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Quantitative Analysis of Hematopoietic and Leukemic Stem Cell Dynamics in Acute Myeloid Leukemia: A Mathematical Approach

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ABSTRACT

This study aims to unravel the growth dynamics of hematopoietic and leukemic stem cells within the bone marrow, viewing them as a complex network of interconnected compartments representing distinct stages of cellular differentiation. Leveraging insights from established models of cancer cell growth, we have undertaken a comprehensive re-examinations and reinterpretation of some classical growth models, subsequently reformulating them into a fractional order derivative-based framework. Employing this innovative approach, we have delved into the intricate interplay between self-renewal and proliferation rates across diverse sub-stages of cellular differentiation. Our investigations illuminate the nuanced regulatory mechanisms governing stem cell dynamics, offering significant insights into the pathophysiology of hematopoietic disorders, notably acute myeloid leukemia.

KEYWORDS: Hematopoietic stem cells, Leukemic stem cells, Bone marrow, Growth dynamics, Compartmental modeling, Fractional order derivatives, Self-renewal, Proliferation rates, Cellular differentiation, Acute myeloid leukemia.

INTRODUCTION

In recent years, scientific investigations have revealed the presence of cell populations within certain cancers, such as leukemia, that exhibit characteristics reminiscent of stem cells. These cells possess the capacity for self-renewal, allowing them to proliferate and generate additional copies of themselves. Additionally, they demonstrate pluripotency, enabling them to differentiate into various cell types observed within the tumor. This discovery holds significant implications for our comprehension of cancer progression mechanisms, shedding light on the intricate processes governing tumor development and metastasis [14, 33, 56, 62,74,95]. Furthermore, it presents novel avenues for therapeutic intervention strategies aimed at selectively targeting these stem cell-like populations, offering promising prospects for enhancing treatment efficacy and patient outcomes. The human bone marrow serves as a dynamic reservoir for hematopoietic stem cells (HSCs) responsible for the continuous replenishment of the body's blood cell populations throughout life. This process involves a finely regulated balance between self-renewal and differentiation, ensuring the production of mature blood cells while maintaining the HSC pool [25, 45, 54, 62, 86]. However, dysregulation of these mechanisms can lead to hematopoietic disorders such as acute myeloid leukemia (AML), characterized by uncontrolled proliferation of leukemic stem cells (LSCs) and impaired differentiation. Cancer is the result of the abnormal growth of cells caused by cellular mutations [2,3,12, 35,51, 65, 84, 96].

Leukaemia is one such cancerous disease in which Hematopoietic Stem Cells show abnormal proliferation, affecting the functionality and population of other blood cells. Hematopoietic stem cells are in the bone marrow and peripheral blood from where they differentiate and proliferate to develop erythrocytes, leucocytes, and platelets. It is believed that leukemic stem cells resulted from acquired mutations in hematopoietic stem cells; leukemic stem cells are considered small population of leukemic cells which develops into mature blasts and are considered the origin of leukaemia development. Understanding the growth dynamics of both normal and leukemic stem cells is crucial for elucidating the pathogenesis of AML and developing effective therapeutic strategies. Mathematical modeling provides a powerful tool for investigating these complex processes, allowing for the simulation and analysis of cellular behaviour under different conditions. In this study, we aim to explore the growth dynamics of HSCs and LSCs within the bone marrow microenvironment using a compartmental

modeling approach. Building upon previous research by some researchers, we have reanalysed and adapted classical models of stem cell growth to incorporate fractional order derivatives [6,11, 19, 21,28,35,41, 63, 83, 97]. This novel approach enables us to capture the non-integer order dynamics inherent in biological systems more accurately. By considering the bone marrow as a system of interconnected compartments representing different stages of cellular differentiation, we seek to elucidate the regulatory mechanisms governing HSC and LSC dynamics.

Through our computational analyses, we aim to investigate the dependence of cellular behavior on key parameters such as self-renewal and proliferation rates. By comparing the predictions of our fractional order derivative-based models with those of classical ordinary differential equation models, we aim to gain deeper insights into the complex regulatory networks underlying hematopoietic and leukemic stem cell dynamics [36,40,43,47,52,58,76,98]. Such insights have the potential to inform the development of novel therapeutic approaches for AML and other hematopoietic disorders [1,4,9]. Since leukemic stem cells have high self-renewal capacity and multi-directional differentiation potential, it can give rise to different types of leukaemia [2,3,30,34,61,75,87]. For instance, stem cells developing into myeloid progenitor can potentially give rise to myeloid leukaemia that affects the erythrocytes and leucocytes, while the lymphoid progenitor affects T and B lymphocytes and given rise to lymphoblastic leukaemia [17, 23, 24,72,79,99]. Mathematical modelling gives an edge in Oncology, especially in blood cancer research, as it has a significant potential to develop strategies for disease characterisation, tumour study, and personalised treatments. Blood cancers, including leukaemia, have been widely studied with applied mathematics [5,7,8,53,71,8189]. Hematopoietic Stem Cells are multipotent stem cells and the building blocks of leukocytes, erythrocytes, and platelets produced regularly with the process of haematopoiesis [12,16,18]. These somatic cells are characterized by their efficiency in proliferation, self-renewal, resistance to apoptosis, and differentiation [8,18,22,27,44,68,77,92].

