Mathematical Modeling of Bone Marrow – Peripheral Blood Dynamics in the Disease State Based on Current Emerging Paradigms, Part II

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Abstract

The cancer stem cell hypothesis has gained currency in recent times but concerns remain about its scientific foundations because of significant gaps that exist between research findings and comprehensive knowledge about cancer stem cells (CSCs). In this light, a mathematical model that considers hematopoietic dynamics in the diseased state of the bone marrow and peripheral blood is proposed and used to address findings about CSCs. The ensuing model, resulting from a modification and refinement of a recent model, develops out of the position that mathematical models of CSC development, that are few at this time, are needed to provide insightful underpinnings for biomedical findings about CSCs as the CSC idea gains traction. Accordingly, the mathematical challenges brought on by the model that mirror general challenges in dealing with nonlinear phenomena are discussed and placed in context. The proposed model describes the logical occurrence of discrete time delays, that by themselves present mathematical challenges, in the evolving cell populations under

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consideration. Under the challenging circumstances, the steady state properties of the model system of delay differential equations are obtained, analyzed, and the resulting mathematical predictions arising therefrom are interpreted and placed within the framework of findings regarding CSCs. Simulations of the model are carried out by considering various parameter scenarios that reflect different experimental situations involving disease evolution in human hosts.

Model analyses and simulations suggest that the emergence of the cancer stem cell population alongside other malignant cells engenders higher dimensions of complexity in the evolution of malignancy in the bone marrow and peripheral blood at the expense of healthy hematopoietic development. The model predicts the evolution of an aberrant environment in which the malignant population particularly in the bone marrow shows tendencies of reaching an uncontrollable equilibrium state. Essentially, the model shows that a structural relationship exists between CSCs and non-stem malignant cells that confers on CSCs the role of temporally enhancing and stimulating the expansion of non-stem malignant cells while also benefitting from increases in their own population and these CSCs may be the main protagonists that drive the ultimate evolution of the uncontrollable equilibrium state of such malignant cells and these may have implications for treatment.

Keywords: healthy cells, cancer stem cells, mathematical models

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1. Introduction

Against the backdrop of the cancer scorecard [1] that shows that more improvements in cancer prevention, detection, treatment, and management may be needed in the future, the cancer stem cell (CSC) hypothesis is gaining increasing attention. However, as this paradigm gains traction, a number of controversies still exist that need to be settled. There are concerns about the scientific foundations of the CSC concept because of significant gaps that exist between research findings and comprehensive knowledge about cancer stem cells [2–5]. It is believed that CSCs may be responsible for causing relapses and engineering the abortion of remissions due to their resistant nature [5]. Apparently, achievement of therapeutic effectiveness takes

place against non-stem cancer cells and not CSCs that are capable of remaining viable after long periods of treatment. Recent evidence suggests that therapeutic stress may also promote cellular plasticity, which mediates the conversion of normal cancer cells to a CSC-like state [2].

In our recent article [6] on the above-stated subject matter, a model of bone marrow - peripheral blood dynamics in the disease state was introduced that sought to present a unified picture of Clarkson's [7] classical view of cancer development with the relatively recent hypothesis on cancer stem cells (CSCs) as described in works such as those in [8–48]. In concluding that article [6], we posed a question about how the dynamics in the disease state could be affected in the presence of a distinct population of CSCs, since the dynamics obeyed by such cells was not explicitly addressed and probed in that discourse. This article is dedicated to investigating this and other questions and since the biomedical literature related to the CSC paradigm was extensively discussed in [6], we will herein shift our attention to discussing recent and relevant CSC-driven mathematical models that have appeared in the literature before moving ahead to consider other modeling issues.

Mathematical modeling of cancer has been progressing steadily over the years as is evidenced by works such as those in [52–60] that focus primarily on disseminated cancers, on one hand, and those in [61–64] that involve investigations of solid tumor cancers, on another hand. To date, we note that CSC-driven mathematical modeling activity that forms the focal point of this discourse is not as yet as extensive as general mathematical modeling of cancer because of the relatively recent nature of the emerging CSC paradigm. However, it is obvious that more CSC-driven models would be appearing in the future as the CSC hypothesis gains wider traction and recognition within the entire community of biomedical research and practice. With the spotlight on CSC-driven mathematical models we now proceed to consider a few models of CSCs that have appeared in the literature in recent times.

