Stability of the Equilibria of a Dynamic System Modeling Stem Cell Transplantation

Local Stability and Stability on Manifolds Analysis

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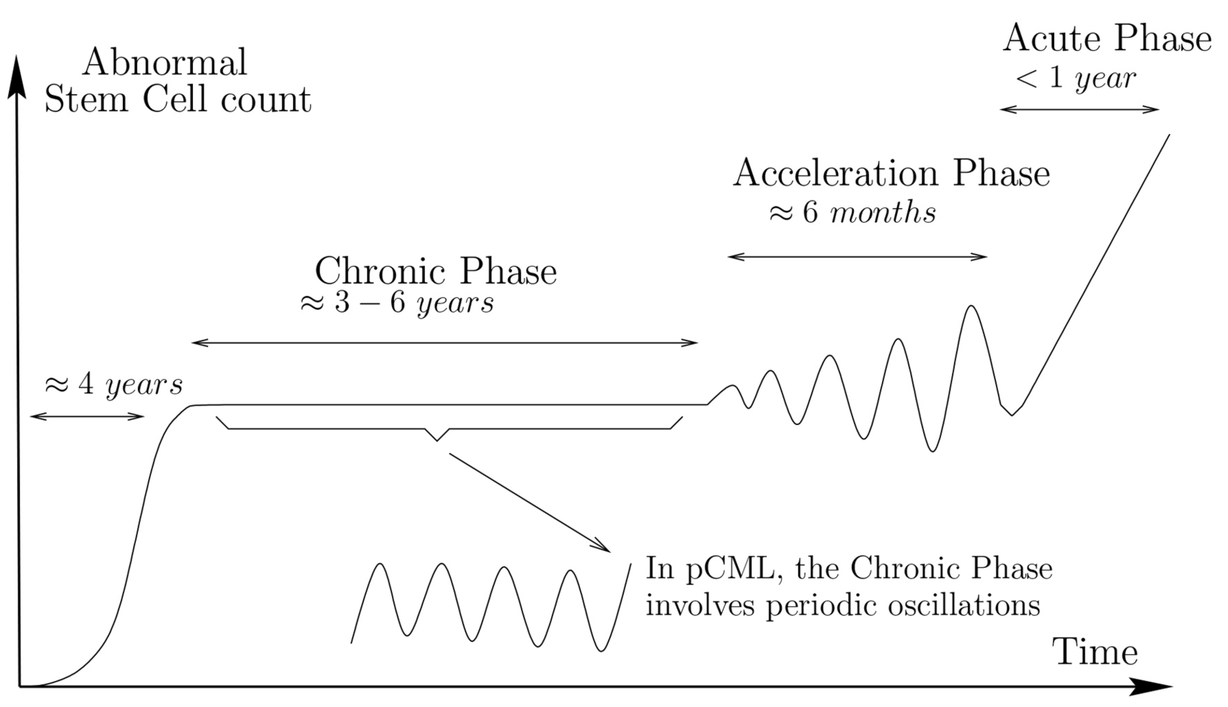
Resumen

In this work we perform a complete analysis of the stability of the steady states for a three-dimensional system modeling cell dynamics after bone marrow transplantation in chronic myeloid leukemia. There are given results for both chronic and accelerated acute phases of the disease. In addition to the theoretical results, numerical simulations are performed to visualize the equilibrium points, one and two-dimensional stable manifolds, and the separation surface between the basins of attraction of the asymptotically stable equilibria. Our results could serve as a basis for further research concerning personalized treatment protocols.

Introduction

Chronic Myeloid Leukemia (CML)

Chronic Myeloid Leukemia, also known as chronic granulocytic leukemia, chronic myelogenous leukemia, and chronic myelocytic leukemia, is a disease of hematopoietic stem cells. Chronic Myeloid Leukemia progresses through three distinct phases. After a relatively quick rise in the cell count, the system reaches a seemingly steady state. After several years, this steady state, called the chronic phase, gives rise to oscillatory instability. This leads to the acute phase which is a sharp, usually fatal, increase in the cell count (see B. Neiman [2]).



