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Leukemia mathematical model

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Abstract. In this paper, we study a mathematical model of leukemia diseases. We find sufficient conditions for existence and local stability of steady states.

1. Introduction

Hematopoietic stem cells are found in the bone marrow and are able to renew themselves through cell division producing blood cells, a significant increase in the number of white blood cells disease causes chronic myeloid leukemia which is characterized by a chromosomal anomaly acquired, that is the translocation between chromosome 9 and 22 giving birth to an abnormal chromosome called the Philadelphia chromosome, this translocation generates a protein from the merger of the Bcr gene on chromosome 22 and Abl genes on chromosome 9, this protein is a tyrosine kinase Bcr-Abl. Generally, tyrosine kinases are components that control cell proliferation, differentiation and apoptosis, they have a very important role in signal transduction because the tyrosine kinase can transfer a phosphate group from adenosine triphosphate to another protein in a cell but the tyrosine kinase Bcr-Abl instructs cells to grow out of control and prevents them from undergoing apoptosis, resulting in the formation of a tumor. Among the treatments can produce a significant chance of cure is IMATINIB [5] which is a competitive inhibitor of the tyrosine kinase activity because it will bind to quote binding of adenosine tri-phosphate prevents tyrosine to give these orders cancerous proliferation. The first mathematical models describing the dynamics of hematopoietic stem cells have been proposed by Mackey [3]. In recent works Adimy & Crauste [1], Dingli & Michor [2] and Michor *et al.* [4] have studied the dynamics of normal and cancer stem cells in chronic myeloid leukemia.

In our work we focus on the development of normal, cancerous and resistant hematopoietic stem cells in chronic myeloid leukemia. We study the existence of equilibrium points, their local stability and we give some numerical simulations.

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2. The model

We consider the following system

$$\begin{cases} x_0' = n\Phi(x_0+y_0+z_0)x_0 - d_0x_0 \\ x_1' = rx_0 - (d-d_2)x_1 \\ y_0' = m\Psi(x_0+\alpha y_0+\alpha z_0)y_0 - g_0y_0 \\ y_1' = qy_0 - \big(g-g_2+h_2(u)\big)y_1 \\ z_0' = m\Psi(x_0+\alpha y_0+\alpha z_0)z_0 - g_{0r}z_0 \\ z_1' = qz_0 - \big(d_r-d_{2r}+h_{2r}(u)\big)z_1 \end{cases} \tag{1}$$

with

$$\Phi(x_0+y_0+z_0) = \frac{1}{1+c_x(x_0+y_0+z_0)}, \quad \Psi(x_0+\alpha y_0+\alpha z_0) = \frac{1}{1+c_y(x_0+\alpha y_0+\alpha z_0)}$$

$$g_{0r} < g_0$$
$$h_2, h_{2r} : [0, u_{max}) \longrightarrow [0,1)$$
$$h_2 \nearrow, h_{2r} \nearrow, h_2(0) = 0 = h_{2r}(0)$$

where

The parameters	meaning
n	division rate of normal stem cells
d_0	death rate of normal stem cells
r	production rate of normal differentiated cells
d	death rate of normal Differentiated cells
d_2	proliferation rate of normal differentiated cells
m	division rate of cancerous stem cells
α	competitif coefficient
g_0	death rate of sensitive cancerous stem cells
q	production rate of cancerous differentiated cells
g	death rate of sensitive cancerous differentiated cells
g_2	proliferation rate of sensitive cancerous differentiated cells
$h_2(u)$	IMATINIB effect on sensitive cancerous differentiated cells
g_{0r}	death rates of resistant cancerous stem cells
d_r	death rate of resistant cancerous differentiated cells
d_{2r}	proliferation rate of resistant cancerous differentiated cells
$h_{2r}(u)$	IMATINIB effect on resistant cancerous differentiated cells
u	drug dose administered

Table of parameters

and

The variables	meaning
x_0	number of normal hematopoietic stem cells
y_0	number of sensitive cancerous hematopoietic stem cells
z_0	number of resistant cancerous hematopoietic stem cells
x_1	number of normal differentiated cells
y_1	number of sensitive cancerous differentiated cells
z_1	number of resistant cancerous differentiated cells

Table of variables

3. Existence and stability of equilibrium

In this section, we analyze the existence and local stability of feasible equilibrium of (1).

3.1 Existence of equilibrium

The equilibrium points of (1) are

$$\mathbb{E}_0 = (0,0,0,0,0,0),$$

$$\mathbb{E}_1 = (x_0^1, x_1^1, 0,0,0,0) \text{ where } x_0^1 = \frac{1}{c_x}\left(\frac{n}{d_0} - 1\right) \text{ and } x_1^1 = \frac{r}{(d-d_2)}\left[\frac{1}{c_x}\left(\frac{n}{d_0} - 1\right)\right],$$

$$\mathbb{E}_2 = (x_0^2, x_1^2, y_0^2, y_1^2, 0, 0) \text{ where } x_0^2 = \frac{1}{(1-\alpha)}\left[\frac{1}{c_y}\left(\frac{m}{g_0} - 1\right) - \frac{\alpha}{c_x}\left(\frac{n}{d_0} - 1\right)\right],$$