Proliferation refers to the process by which stem cells divide and give rise to daughter cells that can further differentiate into specialized cell types. This ability of stem cells to undergo mitotic division plays a crucial role in replenishing the pool of progenitor cells and maintaining tissue homeostasis. On the other hand, self-renewal rate refers to the capacity of stem cells to maintain their undifferentiated state and continue to exist within the same compartment or niche where they originate. This process ensures the long-term maintenance of the stem cell population and is essential for sustaining tissue regeneration and repair over time. Apoptosis, also known as programmed cell death, is a highly regulated process in which cells undergo self-destruction in response to various stimuli or as part of normal physiological processes [9,13,15,26,42,55,73,94]. When a cell is damaged beyond repair or becomes obsolete, apoptosis allows it to be eliminated from the tissue without causing inflammation or damage to neighboring cells. This mechanism plays a crucial role in maintaining tissue homeostasis, eliminating potentially harmful or abnormal cells, and regulating cell population size during development and throughout life. It is an essential component to maintain the immunity and human health conditions. However, resistance to apoptosis leads to the development of tumour cells. Hematopoietic stem cells generate multiple lineages of post-mitotic mature cells through successive production of intermediate progenitors [18,20,37,44,48,57,69,90]. They undergo multiple cellular divisions, giving rise to myeloid and lymphoid progenitors. While lymphoid cells produce natural killer cells and lymphocytes (give rise to T & B lymphocytes), myeloid cells undergo further division to produce a variety of cells including erythrocytes, thrombocytes, and other myeloblast cells [8,10,22,31,39,59,80].

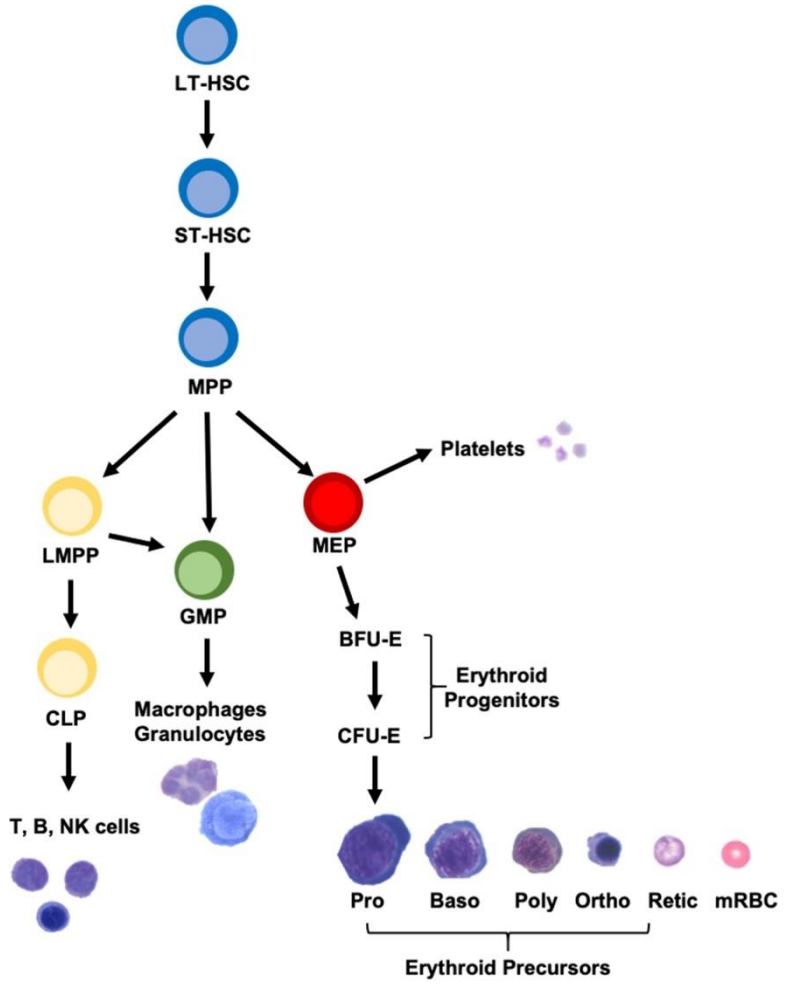

Fig.1: Development of the different blood cells from haematopoietic stem cell to mature cells

Based on this cell differentiation, leukaemia can be myeloid and lymphoblastic. Therefore, we classify leukaemia into four categories, Acute Myeloid Leukaemia, Chronic Myeloid Leukaemia, Acute Lymphoblastic Leukaemia, and Chronic Lymphoblastic Leukaemia [4,23,29,46]. Myeloid leukaemia is believed to be more organized than lymphoblastic leukaemia and are more common among adults. Acute myeloid leukaemia is widely studied as it is most common among adults with nearly 80% of all the cases [1]. The mutation of the genes involved in haematopoiesis results in acute myeloid leukaemia, however, the exact cause of mutation is unknown. It affects the bone marrow and the only treatment is chemotherapy followed by bone marrow transfusions [12,23,38,60,67]. Another group of myeloid leukaemia is chronic myeloid leukaemia caused by unregulated signal transduction by tyrosine kinase, a type of cytokine signalling [2,18,78,88]. It is characterised by consistent chromosomal abnormality called the Philadelphia (Ph) chromosome, generated by a reciprocal translocation between chromosomes 9 and 22. BCR-ABL is the hallmark hybrid gene present in Ph chromosome responsible for tyrosine kinase signalling. Thus, the resulting abnormalities characterize the chronic myeloid leukaemia [22,25,82,91].