The Mathematical Model

The basic ideas of mathematical modeling of stem cell transplantation appear in the papers of R. Precup et al. [5, 6, 7]. The idea consists in adding, at time $t = 0$, in competition with x_0 and y_0 (host cells) a new population z_0 (donor cells). If the combativeness of z against x and y (graf versus host and graf versus abnormal) compensates that of the x and y against z (anti graf effect), and if the initial conditions x_0 and y_0 are small enough as compared with z_0, then in time, host cells are eliminated and they are replaced by donor cells, guaranteeing the elimination of leukemia (a cancer of the blood).

From a mathematical point of view, this means that a new equation in z is added to the initial system, in x and y, considered by L.G. Parajdi et al. [3, 4]. This new three-dimensional mathematical model is modified to incorporate the new competition between the donor cell population noted by z and normal respectively abnormal cell populations noted by x respectively y. Supposing that the intrinsic growth rate, bone marrow microenvironment sensitivity, and the death rate of the donor cell population are those of the normal host cell population, namely, a, b_1, b_2 and c.

Compared with the initial model considered by R. Precup et al. [6], our mathematical model makes the distinction between the chronic and accelerated acute phases at transplantation. Starting from the normal-abnormal mathematical model in two dimensions considered by L.G. Parajdi et al. [4], we consider the following model for the post-transplant cell evolution

$$
\begin{aligned}
x'(t) &= \frac{ax(t)}{1+b_1(x(t)+z(t))+b_2y(t)}\frac{x(t)+y(t)}{x(t)+y(t)+gz(t)} - cx(t),\\
y'(t) &= \frac{Ay(t)}{1+B(x(t)+y(t)+z(t))}\frac{x(t)+y(t)}{x(t)+y(t)+Gz(t)} - Cy(t),\\
z'(t) &= \frac{az(t)}{1+b_1(x(t)+z(t))+b_2y(t)}\frac{z(t)}{z(t)+h(x(t)+y(t))} - cz(t),
\end{aligned}
\tag{1}
$$

where x, y, z stand for normal host cells, leukemic host cells and donor cells, and the parameters g, G, h express the intensity of the anti-host, anti-leukemia and anti-graft effects.

Steady States

We can illustrate the bifurcation analysis of our system (1) in the next Figure 1.

Figure 1: Diagram of the transition from normal hematopoiesis to chronic and accelerated acute phases in chronic myeloid leukemia

Steady states for the chronic phase of CML

We consider the system (1) in the chronic phase. Thus

$$a > c,\ \ A > C,\ \ b_1 > b_2 > B\ \text{ and }\ d < D < \alpha d. \tag{2}$$

The solutions of the algebraic system obtained from (1) in the conditions denoted by (2) are the admissible points, namely

$$
\begin{gathered}
P_0(0,0,0);\ \ P_1(d,0,0);\ \ P_2(0,D,0);\ \ P_3(0,0,d);\\
P_4(x^*,y^*,0);\ \ P_5(x^+,0,z^+);\ \ P_6(0,y^{++},z^{++})\ \text{ and }\ P_7(x^\#,y^\#,z^\#),
\end{gathered}
\tag{3}
$$

where d and D are given by

$$d = \frac{1}{b_1}\left(\frac{a}{c}-1\right),\ \ D = \frac{1}{B}\left(\frac{A}{C}-1\right)\ \text{ and }\ \alpha = \frac{b_1}{b_2}(>1). \tag{4}$$

In the O_{xy} plane, we have the steady state $P_4\,(x^*, y^*, 0)$ with the components

$$x^* = \frac{b_2}{b_1-b_2}(\alpha d - D)\ \text{ and }\ y^* = \frac{b_1}{b_1-b_2}(D-d), \tag{5}$$

in the O_{xz} plane, we have the steady state $P_5\,(x^+, 0, y^+)$, with the components

$$x^+ = \frac{\frac{a}{c(1+\sqrt{gh})}-1}{b_1\left(1+\sqrt{\frac{h}{g}}\right)}\ \text{ and }\ z^+ = \sqrt{\frac{h}{g}}x^+ \tag{6}$$

and in the O_{yz} plane, we have the steady state $P_6\,(0, y^{++}, z^{++})$, with the components which are given by the following two-dimensional algebraic system

$$
\begin{cases}
\frac{A}{1+B(y+z)}\frac{y}{y+Gz} - C = 0\\
\frac{a}{1+b_2y+b_1z}\frac{z}{z+hy} - c = 0.
\end{cases}
\tag{7}
$$

