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Mathematical Models of the Leukemic Hematopoiesis

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Abstract. Starting from a classification of acute myeloid leukemias which takes into account the vital characteristics of the leukemic clones, we present several mathematical models for the understanding of the origin and the dynamic of these diseases and for providing a theoretical basis of more adapted therapeutic approaches.

Key Words: Hematopoiesis, Acute myeloid leukemia, Dynamic system, Numerical simulation

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1 Leukemic hematopoiesis

Acute myeloid leukemias (AML) are a group of clonal diseases originating in the myeloid stem cells or myeloid progenitors. They are characterized by the accumulation of immature (blastic) myeloid cells in bone marrow, blood and less often in other areas and by a syndrome of bone marrow failure [8]. According to the World Health Organization (WHO) classification of hematological malignancies, the determining criterion for AML diagnosis is a bone marrow blast percentage higher than 20% [12]. The incidence of AML is about 1/100,000/year under 30 years but grows steadily, reaching 10-12/100,000/year in the population over 60 years old. The natural clinical course is fatal, in a matter of days, up to several months from diagnosis, mainly from complications due to the bone marrow insufficiency, especially neutropenia-related infections and thrombocytopenia-related hemorrhage. Over the past five decades, due to steady improvements in therapy, survival was significantly prolonged, many patients actually being cured.

Even though individual AML cases share many clinical and hematological features, it has become apparent over the years that AML is in fact a very heterogeneous disease, some cases having a more indolent, protracted clinical course with relatively slow tumor growth while in other cases the evolution is aggressive, with a rapidly growing tumor burden. The response to chemotherapy also varies widely, some cases displaying rapid, complete and lasting responses, while others are primarily refractory to chemotherapy or experience only transitory responses. There have been many attempts to devise prognostic models, and the impact of several prognostic factors present at diagnosis was assessed in a number of clinical studies. Initial characteristics such as old age, previous treatment for other cancers, increased white blood cell count, certain cytological subentities and more importantly the presence of certain genetical abnormalities in leukemic cells were found to have a negative impact on the probability of response to therapy and overall survival. It has been shown that most AML clones are characterized by genetic defects leading to disorders of intracellular signaling mechanisms that govern the proliferation and differentiation processes

in myeloid cells. These defects consist of gene rearrangements, resulting from many possible mutational events, such as chromosomal deletions, translocations, acquisitions of genetic material, point mutations [11].

However if we now have a sizable amount of knowledge about how certain genetic changes are capable of inducing a leukemic phenotype (i.e. lack of differentiation and increased proliferation) in an individual myeloid clonogenic cell and subsequently in its progeny, it is less clear how such an aberrant clone interacts with the surrounding normal clones and why these normal clones are eventually inhibited, virtually disappearing from the leukemic hematopoietic microenvironment. This aspect is extremely important since it is usually the disappearance of normal cells and not the leukemic proliferation by itself that kills the AML patients.

2 Mathematical modeling of the leukemic-normal cell dynamic process

In [4], 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 first 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. The clinical and paraclinical characteristics of these groups are summarised as follows.

Dominant type AML - high proliferative rate and/or high cell death resistance:

- Similar prevalence in young and elderly adults;
- Sudden onset and rapid progression;
- One or two point mutations involving tyrosine kinases and/or transcription factors are responsible for the leukemic phenotype;
- Relatively senzitive to chemotherapy - high rate of complete remission and cure.

Opportunistic type AML - low proliferative rate and/or low cell death resistance:

- Much more frequent in elderly patients;
- Relatively slow progression; often preceded by myelodysplastic syndrome; sometimes previous exposure to radiotherapy or alkylating agents;
- Often multiple, complex cytogenetic abnormalities involving mostly loss of genetic material;
- Relatively resistant to chemotherapy - low rate of complete remission and cure.

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 $L(t)$ of leukemic cells and the number $N(t)$ of normal cells:

$$S(t) = \frac{L(t)}{N(t)}.$$

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 L_0, N_0 the initial (at time $t_0 = 0$) number of leukemic and normal cells, respectively. Thus $L_0 = L(0)$ and $N_0 = N(0)$. Then the *leukemic cell vitality* LV and *normal cell vitality* NV can be defined by

$$LV := \frac{L_1}{L_0} \quad \text{and} \quad NV := \frac{N_1}{N_0}$$

where L_1, N_1 are the number of leukemic and respectively normal cells at time $t = 1$ (one day, for example), i.e., $L_1 = L(1)$ and $N_1 = N(1)$.