A survey of the literature shows that most CSC-driven mathematical models have in the main utilized ordinary differential equation (ODE) approaches. This may be due to the fact that such approaches are more suited to capturing the hierarchically

structured nature of CSC development that is amenable to compartmentalization. The models have tended to focus more on studies of cell population dynamics and the treatment implications they engender and less on the mutation pathways that lead to the heterogeneous mixture of cells. Nonetheless, some of the ODE models have yielded certain projections about mutation acquisition. In [65], Ganguly and Puri introduced a system of ordinary differential equations (ODEs) detailing seven cell types that make up the model compartments: normal stem, early progenitor, late progenitor, and mature cells, and their abnormal counterparts, respectively. The simulations showed that an oncogenic event in normal stem cells could lead to an increase in abnormal progeny cells, compared to the case of mutations in normal early progenitor cells. This led to the postulation that an increase in the growth rate of abnormal early progenitor cells led to faster proliferation of such cells and increased cancer risk. Calmelet and his coworkers [66] used a similar approach as in [65] to obtain a system of eight nonlinear ODEs that arose from dividing respective subgroups of cells into normal and abnormal stem cells and their early and late progenitors. This model was used to study different disease stages as a tumor progressed from benign to invasive stages and the effects of therapy were investigated through simulations.

Focusing on the exponential growth phase of tumors, Johnston and his coworkers [67] introduced an ODE model that described dynamics of stem cells, progenitor transit-amplifying cells, and fully differentiated cell populations and showed that stem cells could make up any proportion of the tumor. They postulated from model investigations that higher stem cell proportions could yield more aggressive tumors if a certain balance between tumor growth and differentiation rates existed. The model of Molina-Peña and Álvarez [68] also focused on the exponential growth phase of tumors and showed that if certain kinetic relationships were satisfied then the calculated tumor growth and stem cell fractions could be consistent with experimental observation. By basing their investigations on an agent-based model developed by Enderling et. al. [69], Hillen et. al. [70] introduced an integro-differential equation model of cancer stem and non-stem cell populations and showed that the two pop-

ulations interacted with each other in such a way that higher rates of cell death in the non-stem cell compartment led to an enrichment of cancer stem cells, and thus accelerated overall growth. Unlike the works in [67] and [68], Hillen and his coworkers considered tumor growth beyond the exponential growth phase by introducing a cell carrying capacity. They showed that constant cell turnover and competition with the carrying capacity was an indication that the cancer stem cell fraction may not be constant but may be continuously increasing, with a pure cancer stem cell state being the only resulting stable steady state.

Using motivations from the works of Marciniak-Czochra et. al. [72] and Werner et. al. [73], Weeks and her coworkers [71] developed a system of linear ODEs to study the development of a heterogeneous cancer cell population where each tumor subpopulation was assumed to be grouped into multiple compartments comprised of cells of comparable proliferation potential. An outcome of their model analysis was that only low non-stem cancer cell proliferation capacities yielded optimum tumor growth for cell cycle times that were within biologically observed ranges. This indicated that tumors of stem or non-stem cancer cell dynamics either grew with sub-optimal cell cycle times, or that non-stem cancer cells could be short-lived. A slant that veers away from investigations of CSC dictated population dynamics is taken in [74] where Gentry and Jackson study mutational dynamics by introducing a system of eight ODEs that described mutational transformation events in a normal hierarchical tissue. They used their model to investigate how deregulation of the mechanisms preserving tissue homeostasis contributed to cancer. The model predicted that the order in which mutations were acquired significantly affected the pace of tumorigenesis. Their model also predicted that certain types of mutations were more significant than others in dictating cancer onset.

So far, our discussions have centered around CSC-driven mathematical modeling in general. In the particular instance of CSC models within the context of the bone marrow - peripheral blood system that forms the subject matter of this discourse, the only models of relevance that we revisit again later in this discourse appear in the works of Stiehl and Marciniak-Czochra [75] and Stiehl et. al. [76]. In [75] Stiehl and

Marciniak-Czochra develop a model in which healthy or normal hematopoietic cells exist side-by-side with leukemic cells in various respective cell compartments. For the healthy hemopoietic cell line they assumed that the first compartment was made up of healthy stem cells while the compartments that followed were made up of post-mitotic mature cells. In similar fashion, the leukemic cell line had leukemic stem cells (LSC) making up the first compartment. From analysis and simulations, they concluded among other things that their model could engender different types of steady states based on the model parameter space and posited the existence of a unique healthy and a unique purely leukemic steady state, and showed conditions under which composite steady states could arise. In [76], Stiehl and his coworkers employed the model proposed in [75] to study cell division patterns in acute myeloid leukemia (AML) stem-like cells and established that model-driven patient data analysis suggest that proliferation and self-renewal rates of LSC have greater impact on clinical dynamics of AML than self-renewal and proliferation rates of non-stem leukemic cells. Quite practically, due to the limitations placed on us by considerations of brevity, it is not possible for us to discuss all models. As such, we point here to other important works of relevance that are worth reading: [77–88].

