Nonlinear Dynamics and Systems Theory, **13** (1) (2013) 79–92

Asymptotic Stability for a Model of Cell Dynamics after Allogeneic Bone Marrow Transplantation

R. Precup *, M-A. Şerban and D. Trif

Department of Mathematics, Babeş–Bolyai University, 400084 Cluj-Napoca, Romania

Received: March 13, 2012; Revised: January 18, 2013

Abstract: The paper presents stability analysis of steady-states of a dynamic system modeling cell evolution after stem cell transplantation. The border of the basins of attraction of the stable equilibria is found providing the theoretical basis for post-transplant correction therapies.

Keywords: *stability; dynamical system; numerical simulation; mathematical modeling.*

Mathematics Subject Classification (2010): 37C75, 37N25, 34D23.

1 Introduction

In [1] a mathematical model essentially owed to Dingli and Michor [2] was used in order to characterize normal and leukemic states and to explain basic pathways through which the robustness of the hematopoietic system can fail leading to leukemia.

Assume that at each time t, the cell population divides into two: the normal population $x(t)$ and the leukemic population $y(t)$. By x_0, y_0 we denote the normal and leukemic populations at a fixed moment of time $t = 0$. Denote by a, b, c and A, B, C (model parameters) the intrinsic (i.e., in the absence of any constraints) growth, microenvironment sensitivity and death rates of normal and leukemic cells, respectively. The conservation laws for normal and leukemic cells can be expressed as a system of two differential equations:

$$\begin{cases} x' = \frac{a}{1+b(x+y)}x - cx, \\ y' = \frac{A}{1+B(x+y)}y - Cy. \end{cases} \tag{1}$$

* Corresponding author: mailto:r.precup@math.ubbcluj.ro

Here the term $\frac{a}{1+b(x(t)+y(t))}x(t)$ represents the new normal cell population at time t, and $cx(t)$ are the removed normal cells at time t. Similar interpretations hold for y. The terms $\frac{1}{1+b(x+y)}$ and $\frac{1}{1+B(x+y)}$ simulate the crowding effect in the bone marrow microenvironment and introduce competition between normal and leukemic cells. The cell proliferation is faster while the total cell population $x+y$ is small, and slower for large $x+y$. Thus these terms simulate the feedback of the proliferation system. We assume that for both cell populations, the intrinsic growth rate is greater than the death rate, i.e., $a>c$ and $A>C$. Denote

$$d := \frac{1}{b}\left(\frac{a}{c}-1\right) \quad \text{and} \quad D := \frac{1}{B}\left(\frac{A}{C}-1\right).$$

Then the *steady-states* or *equilibria* of system (1) are:

$$(0,0)\,; \;\; (d,0)\,; \;\; (0,D)$$

if $d \neq D$, and

$$(0,0)\,; \;\; (\alpha, d-\alpha) \;\; \text{for} \;\; 0 \leq \alpha \leq d$$

when $d = D$.

The stability analysis in [1] shows that the zero solution $(0,0)$ is always unstable and if $d > D$, then $(d,0)$ is the unique asymptotically stable equilibrium and the normal cell population $x(t)$ approaches the equilibrium abundance d (normal homeostatic level) while the leukemic cell population $y(t)$ tends to zero; if $d < D$, then $(0,D)$ is the unique asymptotically stable equilibrium and the leukemic cell population becomes dominant approaching to its equilibrium abundance D (leukemic homeostatic level) and leads in the limit to the elimination of the normal cells, that is $x(t)$ tends to zero. These happen no matter the initial concentrations $x_0 > 0$, $y_0 > 0$ are. Thus we may say that the normal hematopoietic state is characterized by the inequality $d > D$, the leukemic hematopoietic state corresponds to the inequality $d < D$ and that equality $d = D$ characterizes the transitory state between normal and leukemic states.

The basic idea of the stem cell transplantation (see [5, 7]) consists in adding, say at time $t = 0$, in competition with x_0, y_0 (host cells) a new population (donor cells) z_0. If the aggressiveness of z against x, y (graft-versus-host and graft-versus-leukemia) compensates that of the x and y against z (anti-graft effect), and if the initial concentrations x_0, y_0 are smaller enough as compared with z_0, then, in time, host cells are eliminated and completely replaced by donor cells guaranteeing the elimination of cancer.

Mathematically, this means that a new equation in z is added to the previous system in x and y which is itself modified in order to incorporate the new competition (mutual "aggressiveness") between z, on one side, and x and y, on the other. Assuming that intrinsic growth, sensitivity and death rates of the donor cell population are those of the normal host cell population (human invariant kinetic parameters), namely a, b, c, in [5] it was proposed the following model for the cellular dynamics after bone marrow transplantation:

$$\begin{cases} x' = \frac{a}{1+b(x+y+z)}\frac{x+y+\varepsilon}{x+y+\varepsilon+gz}x - cx, \\ \\ y' = \frac{A}{1+B(x+y+z)}\frac{x+y+\varepsilon}{x+y+\varepsilon+Gz}y - Cy, \\ \\ z' = \frac{a}{1+b(x+y+z)}\frac{z+\varepsilon}{z+\varepsilon+h(x+y)}z - cz. \end{cases} \tag{2}$$

Here the growth inhibitory factors

$$\frac{1}{1+g\frac{z}{x+y+\varepsilon}}, \qquad \frac{1}{1+G\frac{z}{x+y+\varepsilon}}, \qquad \frac{1}{1+h\frac{x+y}{z+\varepsilon}}$$

take into account the cell-cell interactions, quantitatively by ratios $\frac{z}{x+y+\varepsilon}$ and $\frac{x+y}{z+\varepsilon}$, and qualitatively by parameters h, g, G standing for the intensity of anti-graft, anti-host and anti-leukemia effects, respectively. Constant $\varepsilon > 0$ is taken in order to avoid singularity.