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

$$\begin{aligned} N(t) &= N_0(1+(NV-1)t) \\ L(t) &= L_0(1+(LV-1)t). \end{aligned} \tag{2.1}$$

These are the growth laws of the normal and leukemic cells, respectively. Consequently, if we let $S_0 = \frac{L_0}{N_0}$, then one has

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

This is Formula (e) from [4] and represents a good estimation of the leukemic status for short time. Indeed, in case that $LV \gg 1$ and $NV = 1$, in other words when the leukemic clone is highly proliferative and /or apoptosis-resistant, and normal clones are healthy [4], we have that $N(t) = N_0$ is constant while, in time, the leukemic cell population increases indefinitely, i.e., $L(t) \to \infty$ as $t \to \infty$, which is physiologically excluded. Notice in this linear model the growth rates of the two cell populations are constant, that is

$$\frac{N(t+h)-N(t)}{h} = r_N \quad \text{and} \quad \frac{L(t+h)-L(t)}{h} = r_L$$

for all t, h, where

$$r_N = N_0(NV-1) \quad \text{and} \quad r_L = L_0(LV-1).$$

In terms of differential equations this can be put under the form of a simple uncoupled system

$$\begin{aligned} N'(t) &= N_0(NV-1) \\ L'(t) &= L_0(LV-1). \end{aligned} \tag{2.2}$$

In reality the growth of cell populations is non-linear 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. Thus

a more realistic approach would be to consider that the rates r_N, r_L depend on time t and on cell populations $N(t), L(t)$ at that time, i.e.,

$$r_N = r_N(t, N(t), L(t)) \quad \text{and} \quad r_L = r_L(t, N(t), L(t)),$$

or even more generally, on t and the evolution (history) of the two cell populations during a time interval $[t-\alpha_t, t-\beta_t]$ before t, where $0 \leq \beta_t \leq \alpha_t$. Hence

$$r_N = r_N(t, N_t, L_t) \quad \text{and} \quad r_L = r_L(t, N_t, L_t),$$

where by N_t, L_t we have denoted the functions

$$N_t(s) = N(t+s), \quad L_t(s) = L(t+s) \quad \text{for} \quad -\alpha_t \leq s \leq -\beta_t,$$

which may be treated as fragments of the functions N and L at the left of the point t, more exactly on the interval $[t-\alpha_t, t-\beta_t]$.

Now in order to estimate $N(t), L(t)$ at a given time t, we shall consider a division of interval $[0,t]$:

$$0 = t_0 < t_1 < ... < t_k < t_{k+1} < ... < t_n = t$$

where the lengths $t_{k+1} - t_k$ $(k = 0, 2, ..., n-1)$ of subintervals are small enough to assume that rates r_L, r_N are constant on each of these subintervals. More exactly, on each interval $[t_k, t_{k+1}]$, we shall approximate r_N, r_L by their values at time t_k, i.e.,

$$r_N \simeq r_N(t_k, N_{t_k}, L_{t_k}) \quad \text{and} \quad r_L \simeq r_L(t_k, N_{t_k}, L_{t_k}).$$

Then we can approximate $N(t)$, $L(t)$ as follows

$$\begin{aligned} N(t) &= N_0 + \sum_{k=0}^{n-1} (t_{k+1} - t_k)\, r_N(t_k, N_{t_k}, L_{t_k}) \\ L(t) &= L_0 + \sum_{k=0}^{n-1} (t_{k+1} - t_k)\, r_L(t_k, N_{t_k}, L_{t_k}). \end{aligned}$$

Obviously, the smaller the lengths of subintervals, the greater is the accuracy of the approximation. Then letting the length of the greatest subinterval , i.e. $\max(t_{k+1}-t_k)$, tends to zero, we obtain the *functional-integral equations*, the analogues of (2.1):

$$\begin{aligned} N(t) &= N_0 + \int_0^t r_N(s, N_s, L_s)\, ds \\ L(t) &= L_0 + \int_0^t r_L(s, N_s, L_s)\, ds \end{aligned}$$

which represent the *growth laws* of leukemic and normal cells. Next differentiation with respect to t gives the *functional-differential equations* [7], the analogues of (2.2):

$$\begin{aligned} N'(t) &= r_N(t, N_t, L_t) \\ L'(t) &= r_L(t, N_t, L_t). \end{aligned}$$

