A MATHEMATICAL MODEL FOR ALLOGENEIC BONE MARROW TRANSPLANTATION

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- S. Arghirescu, A. Cucuianu, R. Precup, M. Serban, *Mathematical modeling of cell dynamics after allogeneic bone marrow transplantation in acute myeloid leukemia*, to appear.
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AIMS: - propose simple models for mathematical understanding of cell dynamics in acute leukemia, before and after allogeneic bone marrow transplantation;

- give mathematical understanding and support to some clinical post-transplant therapies.

Leukemia = abnormal expansion of mutated hematopoietic clones associated with the inhibition of the surrounding normal cells

= evolutionary process of interaction and competition between normal and abnormal (leukemic) hematopoietic cells.

Modeling of leukemia: S.I. Rubinow & J.L. Lebowitz (1976), M.C. Mackey & L. Glass (1977), B. Djulbegovic & S. Svetina (1985), A.S. Fokas, J.B. Keller & B.D. Clarkson (1991: non-delay model), ...

recent contributions: D. Dingli, F. Michor, V. Volpert, L. Pujo-Menjouet, F. Crauste, M. Adimy, A. El Abdllaoui, ...

modeling of bone marrow transplantation: R. DeConde, P.S. Kim, D. Levy & P.P. Lee (2005)

Normal-leukemic system

Dingli & Michor 2006:

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

$x(t) =$ normal cell population
$y(t) =$ leukemic cell population

$a, A =$ growth rates
$b, B =$ microenvironment sensitivity rates
$c, C =$ cell death rates

Natural assumption: $a > c, \quad A > C$

Steady-states (equilibria): $[d, 0]$, $[0, D]$

$d := \frac{1}{b}\left(\frac{a}{c} - 1\right)$ maximal size of normal cell population

$D := \frac{1}{B}\left(\frac{A}{C} - 1\right)$ maximal size of leukemic cell population

Asymptotic stability:

$d > D$ (normal hematopoietic state)
$\Longrightarrow$ $[d, 0]$ is asymptotically stable

$d < D$ (leukemic hematopoietic state)
$\Longrightarrow$ $[0, D]$ is asymptotically stable

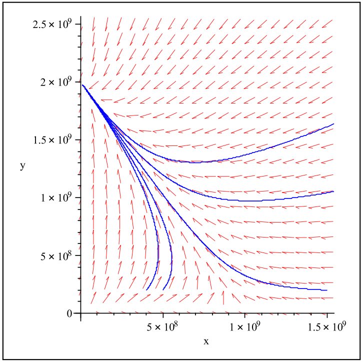

Figure 1: The phase portrait for the leukemic case $d < D$, where $d = 10^9, \;\; D = 2 \times 10^9$.

The orbits $[x(t), y(t)]$ approach the unique asymptotically stable equilibrium $[0, D]$. Hence:

$x(t)$ tends to 0 (no normal cells)
$y(t)$ tends to D (leukemic cells only)

Therapies should reverse inequality $d < D$ by:

- decreasing growth rate A or/and increasing sensitivity rate B and death rate C, when acting against malignant cells, and by
- increasing rate a or/and decreasing parameters b and c, when therapy is directed at normal cells.

If chemotherapy fails and the relation $d < D$ can not be reversed, the much more radical therapy of bone marrow transplantation could be recommended.

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Bone marrow transplantation (BMT) system:

The normal-leukemic system is modified and completed by a third equation corresponding to the infusion of donor's cells:

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

$z(t)$ = new population of donor cells
Here the growth inhibitory factors

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

take into account the cell-cell interactions,
- **quantitatively** by ratios $\frac{z}{x+y}$ and $\frac{x+y}{z}$, and
- **qualitatively** by parameters h, g, G standing for the intensity of *anti-graft, anti-host* and *anti-leukemia* effects

Numerical simulations:

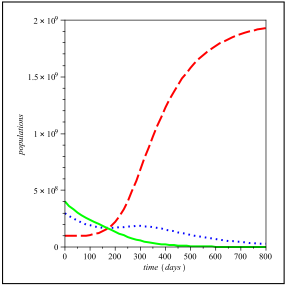
The post-transplant evolution ultimately lead either to:

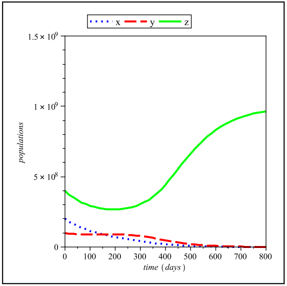
- normal homeostatic equilibrium $[0, 0, d]$ achieved by the expansion of the donor cells and the elimination of the host cells, or to

- 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.





Cases: (2) $g, G \gg h$ (strong anti-cancer, weak anti-graft) $\Rightarrow$ **good** chances:

(3) $g, G \ll h$ (weak anti-cancer, strong anti-graft) $\Rightarrow$ **bad** chances:

(4) $g \gg G, h$ (weak anti-cancer and anti-graft) $\Rightarrow$ chances **sensitive** to initial concentration:

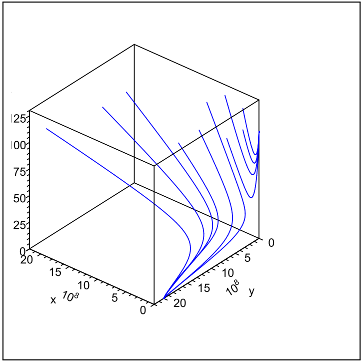


Figure 2: Phase portrait for leukemic case $d < D$, $d = 10^9$, $D = 2 \times 10^9$.

Two attractors exist:
the bad one $[0, D, 0]$ and
the good one $[0, 0, d]$.

Thus the orbits $[x(t), y(t), z(t)]$ approach either the good equilibrium $[0, 0, d]$, or the bad one $[0, D, 0]$ depending on initial concentrations $[x(0), y(0), z(0)]$.

Stability analysis:

Theorem: Assume the leukemic case $d < D$. Then system (BMT) 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) $P_4[x^+,0,z^+]$, if $hg < \left(\frac{a}{c} - 1\right)^2$, where

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

and *d)* $P_5[0,y^*,z^*]$, if $hG < \left(\frac{a}{c} - 1\right)\left(\frac{A}{C} - 1\right)$, where y^*, z^* solve

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

as unstable equilibria. Only one of P_4 or P_5 has a two-dimensional stable invariant manifold which is the border between attraction basins of P_2, P_3.

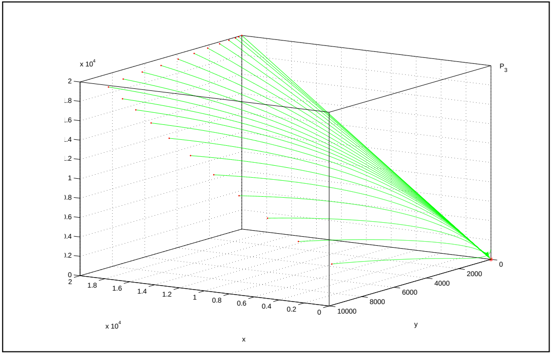


Figure 3: Border between the basins of attraction of the two asymptotically stable equilibria.

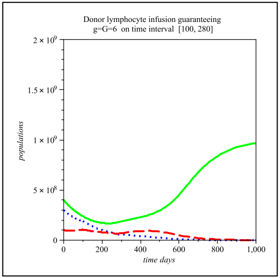
The basin of attraction of the good equilibrium increases (the border goes down) if A/C decreases; g, G increase and/or h decreases, explaining and suggesting post-transplant therapies.

