ISSN: 2834-7706

Research Article

Journal of Mathematical Techniques and Computational Mathematics

Dynamic Modeling of Cytokine-Dependent Proliferation Rates over Time in Cancer: Insights from Scientific Analysis

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Submitted: 2024, Jun 01; **Accepted**: 2024, Jun 21; **Published**: 2024, July 03

Citation: Parambath, A., B., Kasturia, P., Shah, S. R. (2024). Dynamic Modeling of Cytokine-Dependent Proliferation Rates over Time in Cancer: Insights from Scientific Analysis. *J Math Techniques Comput Math, 3*(7), 01-09.

Abstract

Cytokines play a crucial role in regulating cell proliferation rates in cancer, influencing tumor growth and progression. This work employs dynamic modeling to explore how cytokine signals modulate proliferation rates over time in the context of cancer. By integrating scientific analysis with mathematical modeling, we elucidate the complex interactions between cytokine signaling pathways and tumor cell dynamics, offering insights into potential therapeutic strategies and prognostic indicators. This analysis of cell proliferation dynamics highlights clear differences between healthy and leukemic cell compartments 1 and 2. Healthy cells show an initial phase of rapid exponential growth due to regulated division, which is crucial for maintaining tissue function. In leukemic cells exhibit delayed proliferation patterns. Understanding these distinctions is vital for designing precise therapies that can effectively target leukemia while minimizing harm to healthy tissues. This understanding drives the development of personalized treatment approaches aimed at enhancing outcomes in cancer care. Ongoing interdisciplinary collaboration is crucial to translating these insights into practical clinical applications that can improve patient outcomes and advance the field of cancer treatment.

Keywords: Cytokines, Cancer, Proliferation Rates, Mathematical Modeling, Dynamic Systems, Tumor Microenvironment, Therapeutic Strategies

1. Introduction

Cancer, a complex and heterogeneous group of diseases, is defined by uncontrolled cell proliferation resulting from genetic mutations and disrupted signaling pathways within cells. These alterations allow cancer cells to evade normal growth constraints and promote tumor development. However, the progression of cancer is not solely governed by intrinsic genetic changes; rather, the tumor microenvironment plays a critical role in supporting and sustaining malignant growth figure (1). Central to the tumor microenvironment are cytokines, which serve as essential mediators of inflammation and immune responses [1-4]. These small proteins are secreted by various cell types, including immune cells, fibroblasts, and tumor cells themselves, and they exert profound influences on cancer progression. Cytokines can modulate diverse cellular processes within the tumor milieu, including proliferation, survival, angiogenesis, and metastasis. The temporal dynamics of cytokine-dependent proliferation rates are pivotal for comprehending how cancer evolves and responds to therapeutic interventions. Cytokines act through specific receptors on cancer cells, triggering intracellular signaling cascades that alter gene expression patterns and cellular behaviors. For instance, cytokine signaling pathways can promote the proliferation of cancer cells by activating growth-promoting signals and suppressing mechanisms that regulate cell cycle progression or induce cell death (apoptosis) [5-7]. Moreover, cytokines contribute to the establishment of an immunosuppressive and pro-inflammatory microenvironment that fosters tumor growth and metastasis. They facilitate interactions between cancer cells and immune cells, promoting immune evasion and resistance to anti-tumor immune responses. Additionally, cytokines can influence the formation of new blood vessels (angiogenesis) within tumors, which is crucial for supplying nutrients and oxygen to support tumor growth and dissemination. Understanding these dynamic interactions between cytokines and cancer cells is essential for developing targeted therapies. By deciphering the temporal

patterns of cytokine activity and their impact on tumor progression mechanisms, researchers can identify novel therapeutic targets and strategies aimed at disrupting cytokine signaling pathways [8-11]. This approach holds promise for enhancing the efficacy of existing treatments and developing personalized therapies tailored to the unique cytokine profiles of individual tumors. Elucidating the temporal dynamics of cytokine-dependent proliferation rates in cancer is crucial for advancing our understanding of tumor biology and improving clinical outcomes. By integrating insights into cytokine-mediated signaling with sophisticated mathematical models and experimental data, researchers can pave the way for more effective therapeutic interventions that target the complex interplay between cytokines and cancer cells [12- 15].

