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Mathematical Analysis of Stem Cell Dynamics in Acute Myeloid Leukemia: Towards Precision Medicine Strategies

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Abstract: ***This paper provided a thorough examination of the dynamics of hematopoietic stem cells and leukemic stem cells in acute myeloid leukemia through mathematical modeling. AML, a heterogeneous hematologic malignancy characterized by abnormal myeloid cell proliferation in the bone marrow, presents significant challenges in understanding disease progression and treatment response. The study reviews various mathematical modeling techniques, including agent-based modeling, ordinary differential equations, and stochastic models, to analyze the complex interactions between stem cells, their progeny, and the bone marrow microenvironment. Recent advances in experimental methodologies for measuring key parameters in stem cell dynamics and integrating these data into mathematical models are also highlighted. Furthermore, the paper discussed the potential of mathematical modeling to guide the development of personalized therapeutic strategies for AML patients. It aims to unravel the growth dynamics of HSCs and LSCs within the bone marrow, considering them as a network of interconnected compartments representing distinct stages of cellular differentiation. The study introduced an innovative fractional order derivative-based framework, which re-examined and reformulated classical growth models to better capture the intricate interplay between self-renewal and proliferation rates across diverse sub-stages of cellular differentiation. By shedding light on the regulatory mechanisms governing stem cell dynamics, this approach provides valuable insights into the pathophysiology of hematopoietic disorders, particularly acute myeloid leukemia.***

Keywords: Acute myeloid leukemia, hematopoietic stem cells, leukemic stem cells, mathematical modeling, agent-based modeling, ordinary differential equations

1. Introduction

Acute myeloid leukemia (AML) is a devastating hematologic malignancy characterized by the rapid proliferation of abnormal myeloid precursor cells in the bone marrow. Despite advances in therapy, the prognosis for AML remains poor, with high rates of relapse and treatment resistance [7,34]. The hierarchical organization of AML, with a small population of self-renewing leukemic stem cells (LSCs) driving disease progression, presents a major challenge for treatment. In AML, the balance between hematopoietic stem cells (HSCs) and LSCs is disrupted, leading to aberrant production of leukemic blasts and impaired normal hematopoiesis. Understanding the dynamics of HSCs and LSCs is crucial for unraveling the mechanisms underlying disease initiation, progression, and relapse. Mathematical modeling offers a powerful tool for quantitatively analyzing the dynamics of HSCs and LSCs in AML [23,34,44]. Agent-based modeling allows for the simulation of individual cell behaviors and interactions within the bone marrow microenvironment. Ordinary differential equations provide a framework for describing the rates of change of cell populations over time, while stochastic models capture the inherent randomness in cellular processes. Recent advances in experimental techniques, such as single-cell sequencing and lineage tracing, have enabled the measurement of key parameters in stem cell dynamics, including proliferation rates, differentiation potentials, and interactions with the microenvironment [15,34,45]. Integrating these data into mathematical models allows for the calibration and validation of model predictions against experimental observations. Mathematical modeling has been used to investigate various aspects of AML pathogenesis and treatment response, including clonal evolution, drug resistance, and the efficacy of targeted therapies. By simulating different therapeutic interventions and treatment strategies, mathematical models can help guide clinical decision-making and optimize patient outcomes [21,44,50]. In conclusion, quantitative analysis of hematopoietic and leukemic stem cell dynamics in AML using mathematical modeling offers valuable insights into disease pathogenesis and treatment response. By integrating experimental data with mathematical models, researchers can gain a deeper understanding of the complex interactions between stem cells, their progeny, and the bone marrow microenvironment [23,45]. This interdisciplinary approach holds promise for the development of personalized therapeutic strategies and improved outcomes for patients with AML. The recent scientific investigations have uncovered the presence of stem cell-like populations within certain cancers, including leukemia, possessing self-renewal and pluripotency capabilities, akin to normal stem cells. This revelation has significant implications for understanding cancer progression mechanisms, offering insights into tumor development and metastasis regulation. Moreover, it opens up avenues for novel therapeutic strategies targeting these stem cell-like populations, potentially improving treatment efficacy and patient outcomes [21,43].