Acute lymphoblastic leukaemia is observed in both adults and children, but more common among adolescent children. Malignancy of B or T lymphocytes, i.e., uncontrolled proliferation of abnormal, immature lymphocytes and their progenitors characterize acute lymphoblastic leukaemia. [12,32,49] The treatment for ALL include induction therapy, high-dose therapy, and maintenance therapy where different chemotherapeutic drugs are given to the patient. In several cased, bone marrow transplantation is also needed. However, chemotherapy have shown improved results over the time. Recently, the treatment focus has shifted to CAR-T cell immunotherapy. However, the toxic side effects such as cerebral edema and cytokine release syndrome are also present. Chronic lymphoid leukaemia is a chronic abnormal proliferation of mature but dysfunctional B lymphocytes. The disease is characterised by the development of morphologically mature but immunologically dysfunctional B-lymphocytes [4,24,85,93]. Leukaemia stem cells are the immature stem cells that initiates the development of leukemic cell line in the bone marrow and peripheral blood. It is believed to be originated from mutated hematopoietic stem cells and possesses similar basic characteristics compared to normal hematopoietic stem cells, i.e., ability to

proliferate, self-renewal proficiency, response to apoptosis, and multipotent differentiation [6,18, 32,50,70].

Formulation of the Problem: The following mathematical model developed by Thomas Steihl and A. Marciniak-Czochra [6-11] describes the dynamics of hematopoietic and leukemic cells in acute myeloid leukaemia based on three primary parameters, self-renewal rate ($a_i^{c\ or\ l}$), proliferation rate ($p_i^{c\ or\ l}$), and death rate ($d_i^{c\ or\ l}$) [6, 7, 18]. The model is based on the understanding of the haematopoiesis process such that stages of cell differentiation were assumed as compartments (ordered sequence of differentiation)[8,64]. The time-dependent ordinary differential equations were developed to describe the cell densities (or population) for hematopoietic and leukemic cells [6].

Hematopoietic cell line:

$$\frac{dc_1}{dt} = \left(2a_{1,max}^c s(t) - 1\right)p_1^c c_1(t) - d_1^c c_1(t)$$

$$\frac{dc_i}{dt} = 2\left(1 - a_{i-1,max}^c s(t)\right)p_{i-1}^c c_{i-1}(t) + \left(2a_{i,max}^c s(t) - 1\right)p_i^c c_i(t) - d_i^c c_i(t)$$

$$\frac{dc_n}{dt} = 2\left(1 - a_{n-1,max}^c s(t)\right)p_{n-1}^c c_{n-1}(t) - d_n^c c_n(t)$$

Leukemic cell line:

$$\frac{dl_1}{dt} = \left(2a_{1,max}^l s(t) - 1\right)p_1^l l_1(t) - d_1^l l_1(t)$$

$$\frac{dl_i}{dt} = 2\left(1 - a_{i-1,max}^l s(t)\right)p_{i-1}^l l_{i-1}(t) + \left(2a_{i,max}^l s(t) - 1\right)p_i^l l_i(t) - d_i^l l_i(t)$$

$$\frac{dl_m}{dt} = 2\left(1 - a_{m-1,max}^l s(t)\right)p_{m-1}^l l_{m-1}(t) - d_m^l l_m(t)$$

The number of compartments is denoted by n. In the hematopoietic cell line, the first compartment denotes the hematopoietic stem cell population, while the n^{th} compartment denotes the post mitotic mature population [7]. The number of cell compartments in between 1 and n is denoted by i, where $i \in [2, n-1]$. Similarly, the first compartment in the leukemic cell line denotes leukemic stem cell population and the post mitotic mature blasts are denoted by m^{th} compartment. The cell densities of hematopoietic cell population in the compartment j at time t are denoted by $c_j(t)(j = 1, 2, \ldots . n)$, while $l_j(t)(j = 1, 2, \ldots . n)$ denotes the cell densities for leukemic cell population [7]. Fraction of self-renewal rate ($a_i^{c\ or\ l}(t)$): Self-renewal rate is the fraction of daughter cells returning to the compartment where the mother cell is present. It is also assumed that the self-renewal rate is linearly related to the negative feedback signalling. Thus, $a_i = a_{i,max}s(t)$, where $a_{i,max}$ is the maximum self-renewal fraction [17, 23]. Fraction of proliferation rate ($p_i^{c\ or\ l}(t)$): Proliferation rate depicts the fraction of cells divide per unit time such that the proliferation rate for the nature post-mitotic cells is identical to zero, i.e., $p_n^c(t) \equiv 0$ and $p_m^l(t) \equiv 0$ [4, 7].

