x(0) = x_0, y(0) = y_0, x(\theta) = \varphi(\theta), \theta \in [-\tau, 0], \tau \geq 0,$$

where the transform $\tilde{x}(t) = x(t-\tau)$ is defined by (2) and $\varphi : [-\tau, 0] \to \mathbf{R}$ is a differentiable function which describes the behavior of the flow in the O direction. In other words, the initial SODE (1) is replaced by a differential-functional system (3).

3. **Hopf bifurcation**

The stationary points of the system (1) are solutions of the nonlinear system

$$\begin{cases} x - x(x+y) + \dfrac{hxy}{1+kx^2} = 0 \\ -ry + ax(x+y) - \dfrac{hxy}{1+kx^2} = 0. \end{cases}$$

In ([1]) was proven that the system above always admits a solution (x^*, y^*) situated in the first quadrant. Regarding the linearization of the delayed system (2), we can state the following result:

Proposition 3.1. [8] *The following assertions hold true:*
a) The linearized SODE of the differential autonomous system with delayed argument (3) at its equilibrium point (x^*, y^*) is

$$\begin{pmatrix} \dot{x}(t) \\ \dot{y}(t) \end{pmatrix} = M_1 \begin{pmatrix} x(t) \\ y(t) \end{pmatrix} + M_2 \begin{pmatrix} x(t-\tau) \\ y(t-\tau) \end{pmatrix} \tag{4}$$

where

$$M_1 = \begin{pmatrix} \frac{\partial f_1}{\partial x(t)} & \frac{\partial f_1}{\partial y(t)} \\ \frac{\partial f_2}{\partial x(t)} & \frac{\partial f_2}{\partial y(t)} \end{pmatrix}\Bigg|_{(x^*,y^*)}, M_2 = \begin{pmatrix} \frac{\partial f_1}{\partial x(t-\tau)} & 0 \\ \frac{\partial f_2}{\partial x(t-\tau)} & 0 \end{pmatrix}\Bigg|_{(x^*,y^*)},$$

and (f_1, f_2) are the components of the field which provides the SODE (1).
b) The characteristic equation of the differential autonomous system with delayed argument (2) is

$$\det(\lambda I - M_1 - e^{-\lambda\tau} M_2) = 0. \tag{5}$$

Remark 3.1. *The characteristic equation (5) has the form*

$$\lambda^2 + a_1\lambda + a_2 + (a_3\lambda + a_4)e^{-\lambda\tau} = 0 \tag{6}$$

Let $J(\lambda)$ be the characteristic quasi-polynomial function in (6). Looking for the critical values of the parameter τ at which there is an exchange of structural stability, we note that the solutions of the characteristic equation (6) are of the form $\lambda = \lambda(\tau) = u(\tau) \pm i\omega(\tau) \in \mathbf{C}$ and that the equation (6) is equivalent to $\mathrm{Re}(\lambda) = \mathrm{Im}(\lambda) = 0$.

A prerequisite for studying the Hopf bifurcation consists in finding the critical values of the parameter τ, by imposing $u(\tau) = 0$ and $\omega(\tau) \neq 0$. Under these assumptions, we infer the nonlinear system in terms of ω and τ

$$\begin{cases} -\omega^2 + a_2 + a_4 \cos\omega\tau + \omega a_3 \sin\omega\tau = 0, \\ a_1\omega + a_3\omega\cos\omega\tau - a_4 \sin\omega\tau = 0. \end{cases} \tag{7}$$

By squaring every equation of the equivalent system

$$\begin{cases} a_4 \cos\omega\tau + \omega a_3 \sin\omega\tau = \omega^2 - a_2, \\ a_4 \sin\omega\tau - \omega a_3 \cos\omega\tau = a_1\omega, \end{cases} \tag{8}$$

the relation $cos^2\omega\tau + sin^2\omega\tau = 1$ leads to

$$\omega^4 + (a_1^2 - 2a_2 - a_3)\omega^2 + a_2^2 - a_4^2 = 0,$$

which provides a preliminary overset for the solutions ω of (7).