$$x_1^2 = \frac{r}{(d-d_2)(1-\alpha)}\left[\frac{1}{c_y}\left(\frac{m}{g_0} - 1\right) - \frac{\alpha}{c_x}\left(\frac{n}{d_0} - 1\right)\right],\ y_0^2 = \frac{1}{(1-\alpha)}\left[\frac{1}{c_x}\left(\frac{n}{d_0} - 1\right) - \frac{1}{c_y}\left(\frac{m}{g_0} - 1\right)\right] \text{ and}$$

$$y_1^2 = \frac{q}{(g-g_2+h_2(u))(1-\alpha)}\left[\frac{1}{c_x}\left(\frac{n}{d_0} - 1\right) - \frac{1}{c_y}\left(\frac{m}{g_0} - 1\right)\right],$$

$$\mathbb{E}_3 = (x_0^3, x_1^3, 0, 0, y_0^3, y_1^3) \text{ where } x_0^3 = \frac{1}{(1-\alpha)}\left[\frac{1}{c_y}\left(\frac{m}{g_{0r}} - 1\right) - \frac{\alpha}{c_x}\left(\frac{n}{d_0} - 1\right)\right],$$

$$x_1^3 = \frac{r}{(d-d_2)(1-\alpha)}\left[\frac{1}{c_y}\left(\frac{m}{g_{0r}} - 1\right) - \frac{\alpha}{c_x}\left(\frac{n}{d_0} - 1\right)\right],\ z_0^3 = \frac{1}{(1-\alpha)}\left[\frac{1}{c_x}\left(\frac{n}{d_0} - 1\right) - \frac{1}{c_y}\left(\frac{m}{g_{0r}} - 1\right)\right] \text{ and}$$

$$z_1^3 = \frac{q}{(d_r-d_{2r}+h_{2r}(u))(1-\alpha)}\left[\frac{1}{c_x}\left(\frac{n}{d_0} - 1\right) - \frac{1}{c_y}\left(\frac{m}{g_{0r}} - 1\right)\right],$$

$$\mathbb{E}_4 = (0,0,y_0^4, y_1^4, 0, 0) \text{ where } y_0^4 = \frac{1}{\alpha c_y}\left(\frac{m}{g_0} - 1\right) \text{ and } y_1^4 = \frac{q}{g-g_2+h_2(u)}\left[\frac{1}{\alpha c_y}\left(\frac{m}{g_0} - 1\right)\right],$$

$$\mathbb{E}_5 = (0,0,0,0,z_0^5, z_1^5) \text{ where } z_0^5 = \frac{1}{\alpha c_y}\left(\frac{m}{g_{0r}} - 1\right) \text{ and } z_1^5 = \frac{q}{d_r-d_{2r}+h_{2r}(u)}\left[\frac{1}{\alpha c_y}\left(\frac{m}{g_{0r}} - 1\right)\right].$$

Theorem 3.1: *The system (1) admits feasible equilibrium points according to the following conditions.*

1. *The trivial point $\mathbb{E}_0$ exists always.*
2. *If $d_0 < n$ and $d_2 < d$ the equilibrium point $\mathbb{E}_1$ exists.*
3. *If $d_2 < d$, $g_2 < g + h_2(u)$, $g_0 < m$ and $\dfrac{\alpha c_y g_0 n}{\alpha c_y g_0 + c_x(m-g_0)} < d_0 < \dfrac{c_y g_0 n}{c_y g_0 + c_x(m-g_0)}$ the equilibrium point $\mathbb{E}_2$ exists.*
4. *If $d_2 < d$, $d_{2r} < d_r + h_{2r}(u)$, $g_{0r} < m$ and $\dfrac{\alpha c_y g_{0r} n}{\alpha c_y g_{0r} + c_x(m-g_{0r})} < d_0 < \dfrac{c_y g_{0r} n}{c_y g_{0r} + c_x(m-g_{0r})}$ the equilibrium point $\mathbb{E}_3$ exists.*
5. *If $g_0 < m$ and $g_2 < g + h_2(u)$ the equilibrium point $\mathbb{E}_4$ exists.*
6. *If $g_{0r} < m$ and $d_{2r} < d_r + h_{2r}(u)$ the equilibrium point $\mathbb{E}_5$ exists.*

3.2 Local stability of equilibrium

The general form of the Jacobian with respect to each equilibrium point is given by Local Stability of equilibrium points

$$\mathcal{J}_{\mathbb{E}_i} = \begin{pmatrix} n\Phi - d_0 + n\,x_0^i\dfrac{d\Phi}{dx_0^i} & 0 & nx_0^i\dfrac{d\Phi}{dy_0^i} & 0 & nx_0^i\dfrac{d\Phi}{dz_0^i} & 0 \\ r & d_2 - d & 0 & 0 & 0 & 0 \\ my_0^i\frac{d\Psi}{dx_0^i} & 0 & m\Psi - g_0 + my_0^i\dfrac{d\Psi}{dy_0^i} & 0 & my_0^i\dfrac{d\Psi}{dz_0^i} & 0 \\ 0 & 0 & q & g_2 - g - h_2(u) & 0 & 0 \\ mz_0^i\dfrac{d\Psi}{dx_0^i} & 0 & mz_0^i\dfrac{d\Psi}{dy_0^i} & 0 & m\Psi - g_{0r} + mz_0^i\dfrac{d\Psi}{dz_0^i} & 0 \\ 0 & 0 & 0 & 0 & q & d_{2r} - d_r - h_{2r}(u) \end{pmatrix}.$$