Numerical simulations performed in [5] for the leukemic case $d < D$ have proved that the evolution can ultimately lead either to the normal homeostatic equilibrium $(0, 0, d)$ achieved by the expansion of the donor cells and the elimination of the host cells, or to the leukemic homeostatic equilibrium $(0, D, 0)$ characterized by the proliferation of the cancer line and the suppression of the other cell lines. One state or the other is reached depending on cell-cell interactions (anti-host, anti-leukemia and anti-graft effects) and initial cell concentrations at transplantation.

The aim of this paper is to provide a rigorous mathematical base for the conclusions obtained in [5] by simulations. Thus in the present paper we find the equilibria of the system (2), we study their stability and we find the boundary of the attraction basins of the stable equilibria. This boundary allows us to calculate an initial cell concentration (x_0, y_0, z_0) in the attraction basin of the normal homeostatic equilibrium $(0, 0, d)$. Section 2 contains an analysis of the proposed system concerning its dynamics, Section 3 shows some numerical simulations with physiological parameters and in Section 4 a brief summary is given.

2 Equilibria of the Augmented System

Let us consider the system (2) with $\varepsilon \to 0$,

$$\begin{cases} x' = \left(\dfrac{a}{1+b(x+y+z)}\dfrac{x+y}{x+y+gz} - c\right)x \equiv U(x,y,z), \\[2ex] y' = \left(\dfrac{A}{1+B(x+y+z)}\dfrac{x+y}{x+y+Gz} - C\right)y \equiv V(x,y,z), \\[2ex] z' = \left(\dfrac{a}{1+b(x+y+z)}\dfrac{z}{z+h\,(x+y)} - c\right)z \equiv W(x,y,z), \end{cases} \tag{1}$$

where $a, b, c, A, B, C, g, G, h$ are positive parameters and $x \geq 0,\ y \geq 0,\ z \geq 0$ are such that $x + y + z > 0$. The main assumptions on the parameters are

$$a > c, \quad A > C, \quad d < D.$$

a) At the origin $O(0, 0, 0)$ we have

$$\lim_{(x,y,z)\to(0,0,0)} U(x,y,z) = \lim_{(x,y,z)\to(0,0,0)} V(x,y,z) = \lim_{(x,y,z)\to(0,0,0)} W(x,y,z) = 0$$

so that we will define $U(0, 0, 0) = V(0, 0, 0) = W(0, 0, 0) = 0$.

b) On the Ox axis, we have the equilibrium $P_1(d, 0, 0)$. The eigenvalues of the Jacobian calculated by MAPLE at this point are

$$-c, \quad -\frac{c(a-c)}{a}, \quad -\frac{CBa - CBc - Abc + Ccb}{bc + aB - cB}.$$

We have $-c < 0$, $-c(a-c)/a < 0$ and

$$-\frac{CBa - CBc - Abc + Ccb}{bc + aB - cB} = \frac{BC(D-d)}{1+Bd} > 0$$

so that P_1 is an unstable equilibrium for all considered values of the parameters. On the Ox axis, the first equation of (1) becomes

$$x' = bcx\frac{d-x}{1+bx}$$

and the origin $x = 0$ has a behavior of an unstable equilibrium.

c) On the Oy axis we have the equilibrium $P_2(0, D, 0)$. The eigenvalues of the Jacobian at this point are

$$-c, \quad -\frac{C(A-C)}{A}, \quad \frac{CBa - CBc - Acb + Ccb}{CB + Ab - Cb}.$$

Again $-c < 0$, $-C(A-C)/A < 0$ but

$$\frac{CBa - CBc - Acb + Ccb}{CB + Ab - Cb} = \frac{bc(d-D)}{1+bD} < 0$$

so that P_2 is a stable node for all considered values of the parameters – this is the "bad" equilibrium. On the Oy axis, the second equation of (1) becomes

$$y' = BCy\frac{D-y}{1+By}$$

so that the origin $y = 0$ has a behavior of an unstable equilibrium.

d) On the Oz axis the equilibrium is $P_3(0, 0, d)$. The eigenvalues of the Jacobian at this point are $-c < 0$, $-C < 0$, $-c(a-c)/a < 0$, so that P_3 is a stable node for all considered values of the parameters – this is the "good" equilibrium. On the Oz axis, the third equation of (1) becomes

$$z' = bcz\frac{d-z}{1+bz}$$

so that the origin $z = 0$ has again a behavior of an unstable equilibrium.