Finally, in O_{xyz} we have the steady state $P_7(x^\#, y^\#, z^\#)$, with the components

$$x^\# = \frac{b_1\left(1+\sqrt{\frac{g}{h}}\right)\left(1+G\sqrt{\frac{h}{g}}\right)\left(d-\frac{1}{b_1}\sqrt{gh}\right) - \left(1+\sqrt{gh}\right)\left(b_1+b_2\sqrt{\frac{g}{h}}\right)\left(D-\frac{G}{B}\sqrt{\frac{h}{g}}\right)}{(b_1-b_2)\left(1+\sqrt{gh}\right)\left(1+\sqrt{\frac{g}{h}}\right)\left(1+G\sqrt{\frac{h}{g}}\right)}, \tag{8}$$

$$y^\# = \frac{b_1}{b_1-b_2}\left(\frac{\left(1+\sqrt{gh}\right)\left(D-\frac{G}{B}\sqrt{\frac{h}{g}}\right) - \left(1+G\sqrt{\frac{h}{g}}\right)\left(d-\frac{1}{b_1}\sqrt{gh}\right)}{\left(1+G\sqrt{\frac{h}{g}}\right)\left(1+\sqrt{gh}\right)}\right)\ \text{ and }\ z^\# = \frac{D-\frac{G}{B}\sqrt{\frac{h}{g}}}{\left(1+\sqrt{\frac{g}{h}}\right)\left(1+G\sqrt{\frac{h}{g}}\right)}. \tag{9}$$

Steady states for the accelerated acute phase of CML

Next we consider the system (1) in the accelerated acute phase. Thus

$$a > c,\ \ A > C,\ \ b_1 > b_2 > B\ \text{ and }\ \alpha d < D. \tag{10}$$

The solutions of the algebraic system obtained from (1) in the conditions denoted by (10) are the admissible points, namely

$$
\begin{gathered}
O(0,0,0);\ \ P_1(d,0,0);\ \ P_2(0,D,0);\ \ P_3(0,0,d);\\
P_4(x^+,0,z^+);\ \ P_5(0,y^{++},z^{++})\ \text{ and }\ P_6(x^\#,y^\#,z^\#).
\end{gathered}
\tag{11}
$$

Note that an solution (or steady state) of (1) is said to be admissible if all its components x, y, z are nonnegative.

Results

Local Stability

From the study of local asymptotic stability of the stationary solutions of system (1), we obtain the following results:

Stability analysis for the chronic phase of CML

Theorem 1. Let $a, b_1, b_2, c, A, B, C, g, G$ and h be positive parameters such that $a > c$, $A > C$, $b_1 > b_2 > B$, $d < D < \alpha d$. Then system *(1)*, considered for $x \geq 0$, $y \geq 0$ and $z \geq 0$, has the following steady states:

(a) $O(0,0,0)$, $P_1(d,0,0)$ and $P_2(0,D,0)$ are unstable equilibria;

(b) $P_3(0,0,d)$, and $P_4\,(x^*, y^*, 0)$ given by *(5)*, are locally asymptotically stable equilibria;

(c) $P_5\left(x^+,0,z^+\right)$ given by *(6)*, if $gh<\left(\frac{a}{c}-1\right)^2$, and

(d) $P_6\left(0,y^{++},z^{++}\right)$ given by *(7)*, if $Gh<\left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right)$,

both $P_5\left(x^+,0,z^+\right)$ and $P_6\left(0,y^{++},z^{++}\right)$ are hyperbolic unstable equilibria;