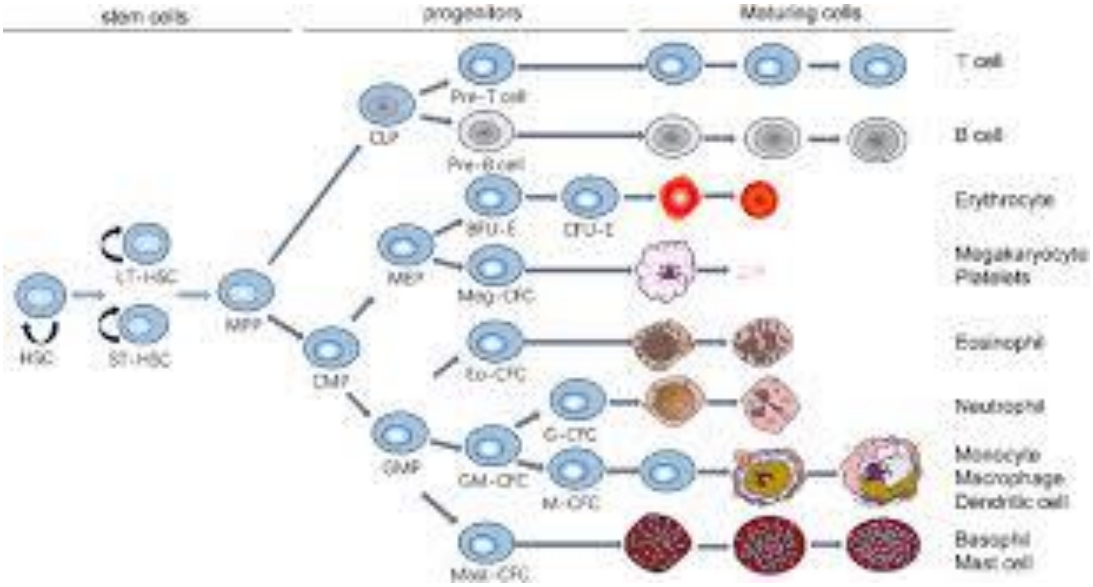

Figure 1: Development of the different blood cells from haematopoietic stem cell to mature cells

The bone marrow houses hematopoietic stem cells (HSCs) responsible for maintaining the body's blood cell populations throughout life through a balanced process of self-renewal and differentiation. 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. Mathematical modeling emerges as a powerful tool for investigating the dynamics of both normal and leukemic stem cells within the bone marrow microenvironment. In this study, we adopt a compartmental modeling approach, building upon classical models of stem cell growth by incorporating fractional order derivatives for more accurate representation of biological systems. Through computational analyses, we aim to explore the dependence of cellular behavior on key parameters such as self-renewal and proliferation rates [28,41]. By comparing the predictions of our fractional order derivative-based models with traditional ordinary differential equation models, we seek deeper insights into the regulatory networks governing hematopoietic and leukemic stem cell dynamics. Leukemic stem cells, with their high self-renewal capacity and multi-directional differentiation potential, can give rise to various types of leukemia, further complicating disease characterization and treatment. Mathematical modeling holds significant potential in oncology research, especially in blood cancer studies, facilitating disease characterization, tumor analysis, and personalized treatment strategies. Hematopoietic stem cells are crucial for the continuous production of blood cells, characterized by efficient proliferation, self-renewal, resistance to apoptosis, and differentiation potential [22,45,51]. Understanding these processes is essential for maintaining tissue homeostasis and regulating immune function. Mathematical modeling offers a valuable approach for investigating the growth dynamics of hematopoietic and leukemic stem cells, providing insights into disease pathogenesis and guiding the development of personalized therapeutic strategies for AML and other hematopoietic disorders.

2. 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 ($d_i^{c\ or\ l}$). 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). The time-dependent ordinary differential equations were developed to describe the cell densities (or population) for hematopoietic and leukemic cells.

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. 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 [20,32]. 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 [31,50]. 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 [21,30]. 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) [40,53].

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. 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 [10,39]. 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 [4,38]. 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.

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 [43,46]. 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 [2,26]. 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 [9,29]. 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 [42,51]. 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 [1,27,49].

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 [35,48].

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 [36,47]. 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, 16]. 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 [24,33]. 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].