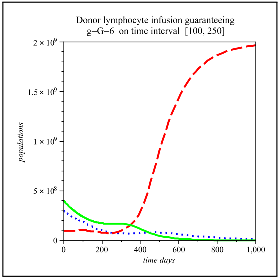
Post-transplant therapeutic scenarios

Numerical simulations with parameter values: $a = 0.23, A = 0.45,\ b = B = 2.2 \times 10^{-8}$, $c = C = 0.01,\ g = G = h = 2$ and initial data $x_0 = 3 \times 10^8, y_0 = 10^8, z_0 = 4 \times 10^8$

(unsuccessful transplant)

- **Scenario 1:** - donor lymphocyte infusions guaranteeing the increasing of parameters g, G from 2 to 6 on time interval after transplant [100,280] (6 months): Therapy successful.
- **Scenario 2:** - the same thepary as in Scenario 1 on time interval [100,250] (only 5 months): Therapy unsuccessful.





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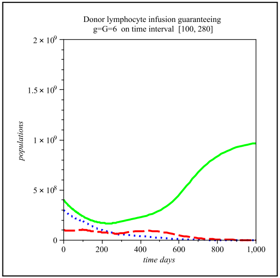
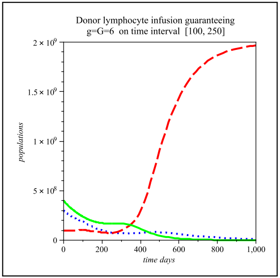
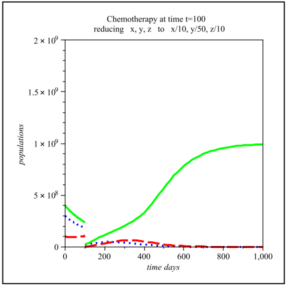
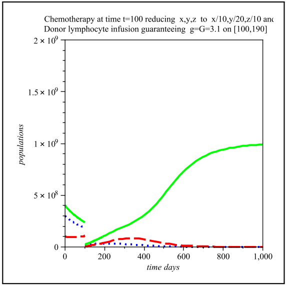




- **Scenario 3:** - chemotherapy at time $t = 100$ guaranteeing differential reduction of cell lines: from x, y, z to $x/10, y/50, z/10$: Therapy successful.
- **Scenario 4:** - chemotherapy at time $t = 100$ guaranteeing differential reduction of x, y, z to $x/10, y/20, z/10$ and additional - donor lymphocyte infusions guaranteeing the increasing of parameters g, G from 2 to 3.1 on time interval $[100, 190]$: Therapy successful.





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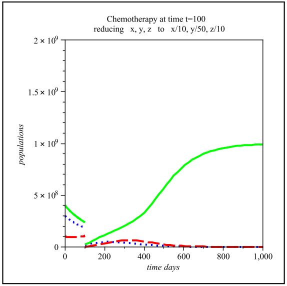

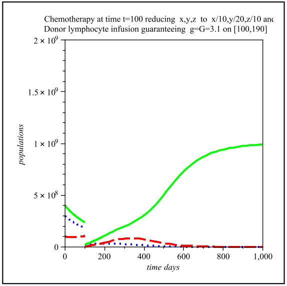

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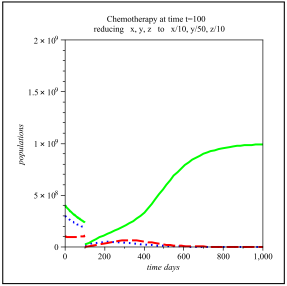

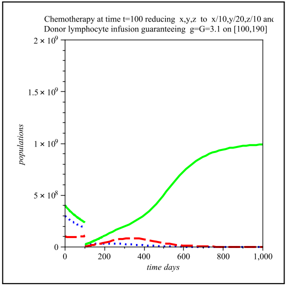

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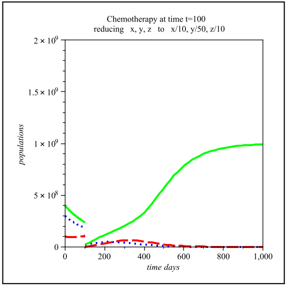

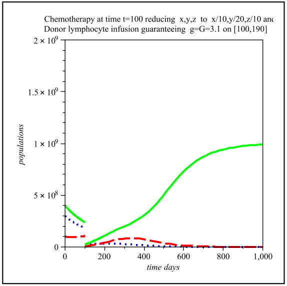

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