We are interested only in the real non-negative solutions. The existence of real solutions is obtained if and only if the condition $a_2^2 - a_4^2 \leq 0$ is fulfilled or the following system

$$\begin{cases} (a_1^2 - 2a_2 - a_3)^2 - 4(a_2^2 - a_4^2) \geq 0, \\ a_1^2 - 2a_2 - a_3 \leq 0, \\ a_2^2 - a_4^2 \geq 0, \end{cases}$$

is satisfied.

Since $\lambda(\tau)$ is a solution of the equation (6), deriving we get

$$\lambda^{/}\left\{2\lambda + a_1 + [a_3 - \tau(a_3\lambda + a_4)]\, e^{-\lambda\tau}\right\} - (a_3\lambda + a_4)\,\lambda e^{-\lambda\tau} = 0.$$

In order to obtain Hopf bifurcation, the transversality condition $\mathrm{Re}\lambda^{/}(\tau_0) > 0$ must be satisfied.

In the following, we shall use the values of the parameters corresponding to three mouse mammary cell lines, namely 66, 67 and 68H ([6]).

3.1. *The case of 66 cell line*

In this case, the values of the parameters are $a = 0.6$, $h = 1$, $k = 1$, $r = 0.075$.

Using Maple 11 software techniques, we can state the following result:

Proposition 3.1.1. *a) The only equilibrium point acceptable from a biological point of view (hence given by non-negative dependent variables) of (3) is*

$$(x^*, y^*) = (0.6089133165, 1.445867165).$$

b) The constitutive matrices of the linearized system (4) are

$$M_1 = \begin{pmatrix} -0.608913316 & -0.1647024673 \\ 0.543435797 & -0.1538628593 \end{pmatrix}, M_2 = \begin{pmatrix} -0.5706064988 & 0 \\ 0.5706064988 & 0 \end{pmatrix}.$$

c) The coefficients of the characteristic equation (6) are

$$a_1 = 0.7627761753, a_2 = 0.1831943605, a_3 = 0.5706064988, a_4 = 0.1817754456.$$

d) The system (7) has two solutions $(\omega_0, \tau_0) \in \mathbf{R}^* \times \mathbf{R}_+^*$*, namely*

$$\omega_{01} = 0.3243946058, \tau_{01} = 8.232227883,$$
$$\omega_{02} = 0.07015086316, \tau_{02} = 43.71641183,$$

with

$$\mathrm{Re}\lambda^{/}(\tau_{01}) = -0.001298881243 < 0, \mathrm{Re}\lambda^{/}(\tau_{02}) = -0.03994091271 \cdot 10^{-4} < 0.$$

In conclusion, because the transversality condition is not satisfied, in the case of 66 cell line, there is no critical value of the delay parameter τ for which the Hopf bifurcation appear.

3.2. *The case of 67 cell line*

Considering the following values of the parameters $a = 0.55$, $h = 1$, $k = 1$, $r = 0.515$, the programming techniques provide us the result described below.

Proposition 3.2.1. *a) The only equilibrium point acceptable from a biological point of view (hence given by non-negative dependent variables) of (3) is*

$$(x^*, y^*) = (0.493776651, 2.582480174).$$

b) The constitutive matrices of the linearized system (4) are

$$M_1 = \begin{pmatrix} -0.493776651 & -0.096791167 \\ 3.457295063 & -0.1463375574 \end{pmatrix}, M_2 = \begin{pmatrix} -0.8139847068 & 0 \\ 0.8139847068 & 0 \end{pmatrix}.$$

c) The coefficients of the characteristic equation (6) are

$$a_1 = 0.6401142084, a_2 = 0.4068936928, a_3 = 0.8139847068, a_4 = 0.1979030635.$$

d) The system (7) has only one solution $(\omega_0, \tau_0) \in \mathbf{R}^* \times \mathbf{R}_+^*$*, namely*

$$\omega_0 = 0.9647909953, \tau_0 = 2.271154272,$$

with

$$\mathrm{Re}\lambda^{/}(\tau_0) = 0.1023641139 > 0,$$

hence the transversality condition is satisfied.

While τ passes through τ_0, the function $u(\tau)$ changes from negative to positive values. It follows that the critical value of τ for which Hopf bifurcation appears is exactly $\tau = \tau_0$.