We have

$$\det\,(\mathcal{J}_{\mathbb{E}_i} - \lambda\mathrm{I}) = \Big(d_{2r} - d_r - h_{2r}(u) - \lambda\Big)\Big(g_2 - g - h_2(u) - \lambda\Big)\Big(d_2 - d - \lambda\Big)\det C_i$$

where

$$C_i = \begin{pmatrix} n\Phi - d_0 + n\,x_0^i\dfrac{d\Phi}{dx_0^i} - \lambda & nx_0^i\dfrac{d\Phi}{dy_0^i} & nx_0^i\dfrac{d\Phi}{dz_0^i} \\ my_0^i\dfrac{d\Psi}{dx_0^i} & m\Psi - g_0 + my_0^i\dfrac{d\Psi}{dy_0^i} - \lambda & my_0^i\dfrac{d\Psi}{dz_0^i} \\ mz_0^i\dfrac{d\Psi}{dx_0^i} & mz_0^i\dfrac{d\Psi}{dy_0^i} & m\Psi - g_{0r} + mz_0^i\dfrac{d\Psi}{dz_0^i} - \lambda \end{pmatrix}.$$

Theorem 3.2:

1. *The equilibrium point $\mathbb{E}_0$ is asymptotically stable if $d_{2r} < d_r + h_{2r}(u)$, $g_2 < g + h_2(u)$, $d_2 < d$, $n < d_0$ and $m < g_{0r}$.*
2. *The equilibrium point $\mathbb{E}_1$ is asymptotically stable if $d_{2r} < d_r + h_{2r}(u)$, $g_2 < g + h_2(u)$, $d_2 < d$, $d_0 < n$ and $\frac{mc_x d_0}{c_x d_0 + c_y(n-d_0)} < g_{0r}$.*
3. *The equilibrium point $\mathbb{E}_2$ is unstable.*
4. *The equilibrium point $\mathbb{E}_3$ is unstable.*
5. *The equilibrium point $\mathbb{E}_4$ is unstable.*
6. *The equilibrium point $\mathbb{E}_5$ is asymptotically stable if $d_{2r} < d_r + h_{2r}(u)$, $g_2 < g + h_2(u)$, $d_2 < d$, $g_{0r} < m$ and $\frac{n\alpha c_y g_{0r}}{\alpha c_y g_0 + c_x(m - g_{0r})} < d_0$.*

Proof:

1. For the equilibrium point $\mathbb{E}_0$ we have

$$\mathcal{J}_{\mathbb{E}_0} = \begin{pmatrix} n - d_0 & 0 & 0 & 0 & 0 & 0 \\ r & d_2 - d & 0 & 0 & 0 & 0 \\ 0 & 0 & m - g_0 & 0 & 0 & 0 \\ 0 & 0 & q & g_2 - g - h_2(u) & 0 & 0 \\ 0 & 0 & 0 & 0 & m - g_{0r} & 0 \\ 0 & 0 & 0 & 0 & q & d_{2r} - d_r - h_{2r}(u) \end{pmatrix}$$

and

$$\det\,(\mathcal{J}_{\mathbb{E}_0} - \lambda\mathrm{I}) = \Big(d_{2r} - d_r - h_{2r}(u) - \lambda\Big)\Big(g_2 - g - h_2(u) - \lambda\Big)\Big(d_2 - d - \lambda\Big)\det C_0$$

where

$$C_0 = \begin{pmatrix} n - d_0 - \lambda & 0 & 0 \\ 0 & m - g_0 - \lambda & 0 \\ 0 & 0 & m - g_{0r} - \lambda \end{pmatrix}.$$

We have

$$\det\,(\mathcal{J}_{\mathbb{E}_0} - \lambda \mathrm{I}) = \Big(d_{2r} - d_r - h_{2r}(u) - \lambda\Big)\Big(g_2 - g - h_2(u) - \lambda\Big)\Big(d_2 - d - \lambda\Big)$$
$$\Big(n - d_0 - \lambda\Big)\Big(m - g_0 - \lambda\Big)\Big(m - g_{0r} - \lambda\Big).$$

Then, the eigenvalues are $\lambda_1 = d_{2r} - d_r - h_{2r}(u)$, $\lambda_2 = g_2 - g - h_2(u)$, $\lambda_3 = d_2 - d$, $\lambda_4 = n - d_0$, $\lambda_5 = m - g_0$ and $\lambda_6 = m - g_{0r}$.

