Mathematical Biosciences 282 (2016) 174–180

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

About the discrete-continuous nature of a hematopoiesis model for Chronic Myeloid Leukemia

Marcos E. Gaudiano[a,b,*], Tom Lenaerts[c,d], Jorge M. Pacheco[b,e]

[a] CIEM-CONICET & Universidad Nacional de Córdoba, Ciudad Universitaria CP 5000, Córdoba, Argentina
[b] ATP-group, P-2744-016 Porto Salvo, Portugal
[c] MLG, Université Libre de Bruxelles, Boulevard du Triomphe CP212, Building O, 8th floor, 1050 Brussels, Belgium
[d] AI lab, Vrije Universiteit Brussel, Pleinlaan 2, 1050 Brussels, Belgium
[e] CBMA & DMA, Universidade do Minho, 4710-057 Braga, Portugal

ARTICLE INFO

Article history:
Received 3 August 2016
Revised 26 October 2016
Accepted 1 November 2016
Available online 2 November 2016

Keywords:
Hematopoiesis
Chronic Myeloid Leukemia
Discrete-continuous model
Moran's process
Peto's paradox

ABSTRACT

Blood of mammals is composed of a variety of cells suspended in a fluid medium known as plasma. Hematopoiesis is the biological process of birth, replication and differentiation of blood cells. Despite of being essentially a stochastic phenomenon followed by a huge number of discrete entities, blood formation has naturally an associated continuous dynamics, because the cellular populations can – on average – easily be described by (e.g.) differential equations. This deterministic dynamics by no means contemplates some important stochastic aspects related to abnormal hematopoiesis, that are especially significant for studying certain blood cancer deceases. For instance, by mere stochastic competition against the normal cells, leukemic cells sometimes do not reach the population thereshold needed to kill the organism. Of course, a pure discrete model able to follow the stochastic paths of billons of cells is computationally impossible. In order to avoid this difficulty, we seek a trade-off between the computationally feasible and the biologically realistic, deriving an equation able to size conveniently both the discrete and continuous parts of a model for hematopoiesis in terrestrial mammals, in the context of Chronic Myeloid Leukemia. Assuming the cancer is originated from a single stem cell inside of the bone marrow, we also deduce a theoretical formula for the probability of non-diagnosis as a function of the mammal average adult mass. In addition, this work cellular dynamics analysis may shed light on understanding Peto's paradox, which is shown here as an emergent property of the discrete-continuous nature of the system.

1. Introduction

Hematopoiesis is the process for the generation of all cellular blood elements. A continuous supply of cells is necessary to compensate for the loss of cells due to apoptotic senescence or migration out of the circulating compartment. Blood cell formation has at its root hematopoietic stem cells (HSC) that have the dual property of self renewal and the ability to differentiate into all types of blood cells [1–3].

Allometric scaling laws of observables in biological organisms are widely known and a general model for the origin of many of them can be found (e.g.) in [4]. The number N of HSC that a mammal possesses is an example of this, because it can be written as a function of the adult average mass M in the form:

$$N = N_{SC} M^{3/4}, \tag{1}$$

with $N_{SC} = 15.9\ \mathrm{kg}^{-3/4}$, as it was stated in [5].

In [6] the authors provided a simple model for human hematopoiesis in which the observed exponential expansion of cells from the active stem cell pool to the mature cells is naturally incorporated, as 32 cellular differentiation stages (compartments) composed of approximately N_i cells satisfying $N_{i+1}/N_i \approx 1.93$ ($i = 1, \ldots, 31$). The same idea was later generalized for mammals [7].

A discrete-continuous model for Chronic Myeloid Leukemia (CML) in humans was developed in [8], able to reproduce the rarely (but statistically significant) cases in which the pacient does not die of cancer, simply because leukemic cancerous cells sometimes by chance do not proliferate. The authors concluded that it was enough to assume just the first $k = 7$ differentiation compartments as discrete/stochastic quantities and continuous/deterministic the rest.