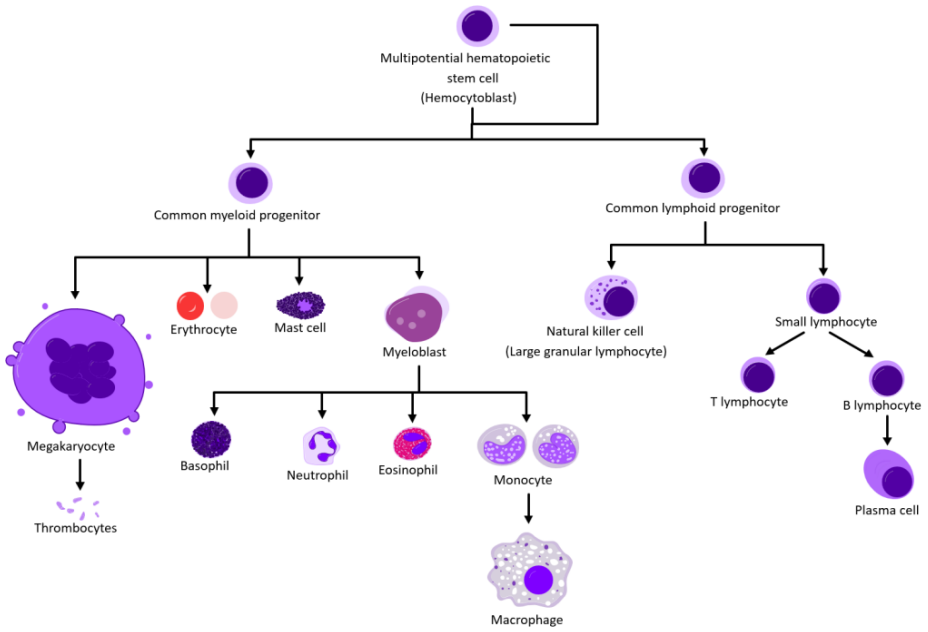

Figure 1: Development of the different Blood Cells from Haematopoietic Stem Cell to Mature Cells

Cytokines play a critical role in cancer by exerting their effects on cancer cells through specific receptors, initiating intricate signaling cascades that profoundly influence various cellular processes essential for tumor development and progression. These signaling pathways, crucial for normal cellular homeostasis, are often dysregulated in cancer, contributing to abnormal cytokine production and altered cellular responses [12,16-18]. Key cytokines implicated in cancer progression include tumor necrosis factor-alpha (TNF-α), interleukins (IL-6, IL-8), and transforming growth factor-beta (TGF-β), among others. Each of these cytokines operates through distinct receptor-mediated mechanisms, triggering signaling events that impact critical aspects of cancer biology. TNF-α is a potent pro-inflammatory cytokine produced primarily by activated macrophages and other immune cells. In cancer, TNF-α can promote tumor growth by enhancing cancer cell survival, inducing angiogenesis (formation of new blood vessels to support tumor growth), and facilitating metastasis [19-22]. Additionally, TNF-α contributes to the recruitment and activation of inflammatory cells within the tumor microenvironment, fostering a pro-tumorigenic milieu. IL-6 is a multifunctional cytokine involved in immune responses, inflammation, and hematopoiesis. In cancer, IL-6 can act as both a pro-inflammatory and anti-inflammatory mediator, depending on the context. It promotes cancer cell proliferation, survival, and migration, and it contributes to the suppression of anti-tumor immune responses. Elevated IL-6 levels are associated with poor prognosis in various cancers due to its role in driving tumor progression and therapy resistance. IL-8 is a chemokine that plays a crucial role in inflammation and immune response. In cancer, IL-8 promotes tumor growth by stimulating angiogenesis and enhancing cancer cell proliferation and survival. It also contributes to the recruitment of immune cells and supports the establishment of a protumorigenic microenvironment. High levels of IL-8 are associated with aggressive tumor behavior and poor clinical outcomes in several types of cancer. TGF-β is a pleiotropic cytokine that regulates various cellular processes, including proliferation, differentiation, apoptosis, and immune responses [23-27]. In cancer, TGF-β has dual roles depending on the tumor stage and context. It can act as a tumor suppressor by inhibiting cell proliferation and promoting apoptosis in early-stage tumors. However, in advanced cancers, TGF-β often promotes tumor progression by enhancing epithelial-to-mesenchymal transition (EMT), facilitating invasion and metastasis, and suppressing anti-tumor immune responses [28-31]. The roles of these cytokines in promoting or inhibiting tumor growth are intricately linked to the specific characteristics of the tumor microenvironment, including cellular interactions, immune cell infiltrates, and the presence of stromal cells. Dysregulation of cytokine signaling pathways can lead to sustained pro-tumorigenic signals within the tumor milieu, promoting tumor survival, progression, and therapy resistance. Understanding the complex interactions between cytokines and cancer cells is crucial for developing targeted therapies aimed at