e) In the Oxy plane the equilibrium conditions lead us to the system

$$\left(\frac{a}{1+b(x+y)} - c\right)x = 0, \qquad \left(\frac{A}{1+B(x+y)} - C\right)y = 0,$$

from where, for $(x, y) \neq (0, 0)$ we obtain $x + y = d = D$. Consequently, this system is inconsistent for $d < D$. In a neighborhood of the origin, the above system becomes

$$x' = bcx\frac{d-(x+y)}{1+b(x+y)}, \qquad y' = BCy\frac{D-(x+y)}{1+B(x+y)},$$

so that $x' > 0$, $y' > 0$ have again a behavior of an unstable equilibrium.

f) In the Oxz plane the equilibrium condition leads us to the system

$$\begin{cases} \dfrac{a}{1+b(x+z)}\dfrac{x}{x+gz} - c = 0, \\ \dfrac{a}{1+b(x+z)}\dfrac{z}{z+hx} - c = 0, \end{cases} \tag{2}$$

from where, for $(x,z) \neq (0,0)$ we obtain $\dfrac{x}{x+gz} = \dfrac{z}{z+hx}$ or $hx^2 = gz^2$. Consequently, we have a solution $P_4(x^+, 0, z^+)$, where

$$x^+ = \frac{\dfrac{a}{c\left(1+\sqrt{hg}\right)} - 1}{b\left(1+\sqrt{\dfrac{h}{g}}\right)}, \quad z^+ = \sqrt{h/g}x^+. \tag{3}$$

There exists an admissible solution $(x^+ > 0, z^+ > 0)$ if and only if

$$\sqrt{hg} < \frac{a}{c} - 1 = bd.$$

We remark here that $z = \sqrt{h/g}x$ is an invariant manifold in Oxz.

In order to study the stability of this solution we calculate the Jacobian J of the system (1) at this point,

$$J = \begin{pmatrix} -\frac{bcx^+}{1+b(x^++z^+)} + \frac{cgz^+}{x^++gz^+} & \square & -\frac{bcx^+}{1+b(x^++z^+)} - \frac{cgx^+}{x^++gz^+} \\ 0 & Q & 0 \\ -\frac{bcz^+}{1+b(x^++z^+)} - \frac{hcz^+}{z^++hx^+} & \square & -\frac{bcz^+}{1+b(x^++z^+)} + \frac{hcx^+}{z^++hx^+} \end{pmatrix},$$

where $\square$ means that the values of J_{12} and J_{32} are useless for the calculation of the eigenvalues. An eigenvalue is

$$Q = \frac{Ax^+}{\left(1+B\left(x^++z^+\right)\right)\left(x^++Gz^+\right)} - C$$

and from the expressions of x^+ and z^+ we obtain

$$Q = \frac{C}{1+\frac{B}{b}\left(\dfrac{a}{c\left(1+\sqrt{hg}\right)} - 1\right)} \frac{\frac{A}{C}\sqrt{gh}}{\sqrt{gh}+Gh} - C.$$

The other two eigenvalues have the product

$$\begin{vmatrix} J_{11} & J_{13} \\ J_{31} & J_{33} \end{vmatrix} < 0$$

so that they have opposite signs. Consequently, the equilibrium $(x^+, 0, z^+)$ is hyperbolic unstable. If $Q < 0$, system (1) has a two-dimensional local stable invariant manifold and a one-dimensional local unstable invariant manifold. If $Q > 0$ the system has a two-dimensional local unstable invariant manifold and a one-dimensional local stable invariant manifold (see [3], Theorem 1.3.2–Stable Manifold Theorem for a Fixed Point).

g) In the Oyz plane the equilibrium condition leads us to the system

$$\begin{cases} \dfrac{A}{1+B(y+z)} \dfrac{y}{y+Gz} = C, \\ \dfrac{a}{1+b(y+z)} \dfrac{z}{z+hy} = c, \end{cases} \tag{4}$$

which becomes

$$F_1(y,z) \equiv CBy^2 + CB(G+1)yz + CBGz^2 + (C-A)y + CGz = 0,$$
$$F_2(y,z) \equiv cbhy^2 + cb(h+1)yz + cbz^2 + chy + (c-a)z = 0.$$

This means that the equilibrium point is the intersection of these two conics and it is admissible if its coordinates are both positive.

Obviously, the two conics pass through the origin. We also have

$$F_1(y,0) = CBy^2 + (C-A)y = 0 \Longrightarrow y = 0,\ y = D,$$
$$F_1(0,z) = CBGz^2 + CGz = 0 \Longrightarrow z = 0,\ z = -\frac{1}{B},$$

and

$$F_2(y,0) = cbhy^2 + chy = 0 \Longrightarrow y = 0,\ y = -\frac{1}{b},$$
$$F_2(0,z) = cbz^2 + (c-a)z = 0 \Longrightarrow z = 0,\ z = d.$$

But

$$\delta_1 = \begin{vmatrix} CB & \frac{CB(G+1)}{2} \\ \frac{CB(G+1)}{2} & CBG \end{vmatrix} = C^2B^2G - \frac{C^2B^2(G+1)^2}{4} = -\frac{C^2B^2(G-1)^2}{4} < 0$$

for F_1 and

$$\delta_2 = \begin{vmatrix} cbh & \frac{cb(h+1)}{2} \\ \frac{cb(h+1)}{2} & cb \end{vmatrix} = c^2b^2h - \frac{c^2b^2(h+1)^2}{4} = -\frac{c^2b^2(h-1)^2}{4} < 0$$

for F_2 so that the conics are hyperbolas if $G \neq 1$, $h \neq 1$, see Figure 1.