Using a similar mathematical model, CML and other hematological deceases were studied across mammals of arbitrary mass M in

* Corresponding author.
E-mail address: marcosgaudiano@gmail.com (M.E. Gaudiano).

http://dx.doi.org/10.1016/j.mbs.2016.11.001
0025-5564/

[9], where the authors mentioned that the total number k of compartments assumed as stochastic is a mass dependent quantity.

This is the starting point of the present work, in which we study –in detail– the M–dependence of the discrete-continuous limit k, in the context of CML. The article is organized as follows: in Section 2 we briefly describe the mathematical model for CML under consideration; in Section 3 we unveil the explicit functional relation between k and M, explaining how it arises from some physical and biological assumptions; this enables us in Section 4 to deduce a theoretical formula for the CML non-diagnosis probability of a mass M mammal, which has a single cancerous stem cell within its bone marrow; some important implications on Peto's paradox [10] are discussed in Section 5.

2. The model

As mentioned above, we follow the CML models of [8] and [9] in which blood is assumed to be produced inside of the bone marrow and composed of cells that can be imagined as distributed along 33 compartments labeled by $i = 0, 1, 2, \ldots, 32$, according to their increasing degree of cellular differentiation. The (*active*) stem cell pool corresponds to $i = 0$, has an approximately constant number N (Eq. (1)) of cells along the life span of the animal and originates all the rest of blood elements [5]. For normal hematopoiesis, every differentiated compartment is in equilibrium, having a cellular population approximately given by

$$N_i = \gamma^i \frac{N}{2\epsilon} \qquad i = 1, \ldots, 32, \tag{2}$$

where $\gamma = 1.93$, N is given by Eq. (1) and $\epsilon = 0.85$ is the probability of differentiation after a cell division.

Leukemic cells are assumed here to be descendent of a single cancerous stem cell that arises in the bone marrow at some time $t = 0$ during the life of the animal. The compartments are also shared by the leukemic cells because these follow the same differentiation tree and replicate each stage at the same rate normal cells do. The distinct feature that characterizes the cancerous cells is a lower probability of differentiation $\epsilon_c = 0.72 < \epsilon$ [9,11], that ultimately triggers the abnormal over-production of blood[1] associated to CML diagnosis. Clearly, this constitutes a Darwinian type selection process, in which the cancerous cells are better fitted to the environment and have potentially a relative advantage with respect to the rest [12].

Lower differentiation compartments cells will be imagined as discrete entities following a stochastic dynamics.

First, in order to reproduce the fact that the stem cell pool undergoes no amplification along the CML decease [8], this compartment will be simulated as a Moran's process. This will be initially composed of $N - 1$ healthy cells (Eq. (1)) and only one leukemic stem cell (LSC) that potentially triggers CML. On average, at a rate $r_0 = RM^{-1/4}$ ($R = 2.9\text{kg}^{1/4}\text{yr}^{-1}$) every cell of this pool is chosen at random for reproduction and subsequently another cell is chosen for export (differentiation), remaining constant the cell population.

Every cell of the subsequent (ith) differentiation compartments ($i = 1, 2, 3, \ldots$) divides into a pair of daughter cells at the specific rate $r_i = RM^{-1/4} r^i$ ($r = 2\epsilon/[\gamma(2\epsilon - 1)] = 1.26$). With a probability ϵ, the daughter cells *differentiate* (becoming members of the following $(i+1)$th compartment), and with a probability $1 - \epsilon$ they just *duplicate* (staying at the same ith compartment). The cancerous cells follow the same dynamics of any normal cell, but with the different probability of differentiation ϵ_c mentioned above. Initially, there are no leukemic cells inside of these differentiated compartments.