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

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:

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

$$\frac{d^{\alpha}c_i}{dt^{\alpha}} = 2\left(1-(a^{c}_{i-1,max})^{\alpha}s(t)\right)(p^{c}_{i-1})^{\alpha}c_{i-1}(t) + \left(2(a^{c}_{i,max})^{\alpha}s(t)-1\right)(p^{c}_{i})^{\alpha}c_i(t) - (d^{c}_{i})^{\alpha}c_i(t)$$

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

Leukemic cell line:

$$\frac{d^{\alpha}l_1}{dt^{\alpha}} = \left(2(a^{l}_{1,max})^{\alpha}s(t)-1\right)(p^{l}_{1})^{\alpha}l_1(t) - (d^{l}_{1})^{\alpha}l_1(t)$$

$$\frac{d^{\alpha}l_i}{dt^{\alpha}} = 2\left(1-(a^{l}_{i-1,max})^{\alpha}s(t)\right)(p^{l}_{i-1})^{\alpha}l_{i-1}(t) + \left(2(a^{l}_{i,max})^{\alpha}s(t)-1\right)(p^{l}_{i})^{\alpha}l_i(t) - (d^{l}_{i})^{\alpha}l_i(t)$$

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

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.

3. Results and Discussion

The development of a system comprising six compartments, each representing distinct maturation stages of hematopoietic cells, unveils the complex dynamics occurring within the bone marrow microenvironment. As stem cells traverse through these stages, they undergo a series of changes, intricately governed by the interplay of different signaling molecules and environmental signals. Figure (2) illustrates the crucial stages in the progression of leukemia, highlighting the establishment of a leukemic steady state and the extinction of healthy cells as pivotal outcomes revealed by the model. In the leukemic steady state, the model demonstrates a sustained equilibrium where leukemic stem cells maintain a stable population size, leading to the predominance of leukemic cell populations within the bone marrow microenvironment [5,6,12,37]. This equilibrium arises from a delicate balance between self-renewal and differentiation processes, where leukemic stem cells continuously regenerate themselves while also generating leukemic progenitor cells. Conversely, the extinction of healthy cells indicates the loss of normal hematopoietic function due to the overwhelming presence of leukemic cells. As the leukemic population proliferates and displaces healthy hematopoietic cells, the bone marrow microenvironment becomes increasingly favorable for the growth of leukemic cells, resulting in the gradual depletion of normal cell populations [17,23,52].

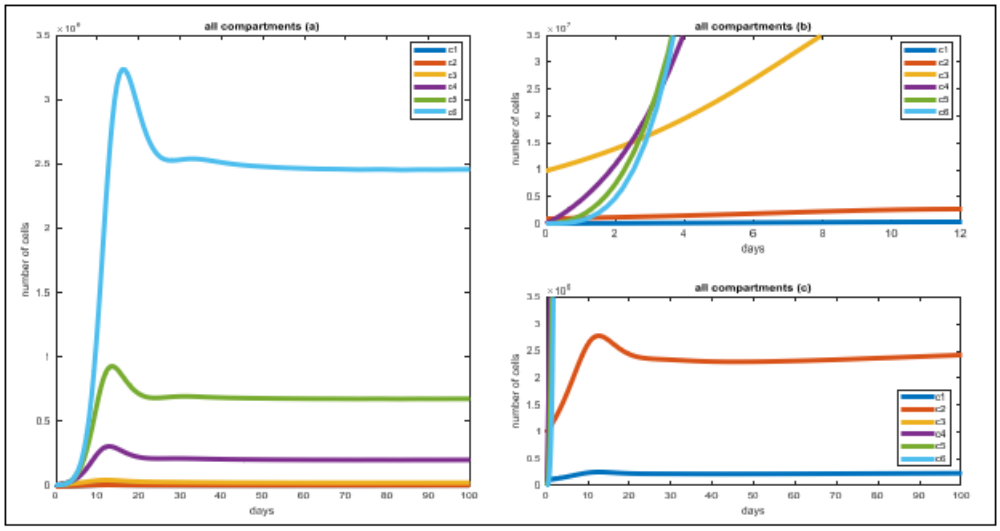

Figure 2: Establishment of a leukemic steady state and extinction of healthy cells