The discussions so far show attempts by various researchers to model CSCs as a hierarchically defined structure with an apex. Some of the ensuing challenges involve finding definitive data from *in vivo* and *in vitro* sources for the appropriate estimation and measurement of model parameters. Because of the relatively "nascent" nature of biomedical work on CSCs, availability of kinetic information on cell types such as stem, early progenitor, late progenitor, and differentiated cells may be lacking or may be scanty at this time and this makes the employment of biomedical data in CSC-oriented models a challenging enterprise. Ironically, however, it is due to the very elusive nature of the search for kinetic information on stem cells that provides the important underpinnings for the use of mathematical models in this area that could provide insights and uncover "hidden" information about such cells and their behavior in order to guide experimentalists in their quest for the most appropriate and relevant data sets, in the first place ([76], [89]) . A way to deal with the scarcity of data in

this endeavor may be to start with models that utilize relatively small parameter spaces and allow easy estimation of relevant parameters. Various techniques could also be employed in identifying the few most important parameters within models that decisively affect model behavior, for which strenuous efforts would have to be made to measure them from experiments or from *in vivo* work. Such techniques could also provide opportunities and underpinnings for assigning arbitrary values to less crucial parameters.

Like was done in the CSC models described earlier, we will also adopt the approach of cell compartmentalization but focus on cell behavior and activity in the bone marrow (BM) and peripheral blood (PB), as was studied in [6]. We consider the CSC population as one distinct subpopulation within the BM that is different from non-stem cancer cells such as blasts. Accordingly, we consider the emergence of a CSC population that exists side by side with non-stem cancer cells and healthy or normal marrow cells in the BM. Consequently, we present a model system of five nonlinear ODEs with two delay terms in the ensuing discourse. In a nutshell, our modeling approaches here shed light and present notable insights into, (1) the occurrence and propagation of delays in the cell development systems that are not considered in most models because of the inherent complexities they present and (2) attempts to link CSC-driven modeling to active investigations of cell dynamics in the bone marrow and peripheral blood. Additionally, since the CSC paradigm remains an evolving idea at this point in time, one of our main objectives in this discourse is to use our model and its implications to affirm and confirm some of the main findings that have so far been obtained about CSC behavior and present modeling scenarios that have treatment implications with the aim of lending mathematical support to the quest of strengthening the scientific foundations of the CSC concept and guaranteeing its plausibility and viability as a new field of active investigation. Consequently in the sequel, we employ our models in studying treatment strategies that are based on the CSC concept as part of our over-arching objectives in this endeavor. With cancer remaining as one of the most challenging and versatile diseases of all time, it is our conviction that mathematical models of diverse kinds are needed in studying,

analyzing, and simulating various strands of this disease and their multiple treatment strategies as biomedicine takes on an increasingly quantitative posture. It is within this context that this article is written. The subsequent sections are arranged as follows: in section two we bring together model assumptions from [6] and the new assumptions stemming from considerations of CSC emergence, section three deals with model analyses, section four addresses model simulations, and discussions and concluding remarks can be found in section five.

2. Model Assumptions and Set-up

Before proceeding with our model assumptions, we first present a compendium of medical facts from the biomedical literature that come from various sources, including [8–48], about CSCs that support and lead in a natural way to these assumptions:

- Many cancers are organized as hierarchies sustained by CSCs at their apex. These CSCs possess self-renewal capabilities similar to their healthy or normal counterparts ([5], [8–26]).
- CSCs are capable of self-renewal and differentiation into nontumorigenic cell progeny ([10–13], [32–38]).
- CSCs are responsible for treatment failure [9–47].
- Tumors are caricatures of normal development with a hierarchical organization ([8–12], [47]).
- Hematopoiesis and leukemia are both hierarchically organized processes originating from hematopoietic stem cells (HSCs) and leukemia stem cells (LSCs), respectively ([9–12], [15, 16]).
- LSCs display many features of healthy HSCs, including quiescence and self-renewal ([9], [15], [39], [49]).
- HSCs and LSCs crucially depend on signals from the BM microenvironment, the so-called niche ([9], [32], [50, 51]).