Death rate ($d_i^{c\ or\ l}(t)$): Death rate is the fraction of cells die per unit time for each compartment. [12, 17] The classical time-based differential equations are based on the treatment of cell cycle as a well-mixed population, from which cell may either proliferate at the rate $p(t)$ or die at the death rate d. For simplicity, death rate can be considered zero for every compartment except the post mitotic cell compartment, i.e., n^{th} compartment [17, 18]. For the i^{th}compartment where $i < n$, the flux to mitosis is given by $p_i(t)c_i(t)$, while the outflux to mitosis, in which the mother cell divides to produce two daughter cells, equals to $2p_i(t)c_i(t)$. In the following process, the fraction of cells that stays within the compartment i, referred to as self-renewal, is given by $2a_i(t)p_i(t)c_i(t)$[2, 18]. It is also assumed that $[1 - a_i(t)]$ is the probability of each daughter cells to move to the next compartment, while $a_i(t)$ fraction ensures that cell population stay in the same compartment from where they have formed. Further, the fraction of cells that differentiates and moves to compartment $i + 1$ is given by $2(1 - a_i(t))p_i(t)c_i(t)$. [8, 16] Cells in the n^{th} compartment have zero proliferation rate, but a non-zero death rate. Therefore, the cell population in the mature compartment depends on the flux of differentiated cells from $(n-1)^{th}$ compartment (1^{st}term) and death of the mature cells (2^{nd}term) [7, 18].

The negative feedback signal of cytokines regulates the formation of blood cells. Cytokines are crucial external signalling molecules in stem cells that regulate the dynamics of cell differentiation and proliferation, but the precise nature is still unknown. [8] When released, cytokines such as erythropoietin (EPO) in erythropoiesis and granulocyte colony stimulating factor (G-CSF) for granulopoiesis in hematopoietic stem cells, and NF-κB and phosphatidyl-inositide-3 kinase (PI3K) in leukemic stem cells regulate the growth of cells in the body [18, 22]. The increase in the concentration of cytokines indicates that there is a need for more blood cells of a certain type such that it stimulates the formation of mature cells [6, 18]. It is also assumed that their densities depend majorly on postmitotic cell densities and leukemic and hematopoietic cells respond to the same cytokines and complete for them. In the following model, cytokine is denoted by $s(t)$ and given by:

$$s(t) = \frac{1}{1 + k_c c_n(t) + k_l l_n(t)} \in (0, 1]$$

where k_c and k_l are positive constants.

The model is based on the core assumption that the hematopoietic and leukemic cell lines are distinguished and an ordered sequence of discrete maturation stages (compartments). Each compartment is treated as a "well mixed tank" of cells and their time evolution are described by ordinary differential equations [6]. In accordance with the biological hypothesis, the mitotic cells are characterised by proliferation, self-renewal capacity, and apoptosis. Further, it was defined that both the cell lines respond to the same

cytokines, which is inversely related only to the mature cell population [6, 13]. The model includes one cell lineage for healthy and one for leukemic cells for the compartment system. For 2-compartment system, the healthy cell lineage consists of hematopoietic stem cells and post-mitotic mature cells, while leukemic stem cells and mature blasts constitutes leukemic cell line [7, 24].