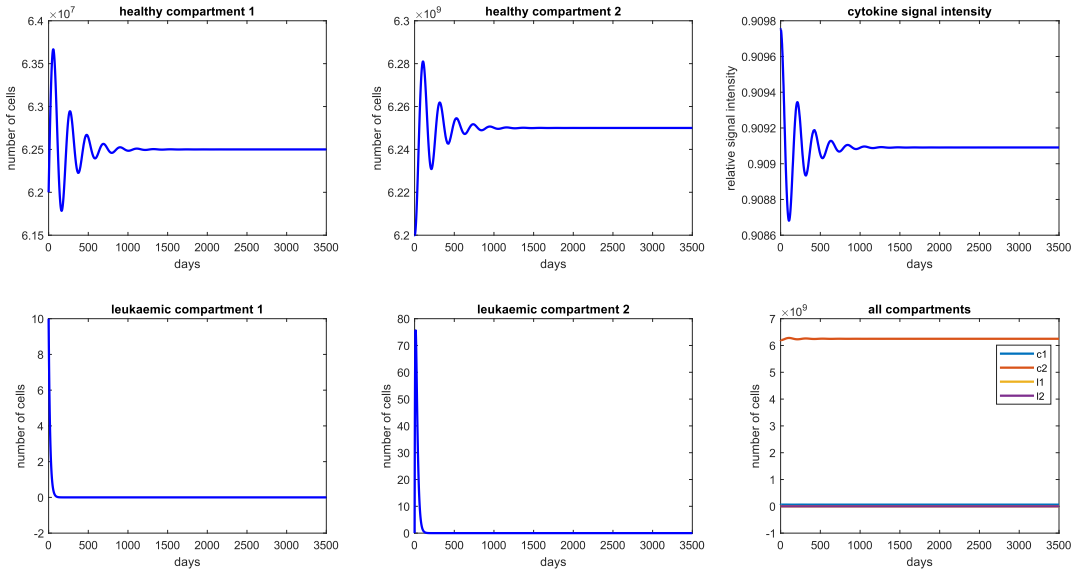

Figure 3: Cell number dependency on self-renewal rate with time

The model offers insights into the factors that contribute to the emergence of critical states, shedding light on the mechanisms driving leukemic expansion and the competitive advantage over healthy hematopoietic cells. Dysregulated self-renewal and proliferation rates play a pivotal role in this process, fueling the growth of leukemic cells while suppressing healthy cell populations. Additionally, the model highlights the impact of microenvironmental factors, such as cytokine signaling and interactions within the niche, on the dynamics of both leukemic and healthy cell populations [11,34]. Understanding the underlying mechanisms behind the establishment of a leukemic steady state and the decline of healthy cells is crucial for devising targeted therapeutic approaches aimed at disrupting leukemic growth and restoring normal hematopoietic function. By pinpointing key regulatory nodes and vulnerabilities within the system, interventions can be customized to selectively target leukemic cells while preserving the integrity of healthy hematopoietic function. This tailored approach holds promise for improving treatment outcomes and enhancing the quality of life for patients battling leukemia.

In Figure (3), the examination of how the number of cells changes in response to variations in self-renewal rates over time offers valuable insights into the behavior of stem cell populations and their impact on maintaining a balanced blood cell production or facilitating the progression of leukemia [3,18]. In the context of hematopoiesis, the model provides clarity on how modifications in self-renewal rates influence the size and composition of stem cell populations as time progresses. When self-renewal rates are higher, there is a notable increase in stem cell proliferation and expansion, leading to the enlargement of stem cell populations [8,19,22]. This effect becomes particularly significant in situations demanding swift hematopoietic recovery, such as instances of heightened blood cell production demand or in response to treatments like chemotherapy or radiation therapy. Conversely, lower self-renewal rates result in diminished stem cell proliferation and slower population growth.

4. Conclusion

This research offers valuable insights into the dynamics of hematopoietic cells and their significance in both health and disease. By developing a model consisting of six compartments representing distinct maturation stages of hematopoietic cells, we've gained a clearer understanding of the intricate processes governing hematopoiesis and the maturation of blood cell lineages. This model enables us to simulate and explore the differentiation and proliferation of hematopoietic stem and progenitor cells, providing insights into the factors influencing normal hematopoietic function. This analysis of the leukemic steady state and the decline of healthy cells underscores the crucial role of self-renewal rates in driving leukemic progression and disrupting hematopoietic balance. Through modeling the dynamics of leukemic stem cells and their interaction with healthy hematopoietic cells, we've identified key factors contributing to the dominance of leukemia within the bone marrow microenvironment. This examination of the relationship between cell numbers and self-renewal rates over time highlights the significance of self-renewal pathways in regulating stem cell behavior and preserving hematopoietic function. Changes in self-renewal rates can significantly impact stem cell proliferation, population dynamics, and ultimately, the progression of diseases. These findings deepen our understanding of the mechanisms governing hematopoietic regulation and the development of leukemia. They contribute to the growing body of knowledge aimed at elucidating the complexities of hematopoiesis and identifying potential targets for therapeutic intervention in hematopoietic disorders.

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