A Mathematical Approach to Cell Dynamics Before and After Allogeneic Bone Marrow Transplantation

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ABSTRACT. We shortly survey our recent contributions for a basic theoretical-mathematical understanding of cell dynamics in acute leukemia, before and after allogeneic bone marrow transplantation. Inspired by Dingli-Michor's approach, our theoretical models are given in terms of two- and three-dimensional ordinary differential systems whose parameters take into account essential biological properties, processes and interactions, and are involved in the characterization of normal or abnormal hematopoietic status, in the description of asymptotically stable steady-states and their basins of attraction and of therapeutic pre- and post-transplant strategies.

KEY WORDS: Dynamic system, Mathematical modeling, Numerical simulation, Hematopoiesis, Acute leukemia, Stem cell transplantation, Therapy.

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"L'essentiel des biomathématiques est la représentation de systèmes biologiques par des systèmes d'équations mathématiques ... qui permet de prédire l'évolution d'un système en fonction de stimuli divers sans avoir à refaire des expériences et surtout ... d'agir sur le système étudié en envisageant, par exemple, la définition de thérapeutiques ou de posologies optimales." (Yves Cherruault, Biomathématiques, Presses Universitaires de France, 1983)

1 From linear to nonlinear models of normal-leukemic cell dynamics

In [2], a theoretical model of leukemic hematopoiesis has been introduced according to the vital characteristics of the leukemic clones (proliferative rate and resistance to apoptosis). Based on this model, the author has proposed a classification of acute myeloid leukemias (AML) into two broad categories: (a) *high leukemic clone vitality* AML or *dominant* type AML, and (b) *low leukemic clone vitality* or *opportunistic* type AML. In this model, the *leukemic status* of a leukemia patient at a certain moment t (time since the initiation of leukemic clone proliferation, or from an arbitrarily chosen moment, for example the moment of diagnosis, the moment of relapse, etc.) is quantified by the ratio $S(t)$ between the number $y(t)$ of leukemic cells and the number $x(t)$ of normal cells: $S(t) = \frac{y(t)}{x(t)}$. Thus, a good leukemic status would be defined by a low ratio (more normal cells, less leukemic cells), and a bad status by a high ratio (more leukemic cells, less normal cells). Denote by y_0, x_0 the initial (at time $t_0 = 0$) number of leukemic and normal cells, respectively. Thus $y_0 = y(0)$ and $x_0 = x(0)$. Then the *leukemic cell vitality* LV and *normal cell vitality* NV can be defined by $LV := \frac{y_1}{y_0}$ and $NV := \frac{x_1}{x_0}$ where y_1, x_1 are the number of leukemic and respectively normal cells at time $t = 1$ (one day, for example), i.e., $y_1 = y(1)$ and $x_1 = x(1)$.

If we assume that the cell number growth is *linear*, then we immediately see that at any time t (in days since $t_0 = 0$),

$$\begin{aligned} x(t) &= (1 + (NV - 1)\, t)\, x_0 \\ y(t) &= (1 + (LV - 1)\, t)\, y_0. \end{aligned} \tag{1}$$

These are the growth laws of the normal and leukemic cells, respectively. Consequently, if we let $S_0 = \frac{y_0}{x_0}$, then one has

$$S(t) = S_0 \frac{1 + (LV - 1)\, t}{1 + (NV - 1)\, t}.$$

This is Formula (e) from [2] and represents a good estimation of the leukemic status for short time. Notice in this linear model the growth rates of the two cell populations are constant, that is

$$\frac{x(t+h) - x(t)}{h} = r_x \quad \text{and} \quad \frac{y(t+h) - y(t)}{h} = r_y$$

for all t, h, where $r_x = (NV - 1)\, x_0$ and $r_y = (LV - 1)\, y_0$. In terms of differential equations this can be put under the form of a simple uncoupled

system

$$\begin{cases} x'(t) = (NV-1)\, x_0 \\ y'(t) = (LV-1)\, y_0. \end{cases} \tag{2}$$