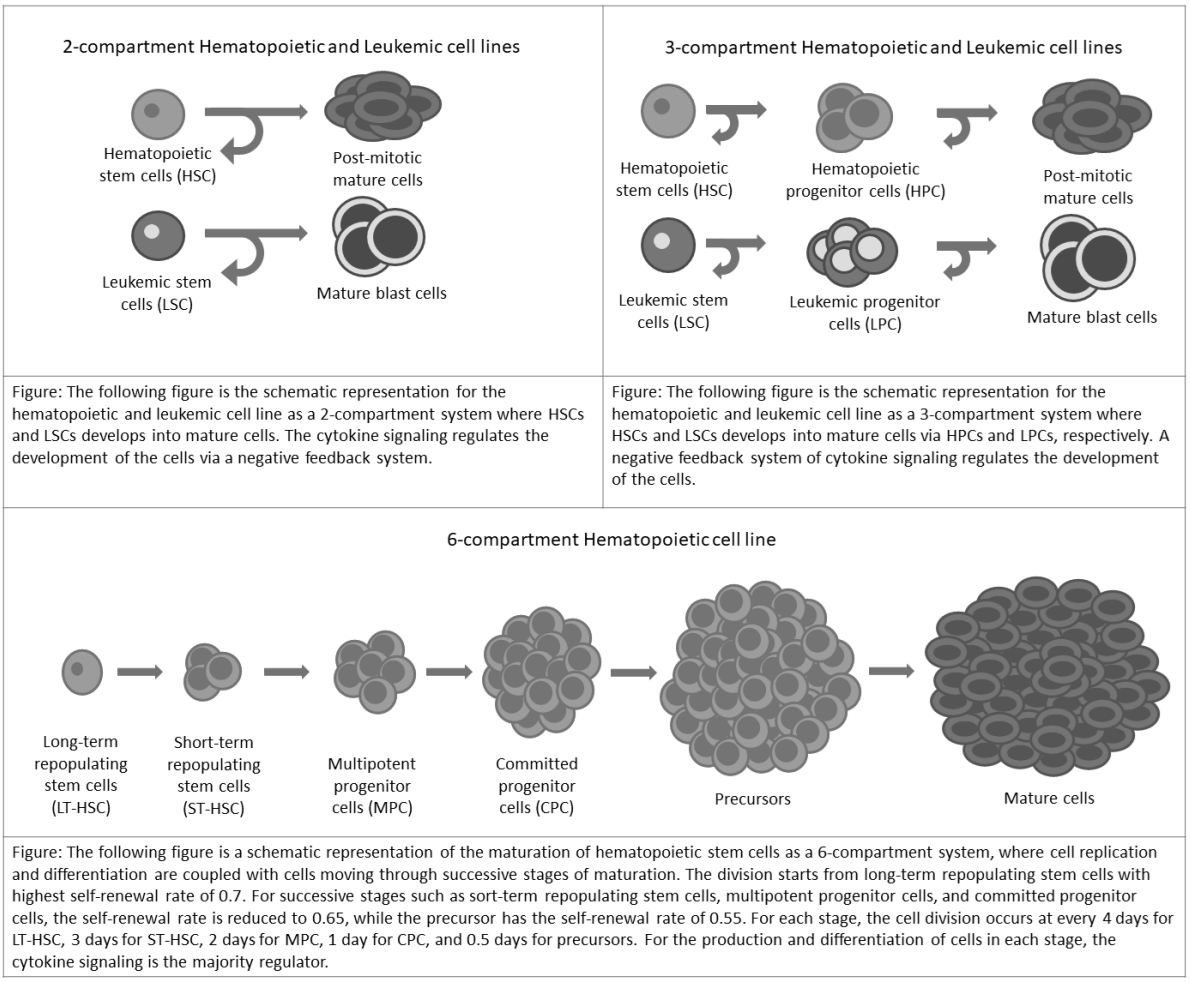

Figure: The following figure is the schematic representation for the hematopoietic and leukemic cell line as a 2-compartment system where HSCs and LSCs develops into mature cells. The cytokine signaling regulates the development of the cells via a negative feedback system.

Figure: The following figure is the schematic representation for the hematopoietic and leukemic cell line as a 3-compartment system where HSCs and LSCs develops into mature cells via HPCs and LPCs, respectively. A negative feedback system of cytokine signaling regulates the development of the cells.

Figure: The following figure is a schematic representation of the maturation of hematopoietic stem cells as a 6-compartment system, where cell replication and differentiation are coupled with cells moving through successive stages of maturation. The division starts from long-term repopulating stem cells with highest self-renewal rate of 0.7. For successive stages such as sort-term repopulating stem cells, multipotent progenitor cells, and committed progenitor cells, the self-renewal rate is reduced to 0.65, while the precursor has the self-renewal rate of 0.55. For each stage, the cell division occurs at every 4 days for LT-HSC, 3 days for ST-HSC, 2 days for MPC, 1 day for CPC, and 0.5 days for precursors. For the production and differentiation of cells in each stage, the cytokine signaling is the majority regulator.

Fig.2: The schematic representation for the Hematopoietic and Leukemic cell line

If we consider the cell lines as 3-compartment system, the healthy cell line consists of the following: hematopoietic stem cells (HSC), hematopoietic progenitor cells (HPC), and post-mitotic mature cells. Similarly, the leukemic cell line consists of the following: leukemic stem cells (HSC), leukemic progenitor cells (HPC), and mature blast cells. For 3-compartment system, it was also assumed that the self-renewal rate for stem cells is higher than the progenitor (non-stem) cells given the condition that all mitotic cells have self-renewal ability and stem cells divide less frequently than progenitor cells [2, 16]. Healthy cell line, when treated as the 6-compartment system, moves through successive stages of maturation where cell replication and differentiation are coupled with cells [8]. For our work, we considered that the division starts from long-term repopulating stem cells with self-renewal rate of 0.7, then proceeds with stages such as sort-term repopulating stem cells, multipotent progenitor cells, and committed progenitor cells, the self-renewal rate is reduced to 0.65 [4, 8]. Finally, the precursor has the self-renewal rate of 0.55. Alongside, for each stage, the cell division occurs at every 4 days for LT-HSC (proliferation rate = 0.25), 3 days for ST-HSC (proliferation rate = 0.33), 2 days for MPC (proliferation rate = 0.5), 1 day for CPC (proliferation rate = 1.0), and 0.5 days for precursors (proliferation rate = 1.5). For the production and differentiation of cells in each stage, the cytokine signaling is the majority regulator [3, 8].

Fractional order derivative-based model: Fractional ordered differential equation, in the recent times, has gained attention due to its ability to provide a better precision between the actual and simulated data as compared to the classical models [3, 13].

The fractional order derivative is advantageous due to its memory effect property which indicate that future state of the system depends on the current state, as well as, the past state [13,24]. FDE is not a new concept, it was introduced back in

1695 by Gottfried Leibniz in a letter written to Guillaume de L'Hôpital [14, 25]. Over the years, mathematicians, namely Riemann–Liouville, Caputo, Jumarie, Hadamard, and Weyl have introduced their own definitions of FDE with some advantages and disadvantages, but the best known is Riemann–Liouville definition [7, 15]. The derivate of order α is given by:

$$D_{0+}^{\alpha} f(t) = \frac{1}{\Gamma(1-\alpha)} \left(\frac{d}{dt}\right)^{n} \int_{0}^{t} \frac{f(s)}{(t-s)^{\alpha-n+1}} ds, \quad n = [\alpha] + 1,$$