For instance, in [5] we have considered the following coupled system

$$\begin{aligned} N'(t) &= \left(\frac{a}{1+b(N(t)+L(t))} - c\right) N(t) \\ L'(t) &= \left(\frac{A}{1+B(N(t)+L(t))} - C\right) L(t). \end{aligned} \tag{2.3}$$

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

$$\frac{1}{1+b(N(t)+L(t))}, \quad \frac{1}{1+B(N(t)+L(t))}$$

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

$$\begin{aligned} N'(t) &= (a-c)\,N(t) \\ L'(t) &= (A-C)\,L(t) \end{aligned}$$

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

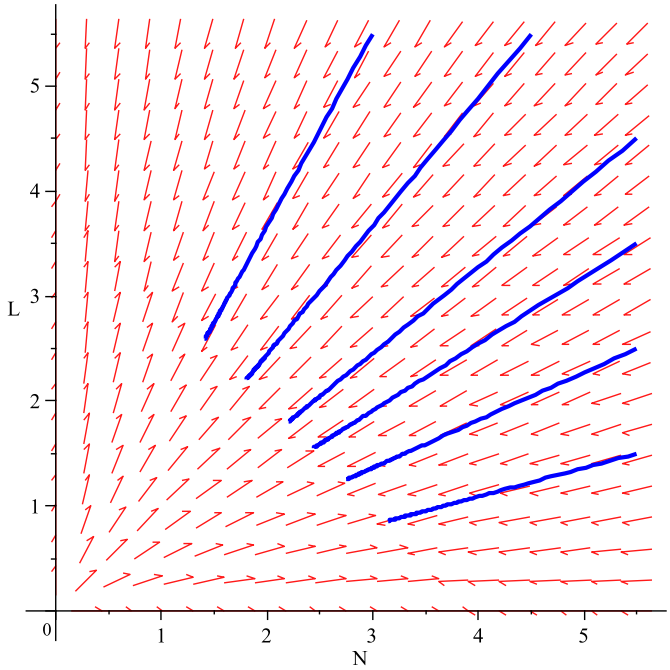

Figure 1: Transition case $d = D$: vector field and phase portret for $a = A = 0.3$, $b = B = 0.5$, $c = C = 0.1$, when $d = D = 4$. The orbits $[N(t), L(t)]$ approach equilibria located on the straight-line segment joining the points $[0, d]$ and $[d, 0]$.

In [5] we have shown that the normal and leukemic hematopoiesis are mathematically characterized by the inequalities

$$d > D \quad \text{and} \quad d < D,$$

respectively, where

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

Also, we have proved that if $d > D$ (normal hematopoiesis), then the pair $[d, 0]$ is the unique asymptotically stable equilibrium of the system, while if $d < D$ (leukemic hematopoiesis), then the unique asymptotically stable equilibrium is $[0, D]$. In the transition case $d = D$, a physiologically unstable situation, the equilibria are all pairs $[\alpha, d - \alpha]$ with $0 \leq \alpha \leq d$. Figure 1 and Figure 2 represent the phase portraits and vector fields of system (2.3) in two cases: $d = D$ and $d < D$, respectively.

We may think that a small total cell population $N(t) + L(t)$ does not influence significantly the growth rates; on the contrary, a large total cell population will reduce significantly these rates. Therefore, a better model (see [3, Section 3.7], [9]) would be the following system

$$\begin{aligned} N'(t) &= \left(\frac{a}{1 + b\left(N(t) + L(t)\right)^n} - c\right) N(t) \\ L'(t) &= \left(\frac{A}{1 + B\left(N(t) + L(t)\right)^n} - C\right) L(t) \end{aligned}$$

with $n > 1$. A further refining of the model could take into account the time lag in the production of cells (the duration of the cell cycle) and so to assume that the number of new cells at time t depends on the cell population at a previous time $t - \tau$, where τ corresponds to the cell development process. Then the model is expressed as a system with two delays τ_N and τ_L:

$$\begin{aligned} N'(t) &= \frac{a\, N(t - \tau_N)}{1 + b\left(N(t) + L(t)\right)^n} - cN(t) \\ L'(t) &= \frac{A\, L(t - \tau_L)}{1 + B\left(N(t) + L(t)\right)^n} - CL(t). \end{aligned}$$

Other models of hematopoiesis take into account age and maturity of cells and consequently are expressed by partial differential equations [1].