- For leukemia patients, studies have established that the vast majority of leukemic blasts are postmitotic and are continuously replenished from a small proliferative fraction of cells. Only a small fraction of leukemic blasts (about 5 percent) are actively cycling *in vivo*. Interestingly, the studies also reveal a rare cellular fraction that remains dormant for weeks to months before beginning to cycle [9].

- CSCs are inherently resistant to a variety of conventional treatments including chemo- and radiation-therapies [9–43].

- Due to their functional similarities with normal stem cells, and the observation that they often share specific surface markers, CSCs may derive from a mutated stem cell. CSCs can be generated experimentally from normal stem cells ([9], [32], [42], [46]).

- CSCs represent a small subpopulation of cells within a tumor that express cell surface markers including CD24, CD44, and/or CD133 ([42], [49]).

- CSCs are tumorigenic and capable of regenerating a tumor when transplanted into an animal host [9–13].

- miRNAs are involved in the regulation of CSCs properties [42, 43].

- CSCs play important roles in cancer relapse and metastasis [9–47].

Using the afore-stated medical facts and facts from the literature in general as a background, we obtain and enumerate the following guiding assumptions:

a) Following their evolution, non-stem malignant cells, herein referred to as blasts, exist side-by-side with healthy or normal cells but hinder healthy cell development ([7], [53], [55], [58], [59]),
b) The blast cells with no self-renewal capabilities are derived from healthy or normal cells that have undergone mutation ([20], [28–30], [32], [45]),

c) The emergence of a small population of CSCs with self-renewal capabilities occurs in the BM. These CSCs are also derived from healthy or normal cells that have undergone mutation ([2], [9], [90]),

d) Healthy cells that include hematopoietic stem cells, non-stem malignant cells, and CSCs, exist side-by-side in the bone marrow (BM). In the peripheral blood (PB), healthy and non-stem malignant cells exist side-by-side ([7], [53], [55], [58], [59]),

e) Healthy cell apoptosis takes place in the bone marrow [91–95],

f) The healthy and non-stem malignant (blasts) marrow cells follow a process of sigmoidal growth while the CSCs obey combinations of exponential and confined exponential growth ([52], [53], [59], [96]),

g) Cells in the BM respond to depletions or over-accumulation of cells in the PB through feedback mechanisms ([59], [97], [98], [99]),

h) Self-renewing and proliferating CSCs get converted into non-stem malignant cells in the BM, due to feedback. The reverse may be considered to be negligible [8–10],

i) Blast and CSC loss from the BM is negligible [59],

j) Blast cell loss takes place in the PB ([53], [59], [100]).

It is important to note that all the above assumptions come from biological experiments and observations except assumption (f) that comes from modeling works. Proceeding from these assumptions, and based on the schematic description in Figure 1, we obtain the following model that captures significant features of the CSC

hypothesis while utilizing the main ingredients of Clarkson's classical view [7]:

$$
\begin{aligned}
\frac{dN_m}{dt} &= \overbrace{\alpha N_m \ln\left(\frac{A_m + A_b}{\kappa_{nm} + N_m}\right)}^{\text{healthy BM cell renewal and growth}} - \overbrace{\alpha_m N_m}^{\text{mutation into blast}} - \overbrace{\frac{\alpha_{mr} N_m e^{-sL_b}}{\kappa_{nb} + N_b}}^{\text{transition to PB}} \\
&\quad - \overbrace{\alpha_c N_m}^{\text{mutation into CSC}} - \overbrace{\alpha_{md} N_m L_m}^{\text{inhibition in BM}} \\
\frac{dN_b}{dt} &= \overbrace{\frac{\alpha_{mr} e^{-\mu T_m - sL_b(t-T_m)} N_m(t-T_m)}{\kappa_{nb} + N_b(t-T_m)}}^{\text{healthy BM cell arrival in PB after time lag}} - \overbrace{\alpha_{bd} N_b L_b}^{\text{inhibition in PB}} - \overbrace{\alpha_b N_b}^{\text{cell loss}} \\
\frac{dL_m}{dt} &= \overbrace{\beta_m L_m \ln\left(\frac{A_w}{\kappa_l + L_m}\right)}^{\text{BM blast cell growth}} + \overbrace{\alpha_m N_m}^{\text{blast mutants}} \\
&\quad - \overbrace{\beta L_m}^{\text{BM blast transition to PB}} + \overbrace{\eta e^{-\phi T_c - \tau L_b(t-T_c)} C(t-T_c)}^{\text{CSC conversion into BM blast after time lag}} \\
\frac{dL_b}{dt} &= \overbrace{\beta L_m}^{\text{BM blast arrival in PB}} - \overbrace{\delta L_b}^{\text{cell loss}} \\
\frac{dC}{dt} &= \overbrace{\beta_c C(1 - \frac{C}{\kappa_c})}^{\text{CSC renewal and growth}} - \overbrace{\eta e^{-\tau L_b} C}^{\text{CSC transition into BM blast}} + \overbrace{\alpha_c N_m}^{\text{CSC mutants}}
\end{aligned}
\tag{1}
$$