disrupting aberrant cytokine signaling and restoring normal cellular homeostasis [32-35]. Therapeutic strategies targeting cytokine receptors or downstream signaling molecules hold promise for improving treatment outcomes and overcoming therapeutic resistance in cancer patients. Moreover, ongoing research into the molecular mechanisms of cytokine action in cancer continues to uncover novel therapeutic targets and biomarkers for predicting patient responses to cytokine-targeted therapies.

2. Formulation of the Problem

The following mathematical model developed by [28] describes the dynamics of hematopoietic and leukemic cells in acute myeloid leukaemia based on three primary parameters, self-renewal rate (a_i^c, a_i^l), proliferation rate (p_i^c, p_i^l), and death rate (p_i^c, p_i^l), [13,14,36]. The mathematical model (Eq. 1-6) is based on understanding of the haematopoiesis process such that stages of cell differentiation are assumed to be compartments (ordered sequence of differentiation). The time-dependent ordinary differential equations were developed to describe the cell densities (or populations) of hematopoietic and leukemic cells Hematopoietic cell line:

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

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

$$\frac{dc_n}{dt} = 2\left(1 - a_{n-1,max}^c s(t)\right)p_{n-1}^c c_{n-1}(t) - d_n^c c_n(t) \#(3)$$

Leukemic cell line:

$$\frac{dl_1}{dt} = \left(2a_{1,max}^l s(t) - 1\right)p_1^l l_1(t) - d_1^l l_1(t) \#(4)$$

$$\frac{dl_i}{dt} = 2\left(1 - a_{i-1,max}^l s(t)\right)p_{i-1}^l l_{i-1}(t) + \left(2a_{i,max}^l s(t) - 1\right)p_i^l l_i(t) - d_i^l l_i(t) \#(5)$$

$$\frac{dl_m}{dt} = 2\left(1 - a_{m-1,max}^l s(t)\right)p_{m-1}^l l_{m-1}(t) - d_m^l l_m(t) \#(6)$$

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 [37-38].

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 the leukemic stem cell population, and the post mitotic mature blasts are denoted by m^{th} compartment. The cell densities of the hematopoietic cell population in the compartment j at time t are denoted by $c_j(t)(j=1,2,....n)$, while $l_j(t)(j = 1,2,.... n)$ denotes the cell densities for the leukemic cell population [39-41].

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 their 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-□B and phosphatidyl-inositide-3 kinase (PI3K) in leukemic stem cells regulate the growth of cells in the body [41,43].

The increase in the concentration of cytokines indicates that there is a need for more blood cells of a certain type, which stimulates the formation of mature cells. 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:

$$s(t) = \frac{1}{1 + k_c c_n(t) + k_l l_n(t)} \in (0,1] \#(7)$$

where k_c and k_l are positive constants.

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. The fractional order derivative is advantageous due to its memory effect property, which indicates that the future state of the system depends on the current state as well as the past state [26,44].