Where $\alpha \in R, [n-1, n)$ and $0 < \alpha < 1$ for $n \in Q$, Γ is the gamma function, and $[\alpha]$ is the greatest integer value of α [13, 14]. Riemann–Liouville satisfies the linear property of fractional derivates, but failed to solve the differentiation of a constant value when replaced by Riemann–Liouville differential operator of order α [13, 15].

$$D^{\alpha} c = \frac{c}{\Gamma(1-\alpha)} t^{-\alpha} \neq 0, \qquad \mathrm{c} = \text{constant}$$

While, the Caputo definition for FDE is as follows.

$$D_{0+}^{\alpha} f(t) = \frac{1}{\Gamma(1-\alpha)} \int_{0}^{t} \frac{f^{n}(s)}{(t-s)^{\alpha-n+1}} ds, \quad n = [\alpha] + 1,$$

Following the Caputo type fractional derivative of order α, the modified model for stem cell growth of hematopoietic and leukemic cell lines is:

Hematopoietic cell line:

$$\frac{d^{\alpha} c_1}{dt^{\alpha}} = \left(2(a_{1,max}^{c})^{\alpha} s(t) - 1\right)(p_1^{c})^{\alpha} c_1(t) - (d_1^{c})^{\alpha} c_1(t)$$

$$\frac{d^{\alpha} c_i}{dt^{\alpha}} = 2\left(1 - (a_{i-1,max}^{c})^{\alpha} s(t)\right)(p_{i-1}^{c})^{\alpha} c_{i-1}(t) + \left(2(a_{i,max}^{c})^{\alpha} s(t) - 1\right)(p_i^{c})^{\alpha} c_i(t) - (d_i^{c})^{\alpha} c_i(t)$$

$$\frac{d^{\alpha} c_n}{dt^{\alpha}} = 2\left(1 - (a_{n-1,max}^{c})^{\alpha} s(t)\right)(p_{n-1}^{c})^{\alpha} c_{n-1}(t) - (d_n^{c})^{\alpha} c_n(t)$$

Leukemic cell line:

$$\frac{d^{\alpha} l_1}{dt^{\alpha}} = \left(2(a_{1,max}^{l})^{\alpha} s(t) - 1\right)(p_1^{l})^{\alpha} l_1(t) - (d_1^{l})^{\alpha} l_1(t)$$

$$\frac{d^{\alpha} l_i}{dt^{\alpha}} = 2\left(1 - (a_{i-1,max}^{l})^{\alpha} s(t)\right)(p_{i-1}^{l})^{\alpha} l_{i-1}(t) + \left(2(a_{i,max}^{l})^{\alpha} s(t) - 1\right)(p_i^{l})^{\alpha} l_i(t) - (d_i^{l})^{\alpha} l_i(t)$$

$$\frac{d^{\alpha} l_m}{dt^{\alpha}} = 2\left(1 - (a_{m-1,max}^{c})^{\alpha} s(t)\right)(p_{m-1}^{l})^{\alpha} l_{m-1}(t) - (d_m^{l})^{\alpha} l_m(t)$$

The above model is based on the simple dimensional analysis that the both, left-hand and right-hand side, has the same dimension of $(\text{time})^{-\alpha}$. To maintain the dimensionality, we introduced the order α on the constants, viz, self-renewal rate, proliferation rate, and death rate at the right-hand side, and changed the order of differentiation to α on the left-hand side. For solving the described ordinary differential equations for the following system and its fractional-order differential equations, we used the MATLAB version R2022b by MathWorks. The ordinary differential equations were numerically solved using 'ode45', while the fractional-ordered differential equations were solved with the MATLAB code based on predictor-corrector algorithms (can be found in MathWorks webpage) [18, 19].

RESULTS AND DISCUSSION

The evolution of a set of six compartments, accounting for six maturation stages of hematopoietic cells, reveals intricate dynamics within the bone marrow microenvironment. As the stem cells progress through these stages, they undergo a series of transformations, regulated by complex interactions between various signaling molecules and microenvironmental cues. The results demonstrate in Fig. (3) that the fractional-order derivative-based model effectively captures the nuanced behavior of hematopoietic cells across these compartments [6,17]. By incorporating fractional calculus into the modeling framework, we gain a more accurate representation of the underlying dynamics, particularly in capturing non-integer order kinetics and memory effects inherent in biological systems.