with initial and time-lag conditions given by

$$
\begin{aligned}
&N_m(0) = N_{m0}, N_b(0) = N_{b0}, L_m(0) = L_{m0}, L_b(0) = L_{b0}, C(0) = C_0 \\
&N_m(t) = N_{mc}, -T_m \le t < 0 \\
&C(t) = C_{mc}, -T_c \le t < 0.
\end{aligned}
\tag{2}
$$

The functions and quantities in model system (1) are all continuously differentiable with respect to their arguments and are defined as follows:

- $N_m = N_m(t)$ is the population of healthy marrow cells/liter at time t,
- $N_b = N_b(t)$ is the population of healthy PB cells/liter at time t,
- $L_m = L_m(t)$ represents the population of non-stem malignant BM cells (blasts)/liter at time t,
- $L_b = L_b(t)$ refers to population of malignant PB cells/liter at time t,

- $C = C(t)$ refers to population of cancer stem cells/liter at time t.

Here, the units of measurement stated as "cells/liter" are understood to be taken with respect to blood, in line with the standard convention adopted in various studies ([15], [38], [50], [92]).

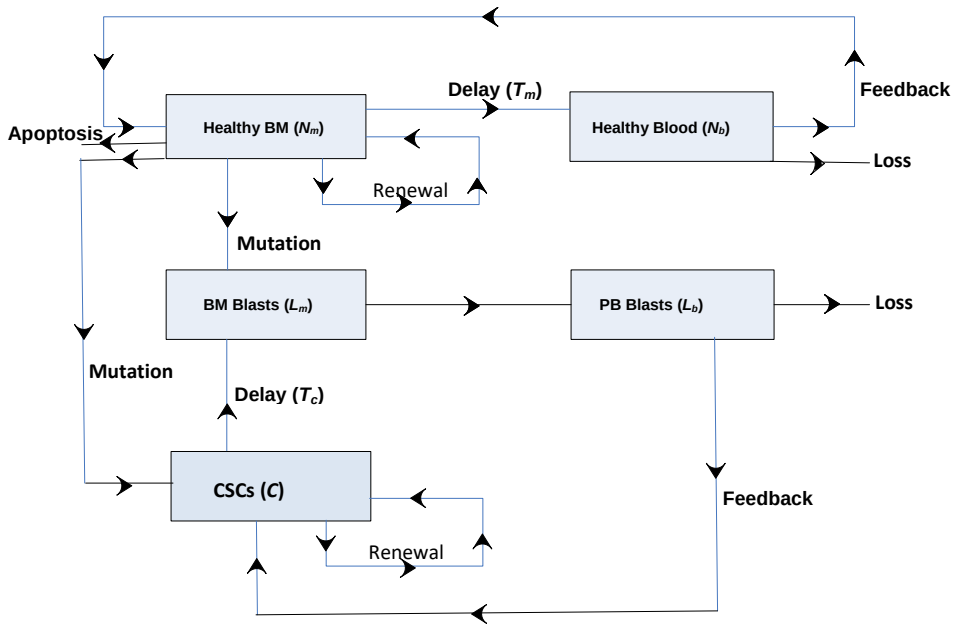

Figure 1: Schematic Description of Bone Marrow – Peripheral Blood – Cancer Stem Cell Dynamics