Fractional Derivative Equations (FDE) is not a new concept; it was introduced back in 1695 by Gottfried Leibniz in a letter written to Guillaume de L'Hôpital. Over the years, mathematicians, namely Riemann-Liouville, Caputo, Jumarie, Hadamard, and Weyl, have introduced their own definitions of fractional order derivatives with some advantages and disadvantages, but the best known is the Riemann-Liouville definition (Abu-Shady & Kaabar, 2021). The derivate of order is given by:

$$D_{0+}^{\alpha} f(t) = \frac{1}{\Gamma(1-\alpha)} \left(\frac{d}{dt}\right)^{n} \int_0^t \frac{f(s)}{(t-s)^{\alpha-n+1}} ds, \quad n = [\alpha] + 1, \#(8)$$

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. 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.

$$D^{\alpha} c = \frac{c}{\Gamma(1-\alpha)} t^{-\alpha} \neq 0, \qquad \text{c} = \text{constant} \#(9)$$

While the Caputo definition for FDE is as follows.

$$D_{0+}^{\alpha} f(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{f^{n}(s)}{(t-s)^{\alpha-n+1}} ds, \quad n = [\alpha] + 1, \#(10)$$

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

Caputo-fractional based hematopoietic cell line:

$$\frac{d^{\alpha} c_1}{dt^{\alpha}} = \left(2\left(a_{1,max}^{c}\right)^{\alpha} s(t) - 1\right)(p_1^c)^{\alpha} c_1(t) - (d_1^c)^{\alpha} c_1(t) \#(11)$$

$$\frac{d^{\alpha} c_i}{dt^{\alpha}} = 2\left(1 - (a_{i-1,max}^{c})^{\alpha} s(t)\right)(p_{i-1}^c)^{\alpha} c_{i-1}(t) + \left(2(a_{i,max}^{c})^{\alpha} s(t) - 1\right)(p_i^c)^{\alpha} c_i(t) - (d_i^c)^{\alpha} c_i(t) \#(12)$$

$$\frac{d^{\alpha} c_n}{dt^{\alpha}} = 2\left(1 - (a_{n-1,max}^{c})^{\alpha} s(t)\right)(p_{n-1}^c)^{\alpha} c_{n-1}(t) - (d_n^c)^{\alpha} c_n(t) \#(13)$$

Caputo-fractional based leukemic cell line:

$$\frac{d^{\alpha} l_1}{dt^{\alpha}} = \left(2\left(a_{1,max}^{l}\right)^{\alpha} s(t) - 1\right)(p_1^l)^{\alpha} l_1(t) - \left(d_1^l\right)^{\alpha} l_1(t) \#(14)$$

$$\frac{d^{\alpha} l_i}{dt^{\alpha}} = 2\left(1 - \left(a_{i-1,max}^{l}\right)^{\alpha} s(t)\right)(p_{i-1}^l)^{\alpha} l_{i-1}(t) + \left(2(a_{i,max}^{l})^{\alpha} s(t) - 1\right)(p_i^l)^{\alpha} l_i(t) - \left(d_i^l\right)^{\alpha} l_i(t) \#(15)$$

$$\frac{d^{\alpha} l_m}{dt^{\alpha}} = 2\left(1 - \left(a_{m-1,max}^{c}\right)^{\alpha} s(t)\right)(p_{m-1}^l)^{\alpha} l_{m-1}(t) - (d_m^l)^{\alpha} l_m(t) \#(16)$$

The above model is based on the simple dimensional analysis that both, left-hand and right-hand sides have the same dimension of (time)$^{-\alpha}$. To maintain the dimensionality, we introduced the order α on the constants, viz., self-renewal rate, proliferation rate, and death rate, on the right-hand side, and changed the order of differentiation to α on the left-hand side.

Hematopoietic stem cells generate multiple lineages of post-mitotic mature cells through successive production of intermediate progenitors [15,41,45,46]. 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.