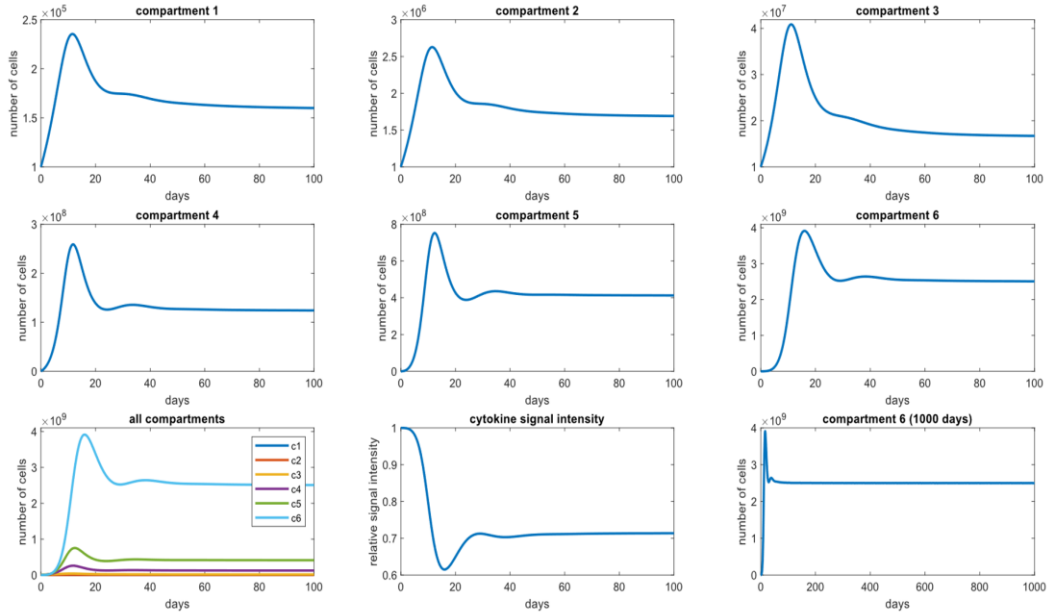

Fig. 3: Evolution of a set 6 compartments accounting for six maturation stages of haematopoietic cells

Analysis of the model reveals the interplay between self-renewal and proliferation rates at different stages of cell maturation. This interdependence influences the overall population dynamics, dictating the balance between stem cell maintenance and differentiation [8, 16]. Furthermore, the simulation of clinically relevant scenarios sheds light on how perturbations in the system, such as changes in cytokine concentrations or mutations associated with leukemia, impact the distribution of cell populations across the compartments. Understanding these dynamics is crucial for elucidating the pathophysiology of hematopoietic disorders and developing targeted therapeutic interventions. Overall, the evolution of the six-compartment model provides valuable insights into the regulation of hematopoietic stem cell dynamics and offers a computational framework for studying the effects of various perturbations on normal and pathological hematopoiesis [6,12].

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Fig.(4) shows the establishment of a leukemic steady state and the extinction of healthy cells represent critical phenomena in the progression of leukemia and are pivotal outcomes elucidated by the model. In the leukemic steady state, the model demonstrates a sustained equilibrium where leukemic stem cells maintain a stable population size, driving the dominance of leukemic cell populations within the bone marrow microenvironment. This steady state arises from a delicate balance between self-renewal and differentiation, where leukemic stem cells continuously replenish themselves while also generating leukemic progenitor cells [5,23]. Conversely, the extinction of healthy cells signifies the loss of normal hematopoietic function due to the overwhelming presence of leukemic cells. As the leukemic population expands and displaces healthy hematopoietic cells, the bone marrow microenvironment becomes increasingly conducive to leukemic cell proliferation, leading to the gradual depletion of normal cell populations

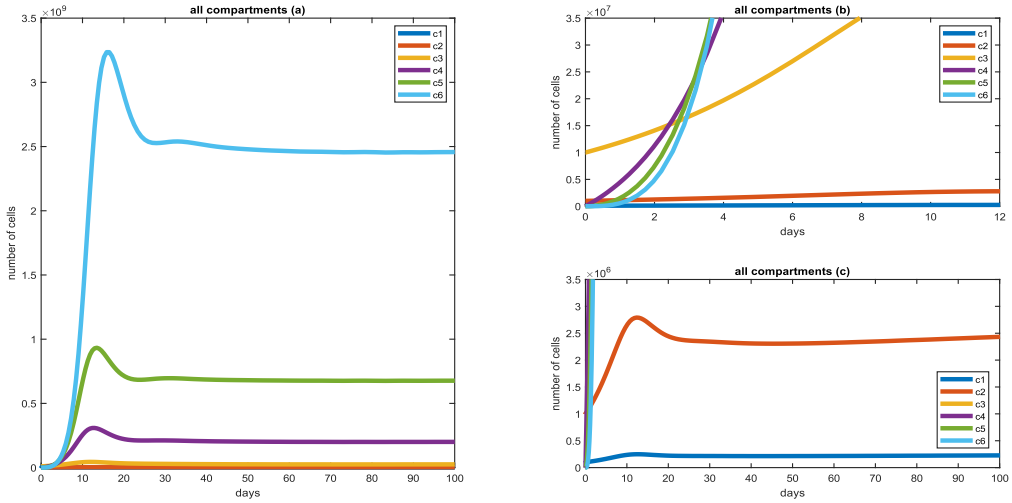

Fig.4: Establishment of a leukemic steady state and extinction of healthy cells

The model provides insights into the factors contributing to the establishment of these critical states. It highlights the role of dysregulated self-renewal and proliferation rates in driving leukemic expansion and outcompeting healthy hematopoietic cells [7,22]. Moreover, the influence of microenvironmental factors, such as cytokine signaling and niche interactions, on the dynamics of leukemic and healthy cell populations is also elucidated. Understanding the mechanisms underlying the establishment of a leukemic steady state and the extinction of healthy cells is essential for developing targeted therapeutic strategies to disrupt leukemic growth and restore normal hematopoietic function. By identifying key regulatory nodes and vulnerabilities within the system, interventions can be tailored to selectively target leukemic cells while preserving healthy hematopoietic function, ultimately improving treatment outcomes for patients with leukemia [8,23].