2. For the equilibrium point $\mathbb{E}_1$ we have

$$\mathcal{J}_{\mathbb{E}_1} = \begin{pmatrix} d_0\Big(\frac{d_0}{n} - 1\Big) & 0 & d_0\Big(\frac{d_0}{n} - 1\Big) & 0 & d_0\Big(\frac{d_0}{n} - 1\Big) & 0 \\ r & d_2 - d & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{m c_x d_0}{c_x d_0 + c_y(n - d_0)} - g_0 & 0 & 0 & 0 \\ 0 & 0 & q & g_2 - g - h_2(u) & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{m c_x d_0}{c_x d_0 + c_y(n - d_0)} - g_{0r} & 0 \\ 0 & 0 & 0 & 0 & q & d_{2r} - d_r - h_{2r}(u) \end{pmatrix}$$

and

$$\det\,(\mathcal{J}_{\mathbb{E}_1} - \lambda \mathrm{I}) = \Big(d_{2r} - d_r - h_{2r}(u) - \lambda\Big)\Big(g_2 - g - h_2(u) - \lambda\Big)\Big(d_2 - d - \lambda\Big)\det C_1$$

where

$$C_1 = \begin{pmatrix} d_0\Big(\frac{n}{d_0} - 1\Big) - \lambda & d_0\Big(\frac{n}{d_0} - 1\Big) - \lambda & d_0\Big(\frac{n}{d_0} - 1\Big) - \lambda \\ 0 & \frac{m c_x d_0}{c_x d_0 + c_y(n - d_0)} - g_0 - \lambda & 0 \\ 0 & 0 & \frac{m c_x d_0}{c_x d_0 + c_y(n - d_0)} - g_{0r} - \lambda \end{pmatrix}.$$

We have

$$\det\,(\mathcal{J}_{\mathbb{E}_1} - \lambda \mathrm{I}) = \Big(d_{2r} - d_r - h_{2r}(u) - \lambda\Big)\Big(g_2 - g - h_2(u) - \lambda\Big)\Big(d_2 - d - \lambda\Big)$$
$$\times\Big(\frac{m c_x d_0}{c_x d_0 + c_y(n - d_0)} - g_0 - \lambda\Big)\Big(\frac{m c_x d_0}{c_x d_0 + c_y(n - d_0)} - g_{0r} - \lambda\Big)$$
$$\times\Big(d_0\Big(\frac{n}{d_0} - 1\Big) - \lambda\Big).$$

Then, the eigenvalues are $\lambda_1 = d_{2r} - d_r - h_{2r}(u)$, $\lambda_2 = g_2 - g - h_2(u)$, $\lambda_3 = d_2 - d$, $\lambda_4 = \dfrac{m c_x d_0}{c_x d_0 + c_y(n - d_0)} - g_0$, $\lambda_5 = \dfrac{m c_x d_0}{c_x d_0 + c_y(n - d_0)} - g_{0r}$ and $\lambda_6 = d_0\Big(\dfrac{n}{d_0} - 1\Big)$.

3. For the equilibrium point $\mathbb{E}_2$ we have

$$\mathcal{J}_{\mathbb{E}_2} = \begin{pmatrix} a_{11} & 0 & a_{13} & 0 & a_{15} & 0 \\ r & d_2 - d & 0 & 0 & 0 & 0 \\ a_{13} & 0 & a_{33} & 0 & a_{35} & 0 \\ 0 & 0 & q & g_2 - g - h_2(u) & 0 & 0 \\ 0 & 0 & 0 & 0 & g_0 - g_{0r} & 0 \\ 0 & 0 & 0 & 0 & q & d_{2r} - d_r - h_{2r}(u) \end{pmatrix}$$

such that

$$a_{11} = \frac{d_0^2}{(1-\alpha)nc_y}\left[\alpha c_y\left(\frac{n}{d_0}-1\right) - c_x\left(\frac{m}{g_0}-1\right)\right],$$

$$a_{13} = \frac{d_0^2}{(1-\alpha)nc_y}\left[\alpha c_y\left(\frac{n}{d_0}-1\right) - c_x\left(\frac{m}{g_0}-1\right)\right],$$

$$a_{15} = \frac{\alpha d_0^2}{(1-\alpha)n}\left(\frac{n}{d_0}-1\right) - \frac{d_0^2 c_x}{(1-\alpha)nc_y}\left(\frac{m}{g_0}-1\right),$$

$$a_{31} = \frac{g_0^2}{(1-\alpha)mc_x}\left[c_x\left(\frac{m}{g_0}-1\right) - c_y\left(\frac{n}{d_0}-1\right)\right],$$

$$a_{33} = \frac{\alpha g_0^2}{(1-\alpha)mc_x}\left[c_x\left(\frac{m}{g_0}-1\right) - c_y\left(\frac{n}{d_0}-1\right)\right],$$

$$a_{35} = \frac{\alpha g_0^2}{(1-\alpha)mc_x}\left[c_x\left(\frac{m}{g_0}-1\right) - c_y\left(\frac{n}{d_0}-1\right)\right],$$

$$a_{55} = g_0 - g_{0r},$$

$$\det\left(\mathcal{J}_{\mathbb{E}_2} - \lambda \mathrm{I}\right) = \left(d_{2r} - d_r - h_{2r}(u) - \lambda\right)\left(g_2 - g - h_2(u) - \lambda\right)\left(d_2 - d - \lambda\right)\det C_2$$

and

$$\det C_2 = (a_{55} - \lambda)[\lambda^2 - (a_{11} + a_{33})\lambda + a_{11}a_{33} - a_{13}a_{31}].$$

We note that a_{55} is a positive eigenvalue, then $\mathbb{E}_2$ is unstable.