In addition to the quantities that have already been defined, the parameters in model system (1) are defined as follows and their value ranges are summarized in Table 1:

- α = intrinsic growth rate or renewal rate of healthy BM cells per unit time,
- α_m = probabilistic rate at which healthy BM cells mutate into non-stem malignant ones,

- α_{mr} = maximal rate of release of mature BM cells to the PB based on feedback,
- α_{md} = degree of inhibition exercised by the malignant cells in the marrow over the healthy BM cells,
- α_{bd} = degree of inhibition exercised by the malignant cells in the blood over the healthy PB cells,
- α_b = death or disappearance rate of healthy PB cells per unit time,
- α_c = probabilistic rate at which healthy BM cells mutate into CSCs,
- β_m = intrinsic growth rate of marrow blasts per unit time,
- β = release rate of BM blasts into the PB,
- δ = death or disappearance rate of blasts in the PB,
- T_m = maturation transit time of healthy BM cells,
- T_c = length of time before which CSCs get converted into non-stem malignant cells,
- β_c = intrinsic growth or renewal rate of CSCs per unit time,
- s = volume growth rate of malignant PB cells after time lag of T_m,
- τ = volume growth rate of malignant PB cells after time lag of T_c,
- μ = arrival rate of healthy BM cells in the PB per unit time after their maturation transit time elapses,
- ϕ = conversion rate of CSCs into non-stem malignant BM after time lag of T_c,
- η = transition or turnover rate of CSCs into the non-stem malignant BM based on feedback,
- A_m = healthy marrow carrying capacity or the maximum allowable number of healthy cells/liter in the BM,

- A_b = carrying capacity of healthy PB cells or the maximum allowable number of healthy cells/liter in the PB,
- A_w = carrying capacity or the maximum allowable number of all cells in the BM and PB/liter,
- κ_c = environmental carrying capacity of CSCs,
- κ_{nm} = constant threshold population level of healthy BM cells/liter that guarantees cell growth and renewal in the BM towards the healthy cell carrying capacity $A_m + A_b$ and could be taken to be the same as quantity N_{mc},
- κ_{nb} = constant threshold population level of healthy BM cells/liter at which the rate of cell movement from the BM to the PB is one-half of the maximal release rate of BM cells to the PB, and
- κ_l = constant threshold population level of malignant BM cells/liter that supports malignant cell growth in the BM towards the carrying capacity A_w.

2.1. Model Motivations

By drawing upon the peculiarities of model system (1) – (6) that was studied in Afenya et. al. [6], some noteworthy things about model system (1–2) are:

i) Its equations bear many similarities to and carry the same characteristics as model system (1) – (6) in Afenya et. al. [6]. The difference between this current model system and the one in [6] is the appearance of a separate population of CSCs.

ii) The Gompertz curve that features the logarithm as reflected in equation $(1)_3$ was found in [56] to be the best-fitting curve to the leukemia data of Skipper and Perry [101]. The logarithmic representation also received validation in [57] and carries over to its use in equation $(1)_1$ because of the similar functional and phenotypic characteristics of these cells [9].

iii) In [100], Clarkson and his coworkers state that instances for the promotion of malignant development include, a) the competition for essential nutrients between healthy and malignant cells that lead to competitive exclusion and extinction of the healthy cell population and b) contact inhibition and production of growth inhibitors by malignant cells. Additionally, in [50, 51], it is pointed out that malignant cells induce a change in the transcriptional programming of healthy cells. The modified niche alters the expressions of cross-talk molecules to provide a distinct, albeit, aberrant cross-talk between healthy and malignant cells that leads to selective suppression of healthy cells and promotion of malignancy [51]. Also, endosteal regions in the niche are remodeled into acquiring reduced capacity to support healthy cells and this correlates with loss of healthy hematopoiesis [50]. Essentially, these show that malignant cells act to impede and replace healthy cells and the reverse does not happen. These statements lend support to the phenomena of inhibition of the healthy cells by the malignant cells in the BM and PB as is modeled by the fifth term on the right hand side of equation $(1)_1$ and the second term on the right hand side of equation $(1)_2$.