3. Results and Discussion

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. 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. The mutation of the genes involved in haematopoiesis results in acute myeloid leukaemia, however, the exact cause of mutation is unknown [47,48]. It affects the bone marrow and the only treatment is chemotherapy followed by bone marrow transfusions. Another group of myeloid leukaemia is chronic myeloid leukaemia caused by unregulated signal transduction by tyrosine kinase, a type of cytokine signalling. Proliferation rate

describes how quickly cells replicate and increase in number through mitotic division. Cells that proliferate rapidly will double their population more frequently compared to cells with a slower proliferation rate. Scientific analysis of cytokine-dependent proliferation rates in cancer reveals intricate mechanisms that drive tumor progression and therapeutic resistance. Studies have shown that cytokine-mediated pathways can enhance cancer cell proliferation by promoting cell cycle progression, inhibiting apoptosis, and stimulating angiogenesis [49,50]. Conversely, some cytokines may exert anti-tumor effects by activating immune responses or inducing tumor cell differentiation. Insights gained from dynamic modeling underscore the importance of targeting cytokine signaling pathways in cancer therapy. Strategies aimed at blocking cytokine receptors or inhibiting downstream signaling molecules have shown promise in preclinical and clinical studies, offering potential avenues for personalized treatment approaches based on cytokine profiles and tumor characteristics. The clinical implications of dynamic modeling in cancer research include the development of novel biomarkers for predicting patient outcomes and guiding treatment decisions. By integrating multi-omics data with mathematical models, researchers can enhance the accuracy of predictive models and identify new therapeutic targets. Future research directions include refining mathematical models to incorporate spatial heterogeneity within tumors, exploring the dynamics of immune-cancer interactions, and evaluating the impact of cytokine-targeted therapies in patient cohorts. Signal intensity and proliferation rate over time in healthy cells is tightly regulated to maintain tissue homeostasis. Cells integrate signals from their environment to modulate proliferation rates appropriately, ensuring balanced growth and function within tissues. This dynamic process underscores the importance of understanding cellular responses to signals in both health and disease condition.

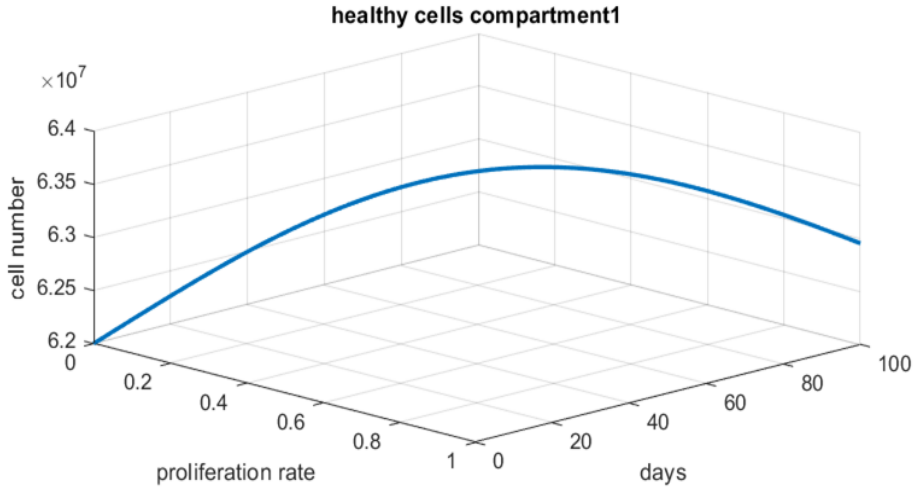

Figure 2: Signal Intensity Dependency on Proliferation Rate with Time for Healthy Cell Compartment 1