4. For the equilibrium point $\mathbb{E}_3$ we have

$$\mathcal{J}_{\mathbb{E}_3} = \begin{pmatrix} a_{11} & 0 & a_{13} & 0 & a_{15} & 0 \\ r & d_2 - d & 0 & 0 & 0 & 0 \\ 0 & 0 & a_{33} & 0 & 0 & 0 \\ 0 & 0 & q & g_2 - g - h_2(u) & 0 & 0 \\ a_{51} & 0 & a_{53} & 0 & a_{55} & 0 \\ 0 & 0 & 0 & 0 & q & d_{2r} - d_r - h_{2r}(u) \end{pmatrix}$$

such that

$$a_{11} = \frac{d_0^2}{(1-\alpha)nc_y}\left[\alpha c_y\left(\frac{n}{d_0}-1\right) - c_x\left(\frac{m}{g_{0r}}-1\right)\right],$$

$$a_{13} = \frac{d_0^2}{(1-\alpha)nc_y}\left[\alpha c_y\left(\frac{n}{d_0}-1\right) - c_x\left(\frac{m}{g_{0r}}-1\right)\right],$$

$$a_{15} = \frac{d_0^2}{(1-\alpha)nc_y}\left[\alpha c_y\left(\frac{n}{d_0}-1\right) - c_x\left(\frac{m}{g_{0r}}-1\right)\right],$$

$$a_{33} = g_{0r} - g_0,$$

$$a_{51} = \frac{g_{0r}^2}{(1-\alpha)mc_x}\left[c_x\left(\frac{m}{g_{0r}}-1\right) - c_y\left(\frac{n}{d_0}-1\right)\right],$$

$$a_{53} = \frac{\alpha g_{0r}^2}{(1-\alpha)mc_x}\left[c_x\left(\frac{m}{g_{0r}}-1\right) - c_y\left(\frac{n}{d_0}-1\right)\right],$$

$$a_{55} = \frac{\alpha g_{0r}^2}{(1-\alpha)mc_x}\left[c_x\left(\frac{m}{g_{0r}}-1\right) - c_y\left(\frac{n}{d_0}-1\right)\right],$$

$$\det\left(\mathcal{J}_{\mathbb{E}_3} - \lambda \mathrm{I}\right) = \left(d_{2r} - d_r - h_{2r}(u) - \lambda\right)\left(g_2 - g - h_2(u) - \lambda\right)\left(d_2 - d - \lambda\right)\det C_3$$

and

$$\det C_3 = (a_{33} - \lambda)[\lambda^2 - (a_{11} + a_{55})\lambda + a_{11}a_{55} - a_{15}a_{51}].$$

According to the conditions of existence of the equilibrium point $\mathbb{E}_3$ we can prove that one of eigenvalues is positive that is $\mathbb{E}_3$ is unstable.

5. For the equilibrium point $\mathbb{E}_4$ we have

$$\mathcal{J}_{\mathbb{E}_4} = \begin{pmatrix} \dfrac{n\alpha c_y g_0}{\alpha c_y g_0 + c_x(m-g_0)} - d_0 & 0 & 0 & 0 & 0 & 0 \\ r & d_2 - d & 0 & 0 & 0 & 0 \\ \dfrac{g_0}{\alpha}\left(\dfrac{g_0}{m}-1\right) & 0 & g_0\left(\dfrac{g_0}{m}-1\right) & 0 & g_0\left(\dfrac{g_0}{m}-1\right) & 0 \\ 0 & 0 & q & g_2 - g - h_2(u) & 0 & 0 \\ 0 & 0 & 0 & 0 & g_0 - g_{0r} & 0 \\ 0 & 0 & 0 & 0 & q & d_{2r} - d_r - h_{2r}(u) \end{pmatrix},$$

$$\det\left(\mathcal{J}_{\mathbb{E}_4} - \lambda \mathrm{I}\right) = \left(d_{2r} - d_r - h_{2r}(u) - \lambda\right)\left(g_2 - g - h_2(u) - \lambda\right)\left(d_2 - d - \lambda\right)\det C_4$$

and

$$C_4 = \begin{pmatrix} \dfrac{n\alpha c_y g_0}{\alpha c_y g_0 + c_x(m-g_0)} - d_0 - \lambda & 0 & 0 \\ \dfrac{g_0}{\alpha}\left(\dfrac{g_0}{m}-1\right) & g_0\left(\dfrac{g_0}{m}-1\right) - \lambda & g_0\left(\dfrac{g_0}{m}-1\right) \\ 0 & 0 & g_0 - g_{0r} - \lambda \end{pmatrix}.$$

We have

$$\det(\mathcal{J}_{\mathbb{E}_4}-\lambda I)=\Big(d_{2r}-d_r-h_{2r}(u)-\lambda\Big)\Big(g_2-g-h_2(u)-\lambda\Big)\Big(d_2-d-\lambda\Big)$$

$$\Big(\frac{n\alpha c_y g_0}{\alpha c_y g_0+c_x(m-g_0)}-d_0-\lambda\Big)\Big(g_0\Big(\frac{g_0}{m}-1\Big)-\lambda\Big)\Big(g_0-g_{0r}-\lambda\Big).$$

Note that $\lambda=g_0-g_{0r}$ is a positive eigenvalue which implies that $\mathbb{E}_4$ is unstable.