iv) The combinations of exponential and confined exponential growth that the CSCs are assumed to obey essentially result in the behavior of sigmoidal growth. Such sigmoidal growth phenomenon may be a direct consequence of the influences exerted by the niche. It is pointed out in [12] that cells may go through a process of rapid exponential growth before lapsing into a resting state of maintenance. This is captured in the second expression on the right hand side of the fifth equation of model system (1). Sigmoidal growth behavior of cell populations in a general sense ([12], [62]) account for the asymptotic bounds A_m, A_b and A_w since there are constraints on the sizes of healthy and malignant niches [50, 51].

v) According to Borkowska et. al. [99], the mechanisms that regulate mobilization of BM cells into the PB across the BM - PB barrier in healthy hematopoiesis are still not well understood. In their quest to study and understand the pro-

cesses, they show that hemopoietic BM cells are released from their niches and circulate at detectable levels in the PB and their number increases in response to systemic or local inflammation, strenuous exercise, stress, tissue/organ injury, and pharmacological agents through the activation of various cascades [99]. Additionally, studies of Zhu et. al. [102] indicate that normal functioning feedback mechanisms dictated by healthy cells and mediated by cytokines and growth factors guarantee recovery of cells in the BM and PB in stress related and other normal malignant-free situations through various signaling pathways [102]. Putting the statements from Item (iii) above together with works such as those in ([47], [99], [102]), it may be reasonable to assume that cell signaling pathways may be aberrant in the malignant niche in such a way that feedback mechanisms may be dictated by malignant PB cells in the transmission of signals from the PB back to cells in the BM across the BM - PB barrier. In quantifying this assumption, the aberrant nature of the feedback and signaling mechanisms are partly captured through the expression e^{-sL_b} in Eqs. $(1)_1$ and $(1)_2$. They are also captured by the expression $e^{-\tau L_b}$ in Eqs. $(1)_3$ and $(1)_5$ and schematically shown in Figure 1, since mechanisms that affect the BM also by implication affect CSCs that are resident in the BM and are said to share similar characteristics with other cells in the BM [2]. It can be observed that the expressions vanish as L_b approaches infinity, that is when the population level of malignant cells in the PB becomes very large. We note that when L_b is relatively small, an indication of no malignant cells, the third term on the right of Eq. $(1)_1$ and the first term on the right of Eq. $(1)_2$ reduce to expressions containing only healthy BM and PB cell populations, the normal state that is discussed in [52]. This assumption also qualitatively highlights the alterations experienced by the hematopoietic system as a result of the emergence of malignancy [50, 51].

vi) Healthy cells, starting from HSCs, that are produced in the BM are said to go through various morphological changes until they reach maturation before crossing the BM - PB barrier into the PB to perform their various functions

[115]. This process of maturation naturally induces a maturation time lag T_m that is modeled in Eq. $(1)_2$. This indicates that BM cells traverse the BM compartment and arrive in the PB T_m time units later. In the case of the CSCs, Yoshida and Saya point out in [103] that such cells have slow cycle times. This suggests that a time lag exists between when CSCs emerge and when they get converted into non-stem BM malignant cells and this is quantified by the quantity T_c that is modeled in Eq. $(1)_3$. Accordingly, following the approach of Mackey in [113], the quantity $e^{-\mu T_m}$ corrects for the probability of cellular loss in the movement of cells from the BM to the PB in Eq. $(1)_2$ and the quantity $e^{-\phi T_c}$ corrects for the probability of cellular loss in the conversion of CSCs into BM non-stem malignant cells in Eq. $(1)_3$.

3. Analytical Results: Model Equilibria and Stability

Since the nonlinear nature of model system (1) cannot admit closed-form solutions, we appropriately consider the long range behavior of the model that affords us the opportunity to glean relevant information about stability properties exhibited by the model. In order to effectively find the model equilibria and efficiently perform stability analyses of model system (1), we define the following threshold variables that play important roles in the ensuing investigations:

$$\begin{cases} R(L) := \frac{\beta_m}{\beta}\left(\ln\left(\frac{A_w}{\kappa_L+L}\right) - \frac{L}{\kappa_L+L}\right) \\ r(L) := \alpha \ln\left(\frac{A_m+A_b}{\kappa_{nm}}\right) - \alpha_m - \frac{\alpha_{mr}e^{-\frac{s\beta}{\delta}L}}{\kappa_{nb}} - \alpha_{md}L \end{cases}$$

where

- $R(0)$ (denoted by R_{L_m} in Afenya et. al. [6]) is the basic reproductive ratio of malignant cells in the BM in the absence of mutation from BM healthy cells, this does not include influx of malignant BM cells from the CSC population. We note here that our choice of defining the function $R(L)$ as such has been done for the sake of notational convenience and provides the basis for using the notations $R(0)$ and $R(L_m^0)$ instead of their long forms in the ensuing discourse.