In reality the growth of cell populations is nonlinear due to temporal variations within each clone, to the competition (proliferation versus inhibition) between normal and leukemic cells originated in the so called "crowding effect" in the bone marrow microenvironment, etc. It was the aim of paper [4] to show the way that *nonlinear* models can be derived from the linear one if we consider that the rates r_x, r_y depend on time t and on cell populations $x(t), y(t)$ at that time, i.e.,

$$r_x = r_x(t, x(t), y(t)) \quad \text{and} \quad r_y = r_y(t, x(t), y(t)).$$

Thus, more realistic models should have the following form

$$\begin{aligned} x'(t) &= r_x(t, x(t), y(t)) \\ y'(t) &= r_y(t, x(t), y(t)). \end{aligned}$$

For instance, inspired by [5], in [3] the following coupled system was considered

$$\begin{cases} x'(t) = \left(\frac{a}{1+b(x(t)+y(t))} - c \right) x(t) \\ y'(t) = \left(\frac{A}{1+B(x(t)+y(t))} - C \right) y(t). \end{cases} \tag{3}$$

Here a, b, c and A, B, C stand for the intrinsic (in absence of any constraints) growth, microenvironment sensibility and death rates of normal cells and leukemic cells, respectively. The terms

$$\frac{1}{1+b(x(t)+y(t))}, \quad \frac{1}{1+B(x(t)+y(t))}$$

simulate the constraint due to the crowding effect in the bone marrow microenvironment and introduce competition between normal and leukemic cells. It is worth to note that if we ignore the crowding effect, that is, if we assume that $b = B = 0$, then the system reduces to the pair of Malthusian equations

$$\begin{cases} x'(t) = (a-c)\, x(t) \\ y'(t) = (A-C)\, y(t) \end{cases}$$

and the growth laws become exponential, which is again non realistic.

The goal of paper [3] was to show that there is a one-to-one correspondence between basic pathways through which the robustness of the

hematopoietic system can fail leading to leukemia, and the disjoint parameter states of system (3):

$$\begin{aligned} a &< A,\ b = B \ \text{ and } \ c = C; \\ a &= A,\ b > B \ \text{ and } \ c = C; \\ a &= A,\ b = B \ \text{ and } \ c > C. \end{aligned}$$

The first parameter state can be put into connection to the following pathways leading to leukemia: (A1) Presence of an abnormal variation occurring early, during the first or second divisions of the offspring stem cells, and (A2) Presence of abnormal variations with exceptional proliferative capacity. The second parameter state corresponds to pathway (B) Change of sensibility of particular clones caused by external catastrophic events or by intrinsic weakness of certain stem cells. Finally, the third parameter state characterizes case (C) Presence of abnormal variations that prevent cell death and confer relative "immortality". Of course two or all three of the parameter states and correspondingly of the above pathways, may occur making more complicated the leukemic status of the system.

Also, in [3] it was shown that (3) has two nonzero equilibria, pairs $[d, 0]$ and $[0, D]$, where

$$d := \frac{1}{b}\left(\frac{a}{c} - 1\right), \qquad D := \frac{1}{B}\left(\frac{A}{C} - 1\right)$$

represent the normal and leukemic homeostatic cell levels, respectively. It was proved that $[d, 0]$ is the unique asymptotically stable equilibrium in case that $d > D$ (normal hematopoiesis), while $[0, D]$ is the unique asymptotically stable equilibrium if $d < D$ (leukemic hematopoiesis). Figure 1 presents the phase portrait of system (3) in the leukemic case, when $d < D$.

According to model (3), to eradicate cancer, therapy should reverse the inequality $d < D$ by decreasing growth rate A or/and increasing sensibility 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.