The center of $F_1(y,z) = 0$ has the coordinates

$$y_0 = \frac{G(C-A) - AG - CG^2}{CB(G-1)^2} < 0, \quad z_0 = \frac{G(C+A) + A - C}{CB(G-1)^2} > 0$$

and the asymptotes are

$$z - z_0 = -\frac{1}{G}(y - y_0), \quad z - z_0 = -(y - y_0).$$

If $G > 1$, the first asymptote intersects Oy at $y_0 + Gz_0 > D$ and intersects Oz at $\frac{y_0+Gz_0}{G} > 0$, while the second asymptote intersects both Oy and Oz at $y_0 + z_0 < -\frac{1}{B}$.

If $G < 1$, the first asymptote intersects Oy at $y_0 + Gz_0 < 0$ and intersects Oz at $\frac{y_0+Gz_0}{G} < -\frac{1}{B}$, while the second asymptote intersects both Oy and Oz at $y_0 + z_0 > D$. Consequently, the hyperbola $F_1(y,z) = 0$ has a unique branch into the first quadrant of Oyz.

Analogously, the center of $F_2(y,z) = 0$ has the coordinates

$$y_0 = \frac{h(c+a) + a - c}{bc(h-1)^2} > 0, \quad z_0 = \frac{h(c-a) - ah - ch^2}{bc(h-1)^2} < 0$$

and the asymptotes are

$$z - z_0 = -h(y - y_0), \quad z - z_0 = -(y - y_0).$$

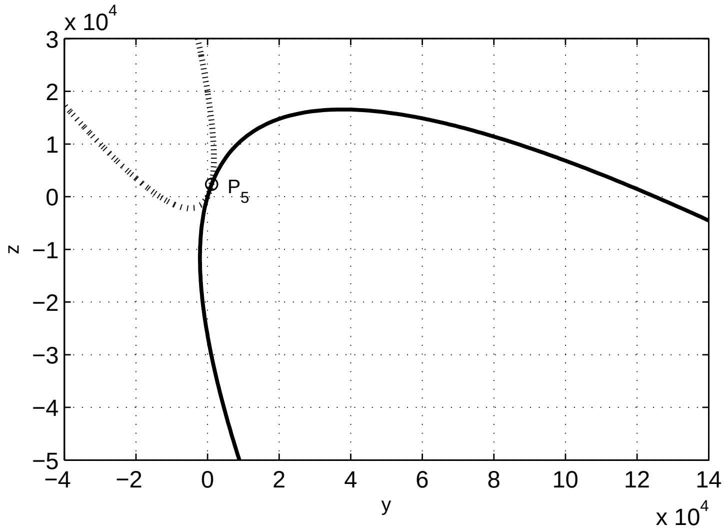

Figure 1: The equilibrium point $P_5 \in Oyz$.

If $h > 1$ the first asymptote intersects Oy at $\frac{hy_0+z_0}{h}$ and intersects Oz at $z_0 + hy_0 > d$ while the second asymptote intersects both Oy and Oz at $y_0 + z_0 < -\frac{1}{b}$.

If $h < 1$ the first asymptote intersects Oy at $\frac{hy_0+z_0}{h} < -\frac{1}{b}$ and intersects Oz at $z_0 + hy_0$ while the second asymptote intersects both Oy and Oz at $y_0 + z_0 > d$.

Consequently, the hyperbola $F_2(y, z) = 0$ has a unique branch into the first quadrant of Oyz.

The intersection of these branches depends on their slopes at the origin

$$z_y = -\frac{F_{1y}(0,0)}{F_{1z}(0,0)} = \frac{A-C}{CG} > 0$$

for F_1 and

$$z_y = -\frac{F_{2y}(0,0)}{F_{2z}(0,0)} = \frac{ch}{a-c} > 0$$

for F_2. We have an intersection point $P_5(0, y^*, z^*)$ solution of the system (4) with positive coordinates if and only if

$$\frac{A-C}{CG} > \frac{ch}{a-c},$$

i.e.

$$hG < BbDd = \left(\frac{A}{C} - 1\right)\left(\frac{a}{c} - 1\right).$$

The stability of this point is given by the eigenvalues of the Jacobian

$$J = \begin{pmatrix} P & 0 & 0 \\ \square & -\frac{BCy^*}{1+B(y^*+z^*)} + \frac{GCz^*}{y^*+Gz^*} & -\frac{BCy^*}{1+B(y^*+z^*)} - \frac{GCy^*}{y^*+Gz^*} \\ \square & -\frac{bcz^*}{1+b(y^*+z^*)} - \frac{chz^*}{z^*+hy^*} & -\frac{bcz^*}{1+b(y^*+z^*)} + \frac{chy^*}{z^*+hy^*} \end{pmatrix}.$$