(e) $P_7\left(x^{\#},y^{\#},z^{\#}\right)$ given by *(8)* and *(9)*, if $Gh<\left(\frac{A}{C}-1\right)\sqrt{gh}<\left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right)$, and

$$\frac{1+\sqrt{gh}}{1+G\sqrt{\frac{h}{g}}}>\frac{d-\frac{1}{b_1}\sqrt{gh}}{D-\frac{G}{B}\sqrt{\frac{h}{g}}}>\frac{\left(1+\sqrt{gh}\right)\left(b_1+b_2\sqrt{\frac{g}{h}}\right)}{b_1\left(1+\sqrt{\frac{g}{h}}\right)\left(1+G\sqrt{\frac{h}{g}}\right)} \tag{12}$$

holds. The equilibrium $P_7\left(x^{\#},y^{\#},z^{\#}\right)$ is locally asymptotically stable if and only if $\delta_1>0$, $\delta_3>0$ and $\delta_1\delta_2>\delta_3$, where $\delta_1,\delta_2,\delta_3$ are given by

$$\begin{aligned}\delta_1 &= -J_{11}-J_{22}-J_{33}=-tr(J),\\ \delta_2 &= J_{11}J_{22}+J_{22}J_{33}+J_{11}J_{33}-J_{13}J_{31}-J_{32}J_{23}-J_{21}J_{12},\\ \delta_3 &= -J_{11}J_{22}J_{33}-J_{21}J_{32}J_{13}-J_{31}J_{12}J_{23}+J_{13}J_{22}J_{31}+J_{23}J_{32}J_{11}+\\ &+ J_{33}J_{12}J_{21}=-\det(J)\end{aligned} \tag{13}$$

and $J_{ij},\ i,j=1,2,3$ are the elements of Jacobian matrix calculated in $(x^{\#},y^{\#},z^{\#})$.

Recall that the equilibrium $P_5\left(x^+,0,z^+\right)$ exists if and only if $gh<\left(\frac{a}{c}-1\right)^2$, and the equilibrium $P_6\left(0,y^{++},z^{++}\right)$ exists if and only if $Gh<\left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right)$.

Hence, only one or both $P_5\left(x^+,0,z^+\right)$ and $P_6\left(0,y^{++},z^{++}\right)$ could exist. When they exist, they are hyperbolic unstable and their local stability on manifolds is specified by the following proposition.

Proposition 1. Assume that $h\geq 1$. Then

(1) If $P_5\left(x^+,0,z^+\right)$ exists and $P_6\left(0,y^{++},z^{++}\right)$ does not, then $P_5\left(x^+,0,z^+\right)$ has a two-dimensional locally stable invariant manifold.

(2) If $P_6\left(0,y^{++},z^{++}\right)$ exists and $P_5\left(x^+,0,z^+\right)$ does not, then $P_6\left(0,y^{++},z^{++}\right)$ has a two-dimensional locally stable invariant manifold.

(3) Assume that both $P_5\left(x^+,0,z^+\right)$ and $P_6\left(0,y^{++},z^{++}\right)$ exists. Then

(a) If $f(\sqrt{\frac{g}{h}})>0$, then $P_5\left(x^+,0,z^+\right)$ has one-dimensional locally stable invariant manifold, and $P_6\left(0,y^{++},z^{++}\right)$ has a two-dimensional locally stable invariant manifold.

(b) If $f(\sqrt{\frac{g}{h}})<0$ and

$$\frac{(b_1-b_2)\sqrt{gh}}{b_1b_2(\sqrt{gh}+\alpha h)}\left(\frac{a}{c}\frac{1}{1+\sqrt{gh}}-1\right)>-f\left(\sqrt{\frac{g}{h}}\right)$$

holds, then $P_5\left(x^+,0,z^+\right)$ has one-dimensional locally stable invariant manifold, and $P_6\left(0,y^{++},z^{++}\right)$ has one-dimensional locally stable invariant manifold.

(c) If $f(\sqrt{\frac{g}{h}})<0$ and

$$\frac{(b_1-b_2)\sqrt{gh}}{b_1b_2(\sqrt{gh}+\alpha h)}\left(\frac{a}{c}\frac{1}{1+\sqrt{gh}}-1\right)<-f\left(\sqrt{\frac{g}{h}}\right)$$

holds, then $P_5\left(x^+,0,z^+\right)$ has two-dimensional locally stable invariant manifold, and $P_6\left(0,y^{++},z^{++}\right)$ has one-dimensional locally stable invariant manifold.