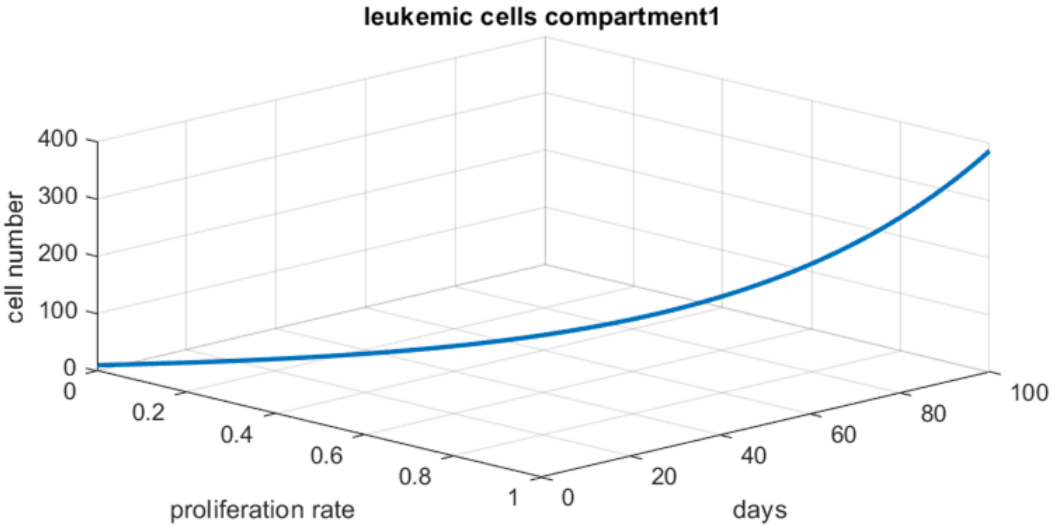

Figure 3: Signal Intensity Dependency on Proliferation Rate with Time for Leukemic Cell Compartment 1

The effect of signal intensity on proliferation rate can change over time. Initially, when cells receive a signal, they may respond by increasing their proliferation rate to meet physiological demands. For instance, during tissue repair or growth phases, cells may proliferate more rapidly in response to growth factors like insulin-like growth factors (IGFs) or epidermal growth factor (EGF).

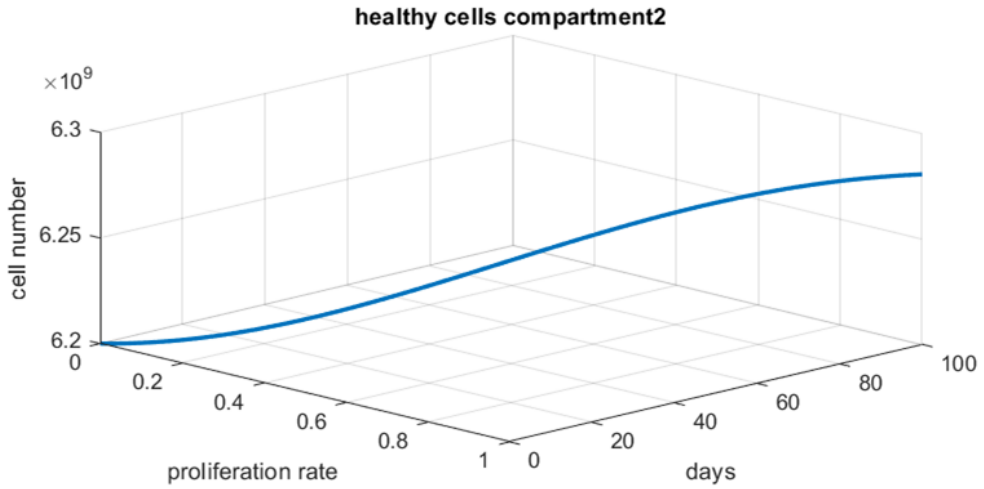

Figure 4: Signal Intensity Dependency on Proliferation Rate with Time for Healthy Cell Compartment 2