One eigenvalue is

$$P = \frac{ay^*}{(1 + b(y^* + z^*))\,(y^* + gz^*)} - c.$$

The product of the other two eigenvalues is

$$\begin{vmatrix} J_{22} & J_{23} \\ J_{32} & J_{33} \end{vmatrix} < 0$$

so that they have opposite signs. Consequently, the equilibrium $(0, y^*, z^*)$ is hyperbolic unstable. If $P < 0$ the system (1) has a two-dimensional local stable invariant manifold and a one-dimensional local unstable invariant manifold. If $P > 0$ the system has a two-dimensional local unstable invariant manifold and a one-dimensional local stable invariant manifold.

From the system (4) verified by (y^*, z^*), we have

$$P = \frac{a\left(hy^{*2} - gz^{*2}\right)}{(1 + b(y^* + z^*))\,(y^* + gz^*)\,(z^* + hy^*)}$$

whose sign is given by $hy^{*2} - gz^{*2}$. More precisely,

$$\frac{y^*}{z^*} < \sqrt{\frac{g}{h}} \Longrightarrow P < 0,$$
$$\frac{y^*}{z^*} > \sqrt{\frac{g}{h}} \Longrightarrow P > 0.$$

In order to evaluate the sign of P, we eliminate $y^* + z^*$ from the system (4). We obtain

$$\frac{B}{A}\frac{a}{b} = \frac{\frac{1}{C}\frac{y^*}{y^*+Gz^*} - \frac{1}{A}}{\frac{1}{c}\frac{z^*}{z^*+hy^*} - \frac{1}{a}}.$$

and by denoting $\frac{y^*}{z^*} = t^*$ we have

$$\frac{A}{B}\left(\frac{1}{C}\frac{t^*}{t^* + G} - \frac{1}{A}\right) = \frac{a}{b}\left(\frac{1}{c}\frac{1}{1 + ht^*} - \frac{1}{a}\right).$$

Consequently, t^* is a positive root of the equation

$$f(t) \equiv \frac{A}{BC}\frac{t}{t + G} - \frac{a}{bc}\frac{1}{1 + ht} - \frac{1}{B} + \frac{1}{b} = 0.$$

But

$$f'(t) = \frac{A}{BC}\frac{G}{(t + G)^2} + \frac{a}{bc}\frac{h}{(1 + ht)^2} > 0,$$

and

$$f(0) = -\frac{a}{bc} - \frac{1}{B} + \frac{1}{b} = \frac{c - a}{bc} - \frac{1}{B} < 0,$$
$$\lim_{t\to\infty} f(t) = \frac{A}{BC} - \frac{1}{B} + \frac{1}{b} = \frac{A - C}{BC} + \frac{1}{b} > 0$$

so that

$$f\left(\sqrt{\frac{g}{h}}\right) > 0 = f(t^*) \Longleftrightarrow t^* < \sqrt{\frac{g}{h}} \Longleftrightarrow P < 0,$$
$$f\left(\sqrt{\frac{g}{h}}\right) < 0 = f(t^*) \Longleftrightarrow t^* > \sqrt{\frac{g}{h}} \Longleftrightarrow P > 0.$$

Consequently, the sign of P is opposite to the sign of

$$f\left(\sqrt{\frac{g}{h}}\right) = \frac{A}{BC}\frac{\sqrt{gh}}{\sqrt{gh}+Gh} - \frac{a}{bc}\frac{1}{1+\sqrt{gh}} - \frac{1}{B} + \frac{1}{b}.$$

If the equilibrium P_5 exists but P_4 does not exist, i.e.

$$Gh < \left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right), \qquad \sqrt{gh} > \frac{a}{c} - 1,$$

then

$$0 < Gh < \left(\frac{A}{C}-1\right)\sqrt{gh}$$

and

$$f\left(\sqrt{\frac{g}{h}}\right) > \frac{A}{BC}\frac{1}{1+\frac{\left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right)}{\sqrt{gh}}} - \frac{a}{bc}\frac{1}{1+\sqrt{hg}} - \frac{1}{B} + \frac{1}{b} >$$
$$> \frac{A}{BC}\frac{1}{1+\frac{A}{C}-1} - \frac{a}{bc}\frac{1}{1+\frac{a}{c}-1} - \frac{1}{B} + \frac{1}{b} = 0.$$

In this case, $P < 0$ and the equilibrium $P_5(0, y^*, z^*)$ has a two-dimensional local stable manifold and a one-dimensional local unstable manifold.

If the equilibrium P_5 does not exist, but P_4 exists, i.e.

$$Gh > \left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right), \qquad \sqrt{gh} < \frac{a}{c} - 1,$$

then

$$Gh > \left(\frac{A}{C}-1\right)\sqrt{gh}$$

and

$$Q = \frac{C}{1+\frac{B}{b}\left(\frac{a}{c\left(1+\sqrt{hg}\right)}-1\right)}\frac{\frac{A}{C}\sqrt{gh}}{\sqrt{gh}+Gh} - C < C\left(\frac{\frac{A}{C}\sqrt{gh}}{\sqrt{gh}+Gh}-1\right) < 0.$$

In this case, $Q < 0$ and the equilibrium $P_4(x^+, 0, z^+)$ has a two-dimensional local stable manifold and a one-dimensional local unstable manifold.