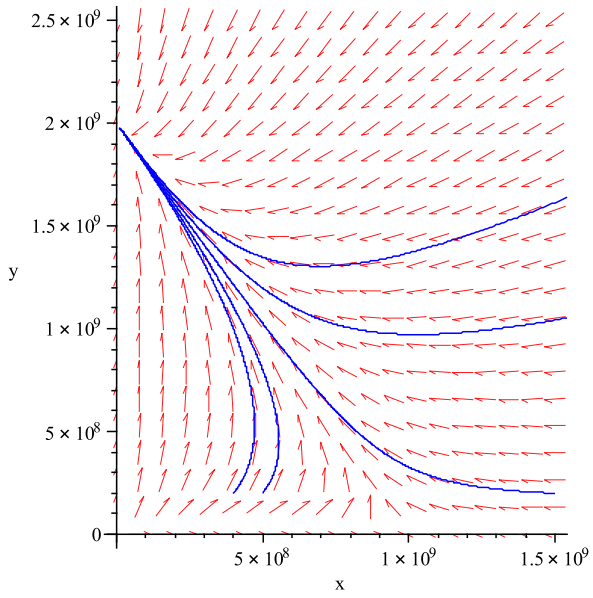

Figure 1: The phase portret of two-dimensional system (3) in the leukemic case $d < D$, where $a = 0.23$, $A = 0.45$, $b = B = 2.2 \times 10^{-8}$, $c = C = 0.01$, and $d = 10^9$, $D = 2 \times 10^9$. The orbits $[x(t), y(t)]$ approach the unique asymptotically stable equilibrium $[0, D]$. Hence $x(t)$ tends to 0 (no normal cells) and $y(t)$ approaches D (leukemic cells only).

2 The extended model to post-transplant cell dynamics

In [1] system (3) was modified and completed by a third equation corresponding to the infusion of donor's cells in case of bone marrow transplantation. Thus a three-dimensional system was introduced as a model of post-transplant cell dynamics:

$$\begin{cases} x' = \left(\frac{a}{1+b(x+y+z)} \frac{x+y+\varepsilon}{x+y+\varepsilon+gz} - c \right) x \\ y' = \left(\frac{A}{1+B(x+y+z)} \frac{x+y+\varepsilon}{x+y+\varepsilon+Gz} - C \right) y \\ z' = \left(\frac{a}{1+b(x+y+z)} \frac{z+\varepsilon}{z+\varepsilon+h(x+y)} - c \right) z. \end{cases} \tag{4}$$

Here z stands for the new population of donor cells, while parameters g, G, h measure the intensity of anti-host, anti-leukemia and anti-graft effects, respectively. The positive parameter ε was introduced in order to avoid singu-

larity, however, as was shown in [6], the mathematical analysis of the system can be realized even if $\varepsilon = 0$.

Numerical simulations performed in [1] 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. This conclusion was rigorously proved in [6] by a complete study of the steady-states of the system, of their asymptotic stability and basins of attraction. Figure 2 presents the phase portrait of the three-dimensional system (4) for the case $d < D$.

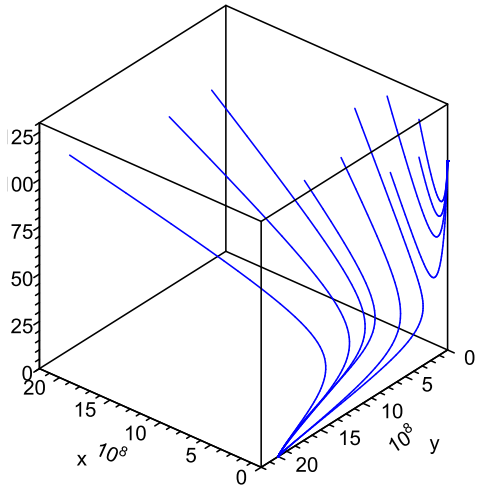

Figure 2: The phase portrait of the three-dimensional system (4) in the leukemic case $d < D$, where $a = 0.23$, $A = 0.45$, $b = B = 2.2 \times 10^{-8}$, $c = C = 0.01$, $g = G = h = 2$ and $d = 10^9$, $D = 2 \times 10^9$. Compared to the two-dimensional case, there exist two attractors: the bad one $[0, D, 0]$ 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 the initial concentrations $[x(0), y(0), z(0)]$.

Also in [1] we have suggested that model (4) can be used to control

the post-transplant patient evolution and guide it to the recovery of normal hematopoietic status. This can be realized step-by-step: we start to apply the model on the time interval $[0, t_1]$ (0 being the transplantation time). At time t_1 the patient state is evaluated and, if necessary, corrections are applied on cell concentrations and some of the parameters (e.g., the intensity of anti-leukemia effect [8]). Under the new parameters and initial data (at time t_1), the model is once again used to obtain solution x, y, z on the next time interval $[t_1, t_2]$. By repeating successively this procedure we can theoretically improve the evolution process and guide it towards normal hematopoiesis. Details and additional elements for a mathematical understanding and support of some clinical correction therapies after allogeneic bone marrow transplantation represent the goal of our forthcoming paper [7].

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