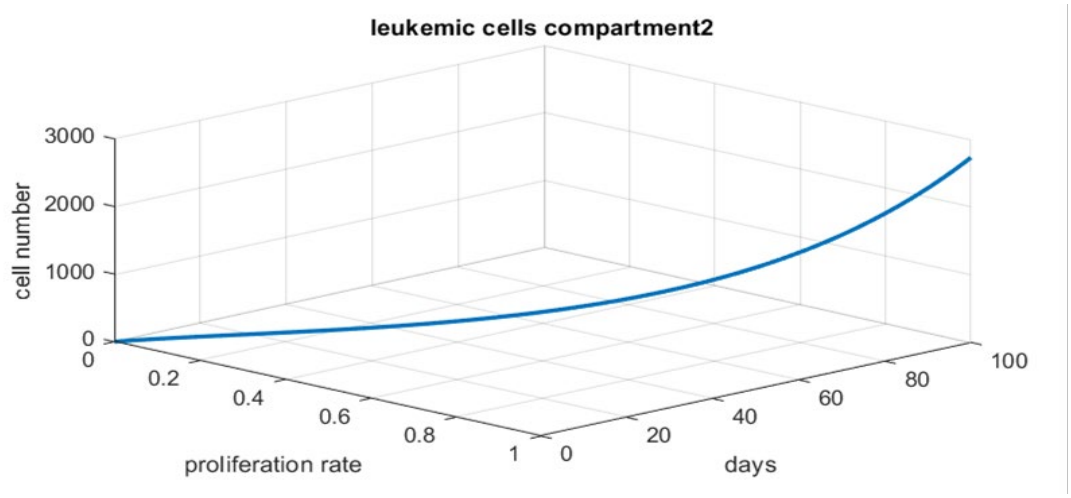

Figure 5: Signal Intensity Dependency on Proliferation Rate with Time for Leukemic Cell Compartment 2

When considering the variation of proliferation for cell number with days in figure (2) we observed an initial population of cells expands over a period as a result of proliferation. The relationship between cell number and time typically follows an exponential growth curve, especially under favorable conditions where cells have ample resources and minimal constraints in healthy cell compartment 1 whereas in the leukemic cell compartment 1 in figure (3) the process of cell growth got delayed. Cell proliferation dynamics depicted in figures (4) and (5), the healthy cell compartment 2 (Figure 3) demonstrates initial population expansion characterized by a noticeable increase in cell numbers over time. This proliferation is driven by cellular division, resulting in an exponential growth curve where each cycle contributes to a progressively larger cell population. Such growth dynamics are typical of healthy tissues, where cells proliferate at controlled rates to sustain tissue function and integrity under optimal conditions [51,52]. Conversely, the leukemic cell compartment 2(Figure 5) exhibits delayed cell growth compared to its healthy counterpart. This delay in cell proliferation reflects the dysregulated nature of leukemic cells, often stemming from genetic mutations or aberrant signaling pathways. The altered growth pattern observed in leukemic cells contrasts sharply with the exponential growth curve seen in healthy cells. Understanding these differences in proliferation dynamics is pivotal for devising targeted therapies that selectively address the unique vulnerabilities of leukemic cells while minimizing harm to healthy tissues. The proliferation behaviors between healthy and leukemic cell compartments1 and 2 underscore the importance of discerning these dynamics for effective therapeutic interventions. Insights gained from such analyses not only deepen our understanding of disease mechanisms but also guide the development of personalized treatment strategies tailored to mitigate the specific challenges posed by leukemia [53,54].

4. Conclusion

Understanding the differences in proliferation dynamics between healthy and leukemic cells is crucial for developing targeted therapies. Therapeutic strategies often aim to selectively target leukemic cells while sparing healthy tissues, leveraging these distinct proliferation characteristics. Dynamic modeling of cytokine-dependent proliferation rates provides valuable insights into the complex interplay between cytokine signaling networks and tumor cell dynamics in cancer. By combining scientific analysis with mathematical approaches, this work contributes to our understanding of cancer biology and informs the development of innovative therapies. In this analysis of cell proliferation dynamics results reveals distinct behaviors between healthy cell compartments and leukemic cell compartments. Healthy cells demonstrate initial exponential growth driven by controlled division, essential for tissue maintenance. In leukemic cells exhibit delayed proliferation. Understanding these differences is crucial for developing targeted therapies that effectively address leukemia's specific challenges while preserving healthy tissue integrity. This insight guides the development of personalized treatment strategies to improve oncological outcomes. Continued interdisciplinary efforts are essential to translating these insights into clinical applications that improve patient outcomes and advance cancer treatment strategies.

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