If both equilibria P_4 and P_5 exist, i.e.

$$Gh < \left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right), \qquad \sqrt{gh} < \frac{a}{c} - 1,$$

we have

$$Q=\frac{C}{1+\frac{B}{b}\left(\frac{a}{c\left(1+\sqrt{hg}\right)}-1\right)}\frac{\frac{A}{C}\sqrt{gh}}{\sqrt{gh}+Gh}-C,$$

$$f\left(\sqrt{\frac{g}{h}}\right)=\frac{A}{BC}\frac{\sqrt{hg}}{\sqrt{hg}+Gh}-\frac{a}{bc}\frac{1}{1+\sqrt{hg}}-\frac{1}{B}+\frac{1}{b}.$$

By eliminating $\frac{\frac{A}{C}\sqrt{gh}}{\sqrt{gh}+Gh}$ we obtain

$$\frac{\frac{A}{C}\sqrt{gh}}{\sqrt{gh}+Gh}=Bf\left(\sqrt{\frac{g}{h}}\right)+\frac{B}{b}\left(\frac{a}{c}\frac{1}{1+\sqrt{hg}}-1\right)+1,$$

$$Q=\frac{C\left(Bf\left(\sqrt{\frac{g}{h}}\right)+\frac{B}{b}\left(\frac{a}{c}\frac{1}{1+\sqrt{hg}}-1\right)+1\right)}{1+\frac{B}{b}\left(\frac{a}{c\left(1+\sqrt{hg}\right)}-1\right)}-C=\frac{BCf\left(\sqrt{\frac{g}{h}}\right)}{1+\frac{B}{b}\left(\frac{a}{c\left(1+\sqrt{hg}\right)}-1\right)}.$$

Consequently, Q has the same sign as $f\left(\sqrt{\frac{g}{h}}\right)$, so that Q and P have opposite signs. This means that either $P_5(0,y^*,z^*)$ or $P_4(x^+,0,z^+)$ has a two-dimensional local stable manifold.

h) Finally, if we search equilibrium points (x,y,z) with $x>0$, $y>0$, $z>0$, we are led to the system

$$\begin{cases}\dfrac{a}{1+b(x+y+z)}\dfrac{x+y}{x+y+gz}-c=0,\\ \dfrac{A}{1+B(x+y+z)}\dfrac{x+y}{x+y+Gz}-C=0,\\ \dfrac{a}{1+b(x+y+z)}\dfrac{z}{z+h\left(x+y\right)}-c=0.\end{cases}$$

By denoting $u=x+y$, this system becomes

$$\begin{aligned}au&=c\left(1+b(u+z)\right)\left(u+gz\right),\\ Au&=C\left(1+B(u+z)\right)\left(u+Gz\right),\\ az&=c\left(1+b(u+z)\right)\left(z+hu\right).\end{aligned}$$

But

$$\frac{u}{z}=\frac{u+gz}{z+hu}=\frac{\frac{u}{z}+g}{1+h\frac{u}{z}},$$

hence we obtain $\frac{u}{z}=\sqrt{\frac{g}{h}}$. Now, from the first equation we get

$$u+z=\frac{1}{b}\left(\frac{\frac{a}{c}}{1+\sqrt{gh}}-1\right).$$

Obviously, $u+z>0$, if $\sqrt{gh}<\frac{a}{c}-1$.

We obtain now from the second equation the consistency condition

$$\frac{\frac{A}{C}\sqrt{gh}}{\sqrt{gh}+Gh}=1+\frac{B}{b}\left(\frac{\frac{a}{c}}{1+\sqrt{gh}}-1\right),\tag{5}$$

from where

$$Gh < \left(\frac{A}{C} - 1\right)\sqrt{gh} < \left(\frac{A}{C} - 1\right)\left(\frac{a}{c} - 1\right).$$

For the existence of such an equilibrium it is necessary that equilibria P_4 and P_5 exist and, moreover, $P = Q = 0$. In this very particular case, the equilibrium is not unique. The solutions (x, y, z) verify $x + y = u_0$, $z = z_0$, where

$$u_0 = \frac{1}{b}\left(\frac{\frac{a}{c}}{1+\sqrt{gh}} - 1\right)\frac{\sqrt{gh}}{\sqrt{gh}+h}, \quad z_0 = \frac{\frac{1}{b}\left(\frac{\frac{a}{c}}{1+\sqrt{gh}} - 1\right)}{1+\sqrt{\frac{g}{h}}}. \tag{6}$$