6. For the equilibrium point $\mathbb{E}_5$ we have

$$\mathcal{J}_{\mathbb{E}_5}=\begin{pmatrix} \frac{n\alpha c_y g_{0r}}{\alpha c_y g_{0r}+c_x(m-g_{0r})}-d_0 & 0 & 0 & 0 & 0 & 0\\ r & d_2-d & 0 & 0 & 0 & 0\\ 0 & 0 & g_{0r}-g_0 & 0 & 0 & 0\\ 0 & 0 & q & g_2-g-h_2(u) & 0 & 0\\ \frac{g_{0r}}{\alpha}\Big(\frac{g_{0r}}{m}-1\Big) & 0 & g_{0r}\Big(\frac{g_{0r}}{m}-1\Big) & 0 & g_{0r}\Big(\frac{g_{0r}}{m}-1\Big) & 0\\ 0 & 0 & 0 & 0 & q & d_{2r}-d_r-h_{2r}(u) \end{pmatrix},$$

$$\det(\mathcal{J}_{\mathbb{E}_5}-\lambda I)=\Big(d_{2r}-d_r-h_{2r}(u)-\lambda\Big)\Big(g_2-g-h_2(u)-\lambda\Big)\Big(d_2-d-\lambda\Big)\det C_5$$

and

$$C_5=\begin{pmatrix} \frac{n\alpha c_y g_{0r}}{\alpha c_y g_{0r}+c_x(m-g_{0r})}-d_0-\lambda & 0 & 0\\ 0 & g_{0r}-g_0-\lambda & 0\\ \frac{g_{0r}}{\alpha}\Big(\frac{g_{0r}}{m}-1\Big) & g_{0r}\Big(\frac{g_{0r}}{m}-1\Big) & g_{0r}\Big(\frac{g_{0r}}{m}-1\Big)-\lambda \end{pmatrix}.$$

We have

$$\det(\mathcal{J}_{\mathbb{E}_5}-\lambda I)=\Big(d_{2r}-d_r-h_{2r}(u)-\lambda\Big)\Big(g_2-g-h_2(u)-\lambda\Big)\Big(d_2-d-\lambda\Big)$$

$$\Big(\frac{n\alpha c_y g_{0r}}{\alpha c_y g_{0r}+c_x(m-g_{0r})}-d_0-\lambda\Big)\Big(g_{0r}-g_0-\lambda\Big)\Big(g_{0r}\Big(\frac{g_{0r}}{m}-1\Big)-\lambda\Big).$$

Then the eigenvalues are $\lambda_1=d_{2r}-d_r-h_{2r}(u)$, $\lambda_2=g_2-g-h_2(u)$, $\lambda_3=d_2-d$, $\lambda_4=\frac{n\alpha c_y g_{0r}}{\alpha c_y g_{0r}+c_x(m-g_{0r})}-d_0$, $\lambda_5=g_{0r}-g_0$ and $\lambda_6=g_{0r}\Big(\frac{g_{0r}}{m}-1\Big)$.

4. Numerical Simulation for the local stability

In this section, we give some numerical simulations for the points E_1 and E_5 to illustrate our results.

4.1 The equilibrium point E_1

The equilibrium E_1 corresponds to the situation where the cancer disappears, and it is important to obtain conditions of stability of E_1 in order to stop the onset of the diseases, in Figs. (1–6) we give numerical simulations for E_1.

Figures 1–6 correspond to the case where conditions of stability of E_1 are satisfied.

The parameters	values
n	50
m	20
α	0.1
q	1.065×10^7
d	9.4
d_0	20
d_2	0.4
d_r	1.4
d_{2r}	0.5
c_x	0.75×10^{-4}
c_y	0.38×10^{-4}
g	1.4
g_0	25
g_{0r}	20
g_2	0.8
h_2	0.7
h_{2r}	0.3
r	1.065×10^7

With the starting point $(20000.01, (2.3667 \times 10^{10}) + 0.01, 0.01, 0.01, 0.01, 0.01)$.

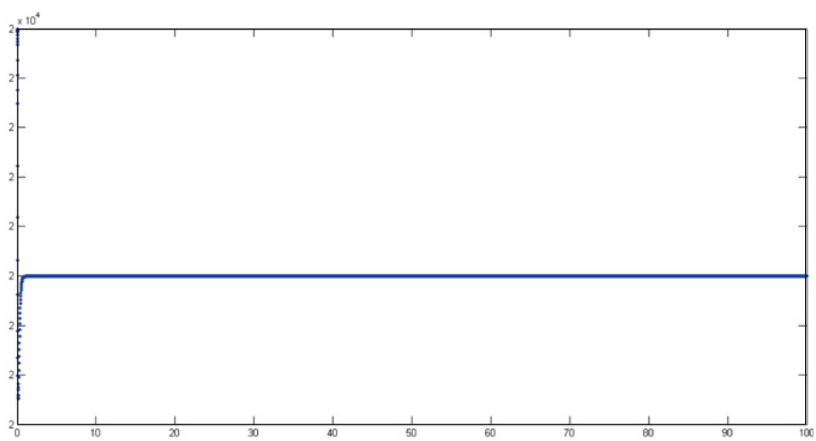

Figure 1. Behavior of normal stem cells x_0.