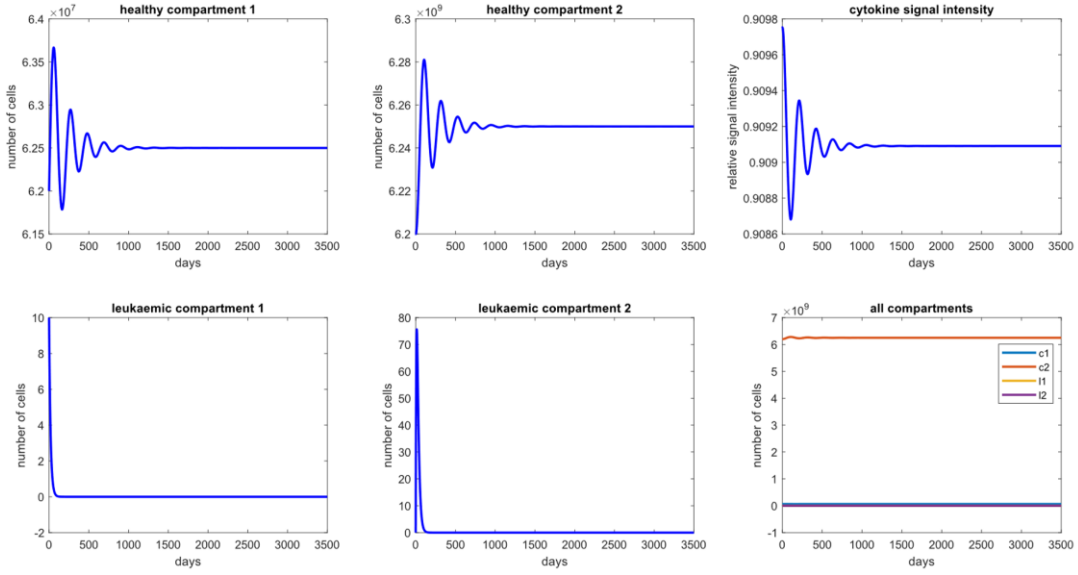

Fig.5: Cell number dependency on self-renewal rate with time

Fig. (5) shows the analysis of cell number dependency on self-renewal rate over time provides valuable insights into the dynamics of stem cell populations and their contribution to hematopoietic homeostasis or leukemic progression. In the context of hematopoiesis, the model elucidates how alterations in the self-renewal rate impact the size and composition of stem cell populations over time [3, 18]. Higher self-renewal rates lead to increased stem cell proliferation and expansion, resulting in larger stem cell populations. This phenomenon is particularly relevant in scenarios where there is a need for rapid hematopoietic recovery, such as during periods of increased demand for blood cell production or in response to hematologic insults like chemotherapy or radiation therapy. Conversely, lower self-renewal rates are associated with reduced stem cell proliferation and slower population growth. This can have

implications for hematopoietic function, as a decline in stem cell numbers may compromise the ability to maintain adequate blood cell production, leading to conditions like bone marrow failure or cytopenias [8,22].

In the context of leukemia, alterations in self-renewal rates can drive aberrant stem cell expansion and leukemic progression. Higher self-renewal rates may promote the clonal expansion of leukemic stem cells, leading to the dominance of leukemic populations within the bone marrow microenvironment. Conversely, interventions that target self-renewal pathways or reduce self-renewal rates may inhibit leukemic cell proliferation and limit disease progression [6, 19]. Overall, the analysis of cell number dependency on self-renewal rate with time provides a comprehensive understanding of the regulatory mechanisms governing stem cell dynamics in both normal and pathological conditions. By elucidating the relationship between self-renewal rates and stem cell populations, this analysis informs the development of therapeutic strategies aimed at modulating stem cell behavior to restore hematopoietic homeostasis or inhibit leukemic growth [7, 24].

CONCLUSION

This study provides valuable insights into the dynamics of hematopoietic cells and their role in health and disease. Through the evolution of a set of 6 compartments representing six maturation stages of hematopoietic cells, we have elucidated the complex processes governing hematopoiesis and the maturation of blood cell lineages. This model allows us to simulate and understand the differentiation and proliferation of hematopoietic stem and progenitor cells, shedding light on the factors influencing normal hematopoietic function. Furthermore, this analysis of the leukemic steady state and the extinction of healthy cells highlights the critical role of self-renewal rates in driving leukemic progression and disrupting hematopoietic homeostasis. By modeling the dynamics of leukemic stem cells and their interaction with healthy hematopoietic cells, we have identified key factors contributing to the establishment of leukemic dominance within the bone marrow microenvironment. Additionally, this investigation into the cell number dependency on self-renewal rate over time underscores the importance of self-renewal pathways in regulating stem cell behavior and maintaining hematopoietic function. Alterations in self-renewal rates can have profound effects on stem cell proliferation, population dynamics, and ultimately, disease progression. Overall, these findings contribute to a better understanding of the mechanisms underlying hematopoietic regulation and leukemic pathogenesis. By elucidating the dynamics of hematopoietic and leukemic stem cells, our study lays the groundwork for the development of targeted therapies aimed at modulating self-renewal pathways to restore hematopoietic homeostasis and inhibit leukemic growth.

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