Stability analysis for the accelerated acute phase of CML

Theorem 2. Let a,b_1,b_2,c,A,B,C,g,G and h be positive parameters such that $a>c$, $A>C$, $b_1>b_2>B$, $\alpha d<D$. Then the system *(1)*, considered for $x\geq 0$, $y\geq 0$ and $z\geq 0$, has the following steady states:

(a) $O(0,0,0)$ and $P_1(d,0,0)$ are unstable equilibria;

(b) $P_2(0,D,0)$ and $P_3(0,0,d)$ are locally asymptotically stable equilibria;

(c) $P_4\left(x^+,0,z^+\right)$ given by *(6)*, if $gh<\left(\frac{a}{c}-1\right)^2$, and

(d) $P_5\left(0,y^{++},z^{++}\right)$ given by *(7)*, if $Gh<\left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right)$,

both $P_4\left(x^+,0,z^+\right)$ and $P_5\left(0,y^{++},z^{++}\right)$ are hyperbolic unstable equilibria;

(e) $P_6\left(x^{\#},y^{\#},z^{\#}\right)$ given by *(8)* and *(9)*, if $Gh<\left(\frac{A}{C}-1\right)\sqrt{gh}<\left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right)$ and *(12)* holds. The equilibrium $P_6\left(x^{\#},y^{\#},z^{\#}\right)$ is locally asymptotically stable if and only if $\delta_1>0$, $\delta_3>0$ and $\delta_1\delta_2>\delta_3$, where $\delta_1,\delta_2,\delta_3$ are given by *(13)*.

Remark 1. Notice that the stability on manifolds of the equilibria $P_4\left(x^+,0,z^+\right)$ and $P_5\left(0,y^{++},z^{++}\right)$ are the same as for the equilibria $P_5\left(x^+,0,z^+\right)$ and $P_6\left(0,y^{++},z^{++}\right)$ from the chronic case.

Numerical Simulations

Assuming the chronic phase of the disease, we analyze the separation surface between the basins of attraction of the asymptotically stable steady states. To verify and illustrate the theoretical results, we perform numerical simulations in two dimensions using the Maple package, and in three dimensions, the Matlab package LaguerreEig. We use the physiological values of parameters from [6]. As shown in [7], the control of the separation surface between the basins of attraction of the asymptotically stable equilibria is essential for the correction scenarios after stem cell transplantation.

The values of the parameters are

$$\begin{aligned}&a=0{,}23,\quad b_1=2{,}2\times 10^{-8},\quad b_2=1{,}1\times 10^{-8},\quad c=0{,}01,\\ &A=0{,}33,\quad B=5{,}5\times 10^{-9},\quad C=0{,}03,\quad g=25,\quad G=4,\quad h=20.\end{aligned}$$

Note that the following conditions hold:

$$a>c,\quad A>C,\quad b_1>b_2>B\quad\text{and}\quad d=10^9<D=1{,}81\times 10^9<\alpha d=2\times 10^9.$$

Also, the conditions for the existence of the equilibria $P_4\left(x^+,0,z^+\right)$ and $P_5\left(0,y^{++},z^{++}\right)$ are satisfied, namely