Based on Maple computations one can derive the following result:

Proposition 3.2.2. *For $\tau = \tau_0$ the equation (6) has two imaginary conjugate roots $\lambda = \pm i\omega$, at least two roots with negative real part and no root with positive real part.*

3.3. *The case of 68H cell line*

In this case, the values of the parameters are $a = 0.31$, $h = 1$, $k = 1$, $r = 0.059 \cdot 10^{-2}$.

We can state the following result:

Proposition 3.3.1. *a) The only equilibrium point acceptable from a biological point of view (hence given by non-negative dependent variables) of (3) is*

$$(x^*, y^*) = (0.0002801120344, 2.432345306 \cdot 10^6).$$

b) The constitutive matrices of the linearized system (4) are

$$M_1 = \begin{pmatrix} 0.809 & -2.18 \cdot 10^{-11} \\ 5.107925335 \cdot 10^6 & 10^{-13} \end{pmatrix}, M_2 = \begin{pmatrix} -0.3816969526 & 0 \\ 0.3816969526 & 0 \end{pmatrix}.$$

c) The coefficients of the characteristic equation (6) are

$$a_1 = -0.809, a_2 = 0.0001113527722, a_3 = 0.3816969526, a_4 = 8.359163262 \cdot 10^{-12}.$$

d) The system (7) has no solutions $(\omega_0, \tau_0) \in \mathbf{R}^* \times \mathbf{R}^*$.

Consequently, in the case of 68 cell line, there is no critical value of the delay parameter τ for which the Hopf bifurcation appear.

4. **Conclusions**

As a consequence of the results above, in the case of 67 cell line, the cancer cell population time-delayed flow becomes subject to the following result, known as the Hopf bifurcation theorem

Theorem 1. *Let $X \in \mathcal{X}(\mathbf{R}^n \times \mathbf{R}) \ni (x, \tau)$, $n \geq 2$ be a $\mathcal{C}^\infty$ vector field, which differentiably depends on the parameter τ and obeys the property that the set $E : X(x, \tau) = 0$ contains the isolated point $x = x(\tau), \tau \in I \subset \mathbf{R}$. Consider in a neighborhood of the stationary point $x = x(\tau)$ the linear approximation $\frac{dx}{dt} = A(\tau)x$ of the system $\frac{dx}{dt} = X(x, \tau)$, where $A(\tau) = \left[\frac{\partial X_i}{\partial x_j}(x(\tau), \tau)\right]$. Denote by $\lambda_1(\tau), \ldots, \lambda_n(\tau)$ the eigenvalues of $A(\tau)$ and assume that*

$$\lambda_1(\tau) = u(\tau) + i\omega(\tau), \quad \lambda_2(\tau) = u(\tau) - i\omega(\tau) = \bar{\lambda}_1(\tau).$$

For $n > 2$, additionally assume that $Re(\lambda_k(\tau)) < 0, k = 3, \ldots n$ and that exists an isolated value $\tau_0 \in I$ such that $u(\tau_0) = 0, \omega(\tau_0) \neq 0$ and $\frac{du}{d\tau} > 0$. Under these hypotheses, one of the following assertions holds true:

a) The stationary point $x = x(\tau_0)$ is a center; for $\tau \neq \tau_0$ neighbor to τ_0, there exists no periodic orbit around $x(\tau)$;

b) There exists a number $b > \tau_0$ s.t. for each $\tau \in (\tau_0, b)$ there exists an unique induced orbit around the stationary point $x(\tau)$ in a neighborhood of this point. This 1-parameter family of closed orbits split at the stationary point $x(\tau_0)$, i.e., for $\tau \to \tau_0$, the diameter of the closed orbit varies with $|\tau - \tau_0|^{1/2}$. In this case, for $\tau \leq \tau_0$, $\tau \in I$, there exist no closed orbit neighbor to $x(\tau)$.

c) There exists a number $a < \tau_0$ s.t. for each $\tau \in (a, \tau_0)$ there exists an unique closed orbit around the stationary point $x(\tau_0)$ in one of its neighborhoods. This 1-parameter family of closed orbits split at the stationary point $x(\tau_0)$, i.e., for $\tau \to \tau_0$, the diameter of the closed orbit varies with $|\tau - \tau_0|^{1/2}$. In this case, for $\tau \geq \tau_0$, $\tau \in I$, there exist no closed orbit neighbor to $x(\tau)$.

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