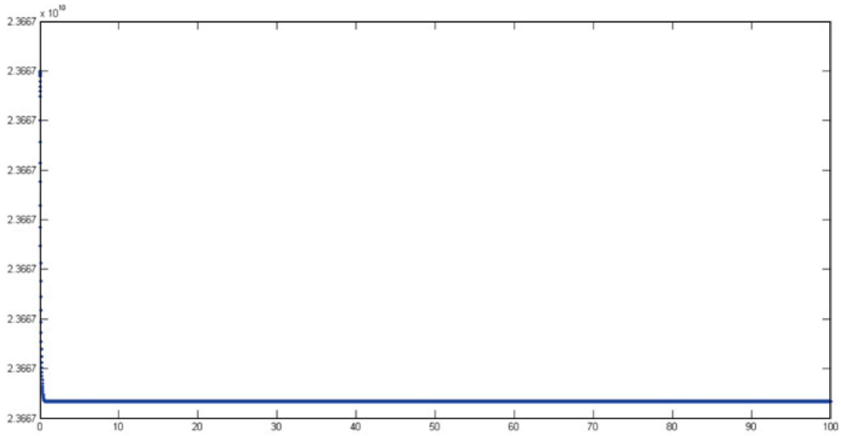

Figure 2. Behavior of normal differentiated cells x_1.

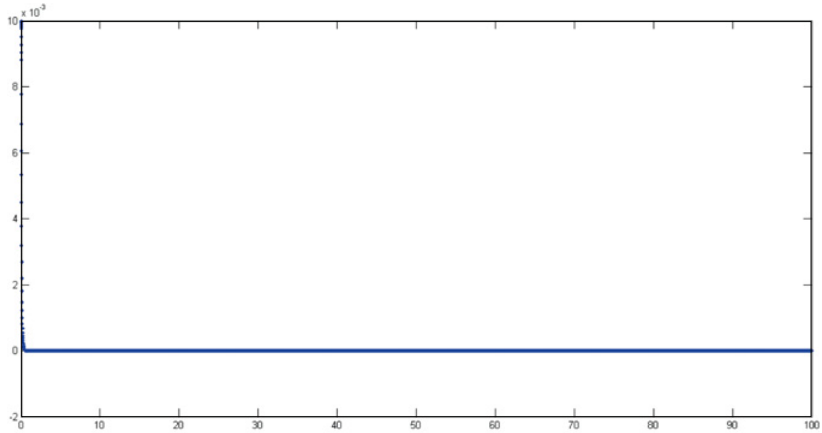

Figure 3. Behavior of sensitive cancerous stem cells y_0.

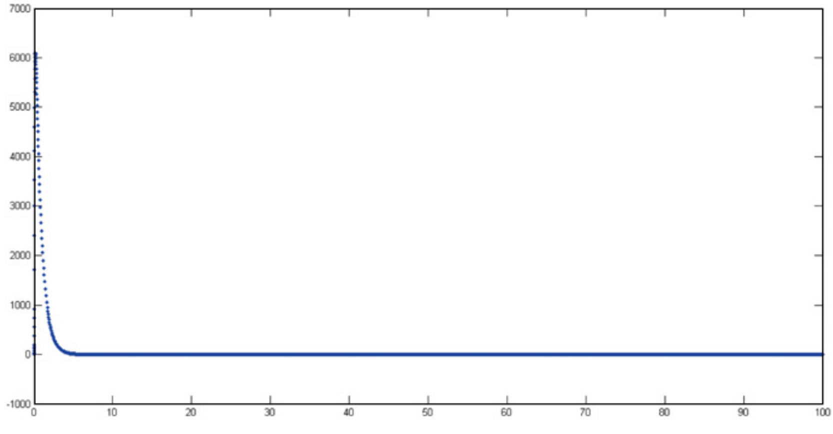

Figure 4. Behavior of sensitive cancerous differentiated cells y_1.

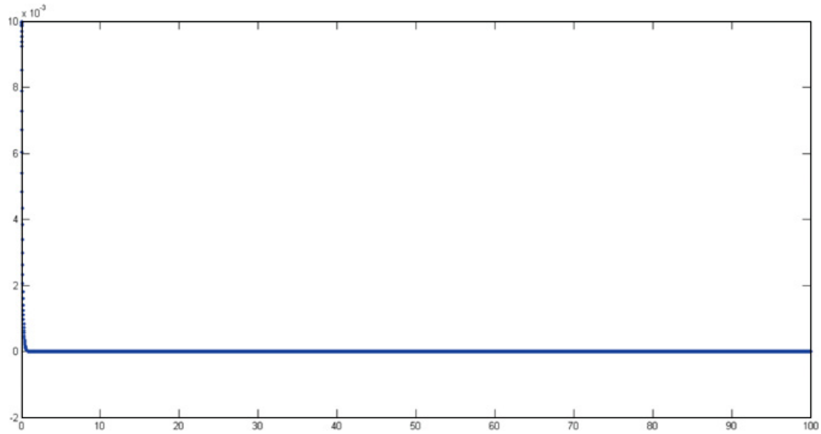

Figure 5. Behavior of resistant cancerous stem cells z_0.