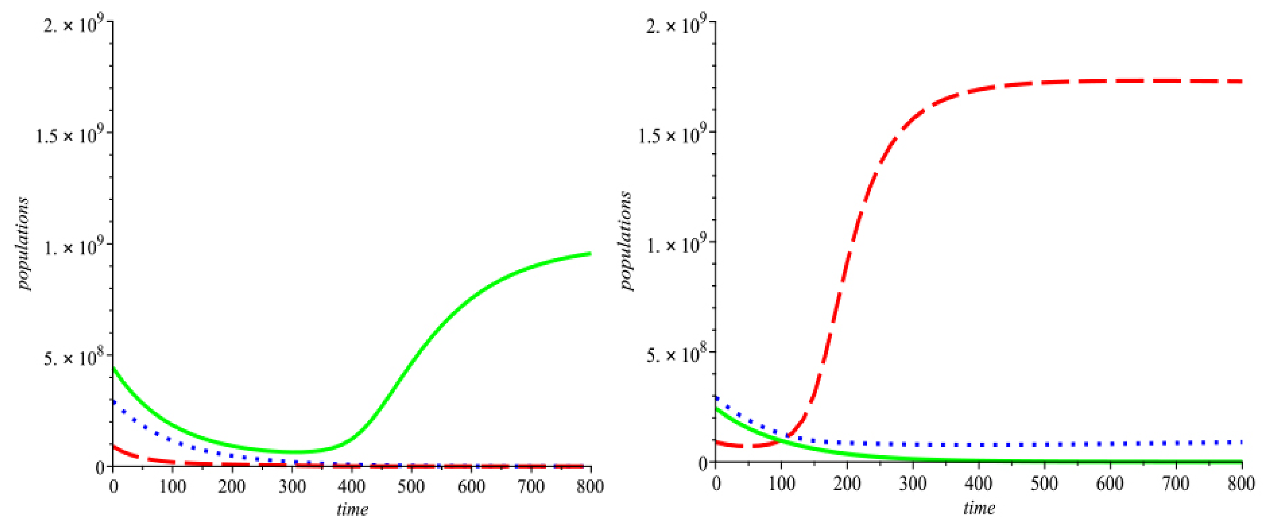
$$gh=500>\left(\frac{a}{c}-1\right)^2=484\ \text{ and }\ Gh=80<\left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right)=220,$$

but the condition for the existence of $P_6\left(x^{\#},y^{\#},z^{\#}\right)$ does not hold since

$$\frac{1+\sqrt{gh}}{1+G\sqrt{\frac{h}{g}}}=5{,}10313>\frac{d-\frac{1}{b_1}\sqrt{gh}}{D-\frac{G}{B}\sqrt{\frac{h}{g}}}=-0{,}01404\not>\frac{\left(1+\sqrt{gh}\right)\left(b_1+b_2\sqrt{\frac{g}{h}}\right)}{b_1\left(1+\sqrt{\frac{g}{h}}\right)\left(1+G\sqrt{\frac{h}{g}}\right)}=3{,}75625.$$

Hence, for this simulation, we have no $P_4\left(x^+,0,z^+\right)$ and $P_6\left(x^{\#},y^{\#},z^{\#}\right)$ as admissible equilibria, but there exists as admissible the equilibrium $P_5\left(0,1{,}85935\times 10^7,3{,}48656\times 10^7\right)$ whose corresponding eigenvalues are $-0{,}541229731006194,\ 0{,}347645655600619,\ 0{,}756347003900000$. Thus $P_5\left(0,y^{++},z^{++}\right)$ is an unstable equilibrium.

First, we perform our simulations in the two-dimensional case using the above values of the parameters. Figure 2(a), shows that the host normal cell population $x(t)$ (blue dotted line) and abnormal (or leukemic) cell population $y(t)$ (red dashed line) are eliminated, while the donor cell population $z(t)$ (green solid line) becomes arbitrarily close to the normal homeostatic amount d. This case corresponds to a successful transplant. In Figure 2(b), donor cell population $z(t)$ approach 0, while the normal and abnormal cell populations $x(t)$ and $y(t)$ tend toward $x^*=1{,}818181820\times 10^8$ and $y^*=1{,}636363636\times 10^9$, respectively. This means that in this case the transplant is unsuccessful.



(a) Successful transplant

(b) Unsuccessful transplant

Figure 2: Behavior of the normal, abnormal and donor cell populations with the initial data: **(a)** $x(0)=2{,}932\times 10^8$, $y(0)=0{,}896\times 10^8$, $z(0)=4{,}438\times 10^8$; **(b)** $x(0)=2{,}932\times 10^8$, $y(0)=0{,}896\times 10^8$, $z(0)=2{,}438\times 10^8$.

Figure 3 illustrates the numerical simulations in three dimensions. In black, it is represented the separation surface between the basin of attraction of the ‘goodéquilibrium $P_3(0,0,10^9)$ and the basin of attraction of the ‘badéquilibrium $P_4(1{,}818181818\times 10^8,\ 1{,}636363636\times 10^9,\ 0)$. The orbits starting from initial points located in the ‘good’basin (green orbits in Figure 2) remain entirely in that basin and in time approach P_3. Similarly, the orbits starting from initial points located in the ‘bad’basin (red orbits in Figure 2) remain entirely in that basin and in time approach P_4.