[1] Specifically, there is an unregulated growth of granulocytes, which are a type of white blood cells

The size of the compartments goes exponentially with the differentiation degree, even for normal hematopoiesis (Eq. (2)). Consequently, higher differentiation compartments become numerically uncontrollable under the above stochastic dynamics. Hence, for some suitable integer k, the time-dependent population $N_i(t)$ of higher compartments healthy cells (i.e. $i > k$) are modelled in a continuous way, as the solution of the following set of differential equations:

$$\begin{aligned} \dot{N}_1 &= (1 - 2\epsilon) r_1 N_1 + r_0 N_0(t) \\ \dot{N}_i &= (1 - 2\epsilon) r_i N_i + 2\epsilon r_{i-1} N_{i-1}, \qquad i = 2, \ldots, 32, \end{aligned} \tag{3}$$

where $N_0(t) = const. = N - 1$, $N_i(0) = N\gamma^i/2\epsilon$ ($i = 1, \ldots, 32$, see Eq. (2)), and where $N_k(t)$ is obtained from the discrete part of the model.[2] Easily, we can see that Eq. (3) are just the *average* deterministic version of the lower compartments stochastic dynamics.

Similarly, by just replacing ϵ by ϵ_c in Eq. (3), we get to the equations for the continuous dynamics of the $N_i^c(t)$ higher compartments cancerous cells ($i > k$), for $N_0^c(t) = const. = 1$ and starting from the initial conditions $N_i^c(0) = 0$ ($i = 1, \ldots, 32$).

The population of the healthy and cancerous cells of each compartment were numerically computed by running the software SCML,[3] which incorporates the discrete-continuous dynamics described above, under the assumption of a simulation time t bounded by the theoretical life span $L = L_0 M^{1/4}$, where $L_0 = 8.6$ $\text{kg}^{-1/4}\text{yr}$ [19].

The number of stochastic compartments is an input of SCML, as well as the mammal mass M. By varying these parameters, the software was run a huge number of times. The final outcome of every simulation was either *alive (non-diagnosed)* or *dead (diagnosed)* according to the same criteria of [9].[4]

By mere stochastic competition, the cancer cells sometimes simply do not proliferate and their total population does not reach the thereshold needed to kill the animal. Consequently, the total number of stochastic compartments (defined by k) must be chosen in order to reproduce this very important fact, that cannot be incorporated by a purely continuous model.[5]

Assuming only the first i compartments to be stochastic, a probability of non-diagnosis $P_i = P_i(M)$ can be statistically computed. Fig. 1 shows the overall numerical result for $M = 105$ kg ($i = 0, 1, 2, 3, \ldots$). The discrete-continuous limit $k = k(M)$ should point out the 1st of the compartments whose stochastic nature does not determine the final state of the system, being the animal's fate (alive or dead) completely predicted by what happens on the first $k(M)$ cellular compartments. Then, it is convenient to choose k as the label i where P_i starts its final convergence towards the *real* probability of non-diagnosis $p = p(M)$. This can be mathematically stated by defining k as the 1st label, for which the relative variation of the P_i's remains bounded by a (given) tolerance T as follows:

$$\frac{|P_{i+1} - P_i|}{P_i} \leq T, \qquad i \geq k \tag{4}$$

(see Fig. 2). In [8] and [9], the authors did not take exactly the same route for defining k. They even considered the convergence of the average *time to diagnosis* $t_i = t_i(M)$ ($i = 0, 1, 2, \ldots$). In any case, they did not study this issue by using a relation like Eq. (4).

[2] Note that $N_k(t)$ determines $N_i(t)$, $i = k+1, k+2, \ldots, 32$

[3] Developed by T. Lenaerts

[4] Specifically, the *diagnosis condition* is reached whenever $N_{32}(t) + N_{32}^c(t) > 3N_{32}$ ($\approx 10^{12}$ for $M = 70$kg, which is the CML diagnosis condition for humans [14])

[5] Due to lower differentiation probability than the rest ($\epsilon_c < \epsilon$), the natural tendency of the cancerous cells will be to overgrow. Even they can often overtake the healthy cells population by far. There is a 100% probability that this will kill an average-sized animal, if every compartment follows a continuous dynamics (Eq. (3)), despite assuming that the cancerous cells were originated by just a single leukemic stem cell [9,13].