Now if we put together the above results, we can state the following

Theorem 2.1 *Let* $a, b, c, A, B, C, g, G, h$ *be positive parameters such that* $a > c$, $A > C$, $d < D$, *where* $d = \frac{1}{b}\left(\frac{a}{c} - 1\right)$ *and* $D = \frac{1}{B}\left(\frac{A}{C} - 1\right)$. *Then system* (1), *considered for* $x \geq 0$, $y \geq 0$, $z \geq 0$, *has the following steady-states:*

a) $O(0, 0, 0)$ *and* $P_1(d, 0, 0)$ *as unstable equilibria,*

b) $P_2(0, D, 0)$ *and* $P_3(0, 0, d)$ *as asymptotically stable equilibria,*

c) $P_4(x^+, 0, z^+)$ *given by* (3) *if* $hg < \left(\frac{a}{c} - 1\right)^2$ *and*

d) $P_5(0, y^*, z^*)$ *given by* (4) *if* $hG < \left(\frac{a}{c} - 1\right)\left(\frac{A}{C} - 1\right)$, *as hyperbolic unstable equilibria. Only one of* P_4 *or* P_5 *has a two-dimensional local stable invariant manifold. Finally, the system* (1) *has*

e) *a line of equilibria* $P(x, y, z)$ *in the case* (5), *where* $x + y = u_0$, $z = z_0$ *are given by* (6).

We remark that the local stable invariant manifolds W^s_{loc} of hyperbolic equilibria have global analogues W^s obtained by letting points in W^s_{loc} flow backwards in time.

These manifolds act as boundaries between different regions of the phase space. For a system with multiple attractors, a boundary of a basin of attraction can often be recovered as a codimension-one stable manifold of a saddle point, such as P_4 or P_5.

In general, such manifolds can not be expressed in closed-form and therefore must be approximated numerically for particular values of the parameters. In our paper we have used an efficient algorithm of Moore [4], based on Laguerre functions and modified in order to apply our MATLAB package *LaguerreEig* [8].

3 Numerical Simulations

In order to verify and to illustrate the above theoretical results, we will perform some numerical tests, with the physiological values of the parameters chosen from [2]:

$$\begin{array}{lll} a = 0.005, & A = 0.0115, & g = 2, \\ b = 0.000075, & B = 0.000038, & G = 2, \\ c = 0.002, & C = 0.002, & h = 2, \end{array}$$

such that

$$a > c, \quad A > C, \quad d = 20000 < D = 125000.$$

The condition

$$Gh = 4 < \left(\frac{A}{C} - 1\right)\left(\frac{a}{c} - 1\right) = 4.75 \times 1.5$$

is fulfilled, but

$$hg = 4 > \left(\frac{a}{c} - 1\right)^2 = (1.5)^2$$

so that we have no equilibrium P_4 in the Oxz plane – in this case $x^+ < 0$. The consistency condition (5) is not satisfied:

$$\frac{\frac{0.0115}{0.002}\sqrt{4}}{\sqrt{4}+4} \neq 1 + \frac{0.000038}{0.000075}\left(\frac{\frac{0.005}{0.002}}{1+\sqrt{4}} - 1\right)$$

or $1.9167 \neq 0.91556$. We have $P_5(0, 1149.089506, 2342.140461)$ and the corresponding eigenvalues of the Jacobian are $-.0003471757542, .002588209809, -.001219452669$. This point P_5 is an unstable equilibrium with a two-dimensional stable manifold. The numerical tests show that this manifold indeed separates the attraction basins of the asymptotically stable equilibria $P_2(0, 125000, 0)$ and $P_3(0, 0, 20000)$ in the computational domain of physiological significance, see Figure 2.

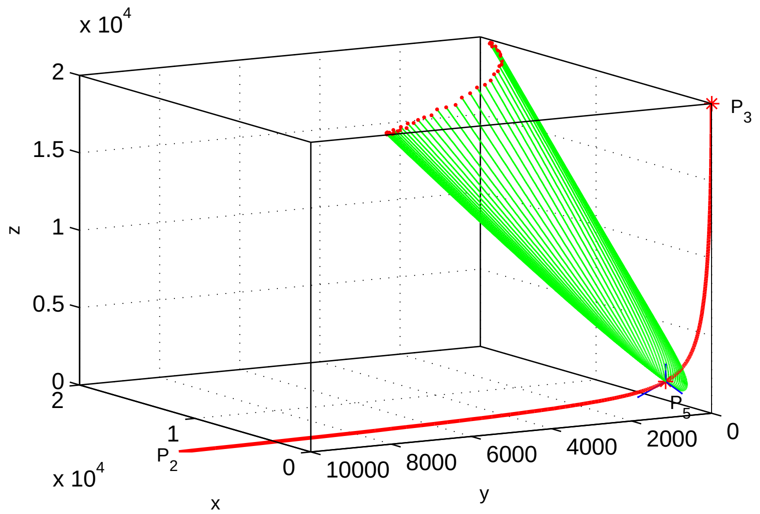

Figure 2: Case $C = 0.002$. The numerically calculated two-dimensional stable manifold of P_5. The continuous line that connects P_5P_2 and P_5P_3 in the plane Oyz is the numerically calculated one-dimensional unstable manifold of P_5.