Of course, similar simulations can be performed for the following cases: (b) $P_4\left(x^+,0,z^+\right)$ is admissible and $P_5\left(0,y^{++},z^{++}\right)$ is not; (c) both $P_4\left(x^+,0,z^+\right)$ and $P_5\left(0,y^{++},z^{++}\right)$ are admissible.

This mathematically confirms the importance for the transplant success of the initial concentration of cells at the moment of transplantation.

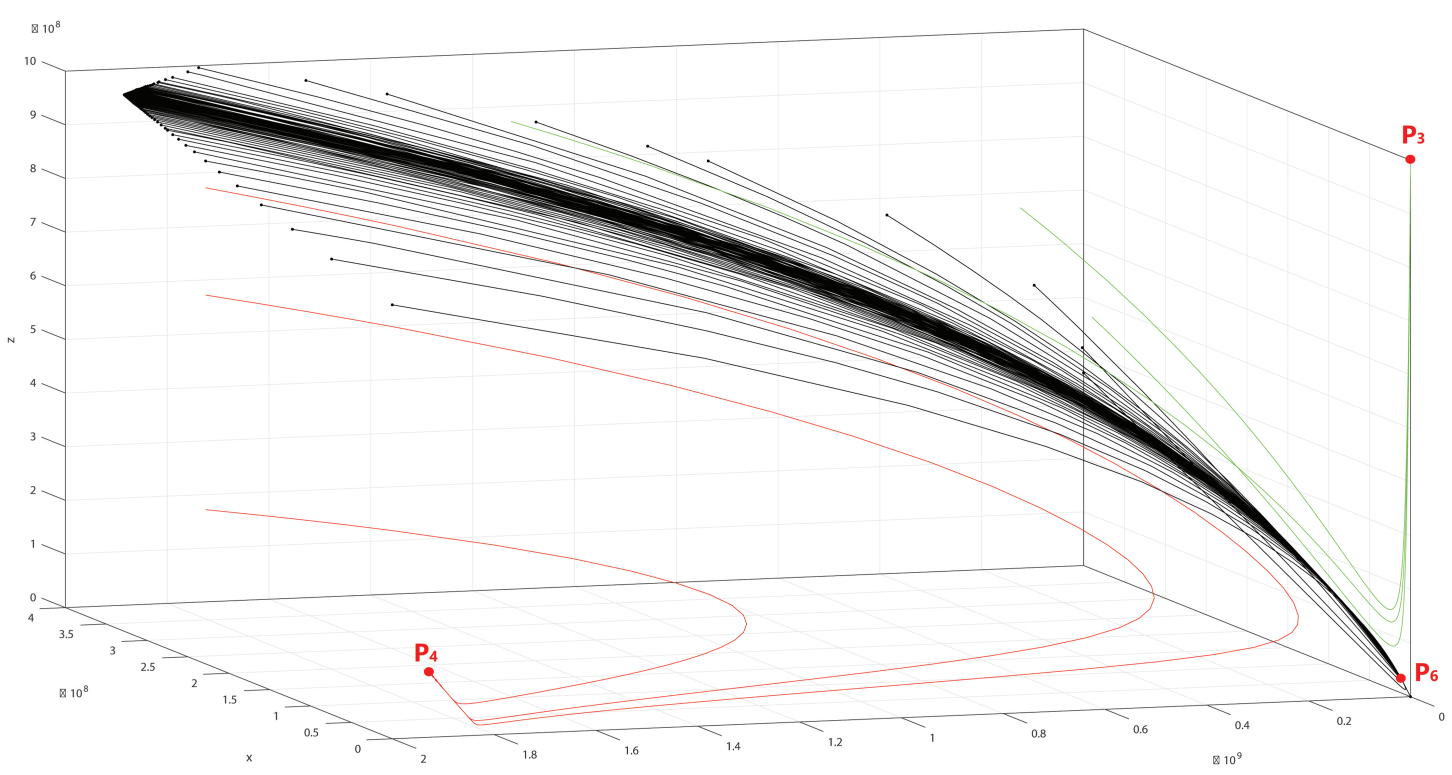


Figure 3: The separation surface between the ’goodánd the ’bad’basins of attraction.

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