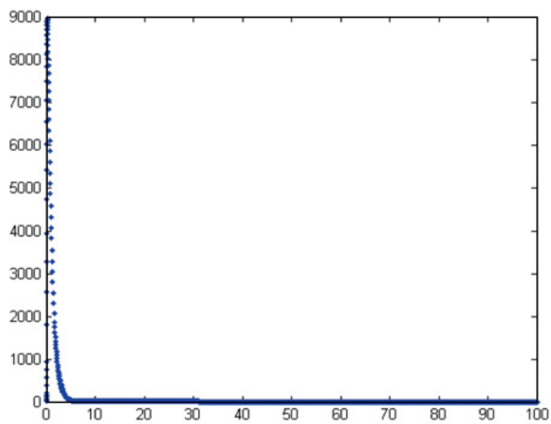

Figure 6. Behavior of resistant cancerous differentiated cells z_1.

4.2 The equilibrium point E_5

The equilibrium point E_5 corresponds to limit situation where normal and sensitive cancerous cells are eliminated and all remaining cells are resistant cancerous cells. (see Figs. 7–9).

The parameters	values
n	50
m	45
α	0.1
q	1.065×10^7
d	9.4
d_0	60
d_2	0.4
d_r	1.4
d_{2r}	0.5
c_x	0.75×10^{-4}
c_y	0.38×10^{-4}
g	1.4
g_0	46
g_{0r}	40
g_2	0.8
h_2	0.7
h_{2r}	0.3
r	1.065×10^7

With the starting point (0.0001, 0.0001, 0.0001, 0.0001, 0.0001475, 421.5626).

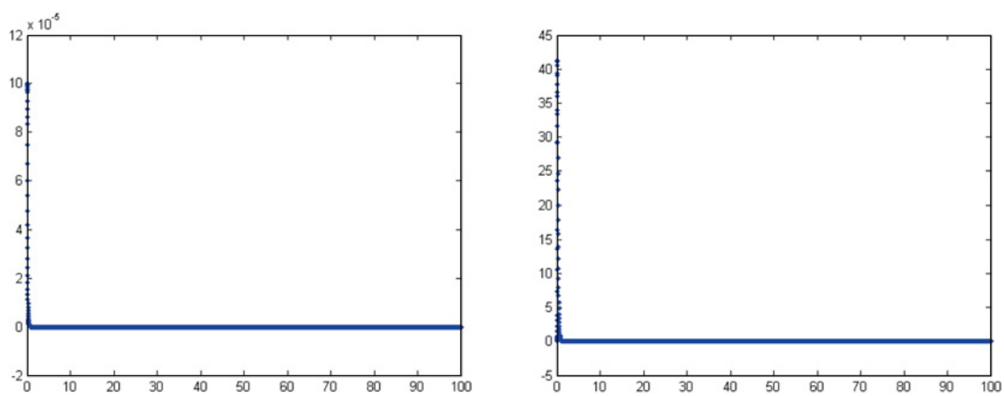

Figure 7. Behavior of normal stem and differentiated cells x_0 and x_1.

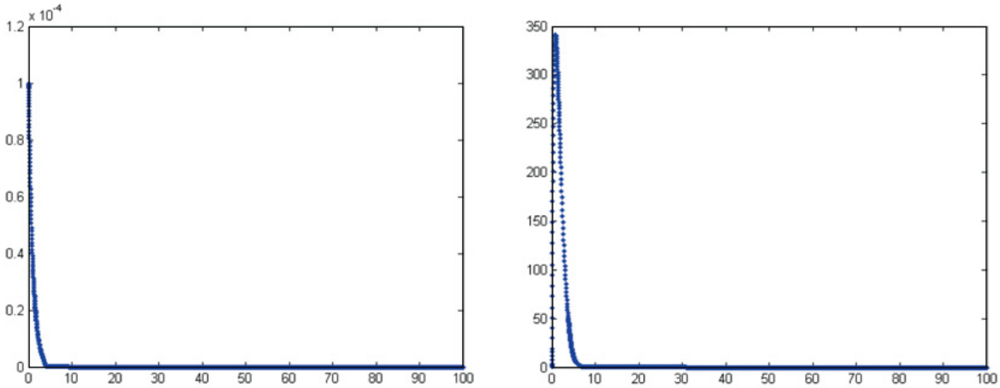

Figure 8. Behavior of sensitive cancerous stem and differentiated cells y_0 and y_1.

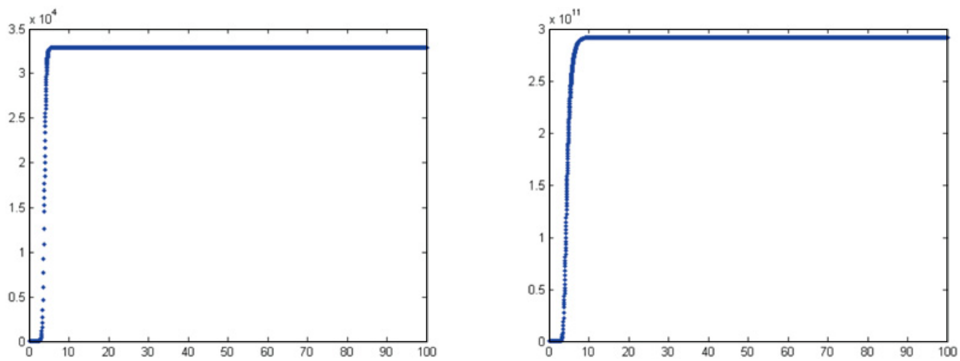

Figure 9. Behavior of resistant cancerous stem and differentiated cells z_0 and z_1.

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