If therapeutic agents are used in order to increase the death rate of the leukemic cells, i.e. to increase C from $C = 0.002$ to $C = 0.006$ for example, the equilibria P_4 and P_5 do not exist in the considered domain. Again $A > C$ and $d < D$, as above, but the numerical tests show that the border between the attraction basins of P_2 and P_3 is now a numerically calculated two-dimensional invariant manifold which behaves as a two-dimensional stable manifold of the origin O. In this case the attraction basin of $P_3(0, 0, 20000)$ increases, see Figure 3.

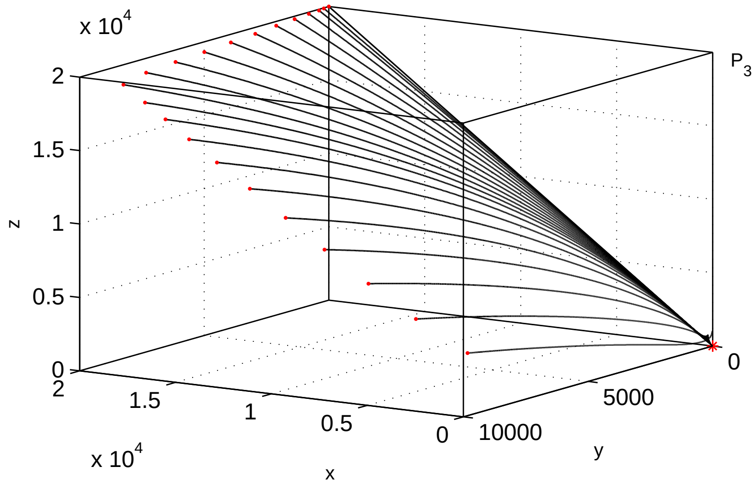

Figure 3: case $C = 0.006$. The border between the attraction basins of P_2 and P_3.

4 Conclusion

A mathematical model of Dingli and Michor [2] was augmented in [5] in order to simulate the cell dynamics after bone marrow transplantation. The new model (1) introduces the parameters h, g, G standing for the intensity of anti-graft, anti-host and anti-leukemia effects.

This model has only two asymptotically stable equilibria, $P_2(0, D, 0)$ and $P_3(0, 0, d)$. Other important unstable hyperbolic equilibria are $P_4(x^+, 0, z^+)$, which exists if and only if $hg < \left(\frac{a}{c} - 1\right)^2$, and $P_5(0, y^*, z^*)$, which exists if and only if $hG < \left(\frac{A}{C} - 1\right)\left(\frac{a}{c} - 1\right)$.

If, after an appropriate therapy, h is sufficiently small, i.e. the anti-graft effect becomes small enough, then one or both equilibria P_4 or P_5 exist and, by the stable manifold theorem for a hyperbolic fixed point, one of them always has a stable two-dimensional invariant manifold.

This stable manifold provides important information about the system's global dynamics, for example it indicates the boundary of the attraction basins of the asymptotically stable equilibria P_2 and P_3. Given the initial host cell concentrations x_0, y_0, we may calculate an initial concentration (dose of infused cells at transplantation) z_0 in the attraction basin of P_3 so that, in time, host cells will be eliminated and completely replaced by donor cells, guaranteeing the elimination of cancer. Based on the stability analysis in this paper, a theoretical basis for the control of post-transplant evolution can be provided and therapy planning algorithms for guiding the correction treatment after transplant can be established. This is the goal of the subsequent paper [6].

Acknowledgment

This work was supported by a grant of the Romanian National Authority for Scientific Research, CNCS UEFISCDI, project number PN-II-ID-PCE-2011-3-0094.

References

[1] Cucuianu, A. and Precup, R. A hypothetical-mathematical model of acute myeloid leukaemia pathogenesis. *Comput. Math. Methods Med.* **11** (2010) 49–65.

[2] Dingli, D. and Michor, F. Successful therapy must eradicate cancer stem cells. *Stem Cells* **24** (2006) 2603–2610.

[3] Guckenheimer, J. and Holmes, P. *Nonlinear Oscillations, Dynamical Systems, and Bifurcation of Vector Fields.* Springer-Verlag, New York, 1983.

[4] Moore, G. Laguerre approximation of stable manifolds with application to connecting orbits. *Math. Comp.* **73** (2004) 211–242.

[5] Precup, R., Arghirescu, S., Cucuianu, A. and Serban, M. Mathematical modeling of cell dynamics after allogeneic bone marrow transplantation in acute myeloid leukemia. *Int. J. Biomath.* **5**(2012), 1250026 [18 pages] DOI: 10.1142/S1793524511001684.

[6] Precup, R., Serban, M-A., Trif, D. and Cucuianu, A. A planning algorithm for correction therapies after allogeneic stem cell transplantation. *J. Math. Model. Algor.* **11** (2012) 309–323.

[7] Precup, R., Trif, D., Serban, M-A. and Cucuianu A. A mathematical approach to cell dynamics before and after allogeneic bone marrow transplantation. *Ann. Tiberiu Popoviciu Semin. Funct. Equ. Approx. Convexity* **8** (2010) 167–175.

[8] Trif, D. *LaguerreEig* (2009), Available from:
http://www.mathworks.com/ matlabcentral/fileexchange/24266-laguerreeig.