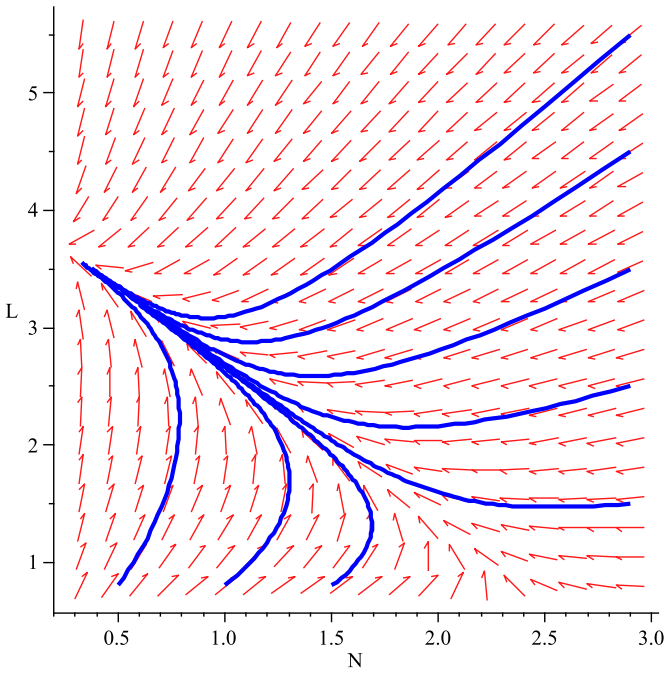

Figure 2: Leukemic case $d < D$: vector field and phase portret for $a = 0.25$, $A = 0.3$, $b = B = 0.5$, $c = C = 0.1$, when $d = 3$, $D = 4$. The orbits $[N(t), L(t)]$ approach the unique asymptotically stable equilibrium $[0, D]$. Hence $N(t)$ tends to 0 (no normal cells) and $L(t)$ approaches D (leukemic cells only).

3 Some open problems

1. Therapeutic and prognostic implications

The categorization of AML in dominant and opportunistic types may have therapeutic and prognostic implications. The natural history of AML is hard to observe nowadays in the developed world as most patients will receive some form of treatment, most patients with a good performance status receiving aggressive chemotherapy with curative intent. Even so, it is obvious to most clinicians that the cases with the

most "spectacular" and severe presentation symptoms such as severe hemorrhage, infection or leukostasis, are those with a high proliferative leukemic rate, while in those with a low proliferative rate, often with dysplastic features, the main presenting feature is anemia, sometimes of long duration and that such cases might survive for months on supportive therapy. Somewhat paradoxically, nowadays many of the former patients can be cured while practically none in the latter group achieve long lasting remissions.

Even though the standard approach to AML therapy is still aggressive combination therapy, new approaches are urgently needed. The description of recurring abnormalities in certain types of AML raises the hope that targeting such abnormalities might reverse the leukemic process. So far the best results in AML are reported with bone marrow transplantation (BMT). BMT is a complex treatment that combines the cytoreductive effects of high-dose chemo/radiotherapy with the immune benefits of the graft-versus-host/leukemia effect and the replacement of the hematopoietic environment with one obtained from a healthy donor. BMT in its standard form is however hampered by a high toxicity, leading to a high treatment-related mortality, making it largely unsuitable to elderly patients. Recently however, the advent of low-toxicity "miniallografts" in which the main benefits come from the graft-versus-host/leukemia and the marrow repopulating effects might make it much more suitable in opportunistic type AML in which the reestablishment of a normal environment and not a cytoreductive effect should be the main goal of treatment [10].

2. **Numerical simulation and therapeutic scenarios**

One major problem is to investigate the behavior of the mathematical model under non-constant parameters. For example, a death rate of cells which is constant on each interval from of a series of time intervals could be put in connection to recurrent chemotherapies. More generally, the constant system parameters can be replaced by control functions simulating the drugs effect. Numerical simulations of the resulted mathematical model could suggest better therapeutic strategies.

3. **Resonant chemotherapy**

Give a mathematical proof of the higher chance of chemotherapy (resonance [2]) in case of "true de novo" AML, when there is a fast proliferation of the cancer cells [6]. The mathematical model will take into account the shorter time interval between divisions.

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