- $r(0) := \alpha \ln\left(\frac{A_m+A_b}{\kappa_{nm}}\right) - \alpha_m - \frac{\alpha_{mr}}{\kappa_{nb}}$ (denoted by $r^0_{N_m}$ in Afenya et. al. [6]) is the net growth rate, at the malignant cell free equilibrium, of BM healthy cells. The first term on the right hand side of this expression represents the basic growth rate, the second term describes the mutation rate, while the third is the rate of transformation of healthy BM cells into healthy PB cells.

- $r(L^0_m)$ (denoted by $r^L_{N_m}$ in [6]) is the net growth rate of BM healthy cells, evaluated at the CSC free and malignant cell equilibrium $L^0_m = A_w e^{-\frac{\beta}{\beta_m}} - \kappa_l$ (see the analysis below).

Now, by setting the right hand sides of model system (1) equal to zero and letting, 1) $\bar{N}_m$ and $\bar{N}_b$ represent the respective healthy cell steady states in the BM and PB, 2) $\bar{L}_m$ and $\bar{L}_b$ be the respective malignant cell steady states in the BM and PB, and 3) $\bar{C}$ represent the CSC steady state, we obtain the following system:

$$\begin{cases} \bar{N}_m \left[\alpha \ln\left(\frac{A_m+A_b}{\kappa_{nm}+\bar{N}_m}\right) - \frac{\alpha_{mr}e^{-s\bar{L}_b}}{\kappa_{nb}+\bar{N}_b} - \alpha_{md}\bar{L}_m - \alpha_m - \alpha_c\right] = 0 \\ \frac{\alpha_{mr}e^{-\mu T_m - s\bar{L}_b N_m}}{\kappa_{nb}+\bar{N}_b} - \left(\alpha_{bd}\bar{L}_b + \alpha_b\right)\bar{N}_b = 0 \\ \bar{L}_m\left(\beta_m \ln\left(\frac{A_w}{\kappa_l+\bar{L}_m}\right) - \beta\right) + \alpha_m\bar{N}_m + \eta e^{-\phi T_c - \tau\bar{L}_b}\bar{C} = 0 \\ \bar{L}_b = \frac{\beta}{\delta}\bar{L}_m \\ \beta_c\bar{C}\left(1 - \frac{\bar{C}}{\kappa_c}\right) - \eta e^{-\tau\bar{L}_b}\bar{C} + \alpha_c\bar{N}_m = 0 \end{cases} \tag{3}$$

In solving system (3), we first of all note from equation $(3)_3$ that $\bar{L}_m \neq 0$ unless $\bar{N}_m = \bar{C} = 0$. Moreover, using equation $(3)_1$ we obtain $\bar{N}_m = 0$ or $\alpha \ln\left(\frac{A_m+A_b}{\kappa_{nm}+\bar{N}_m}\right) - \frac{\alpha_{mr}e^{-s\bar{L}_b}}{\kappa_{nb}+\bar{N}_b} - \alpha_{md}\bar{L}_m - \alpha_m - \alpha_c = 0$. These consequently lead to the following cases and subcases:

3.1. Case I: $\bar{N}_m = 0$:

In this case, we obtain from equation $(3)_2$ that $\bar{N}_b = 0$ reducing equations $(3)_3 - (3)_5$ to $\bar{L}_b = \frac{\beta}{\delta}\bar{L}_m$ and

$$\begin{cases} \bar{L}_m \left(\beta_m \ln\left(\frac{A_w}{\kappa_l + \bar{L}_m} \right) - \beta \right) + \eta e^{-\phi T_c - \frac{\tau\beta}{\delta}\bar{L}_m} \bar{C} = 0 \\ \bar{C} \left(\beta_c \left(1 - \frac{\bar{C}}{\kappa_c} \right) - \eta e^{-\frac{\tau\beta}{\delta}\bar{L}_m} \right) = 0 \end{cases} \tag{4}$$

with equation $(4)_2$ implying that $\bar{C} = 0$ or $\bar{C} = \kappa_c \left(1 - \frac{\eta e^{-\tau \bar{L}_b}}{\beta_c} \right)$, leading to,

3.1.1. Subcase I.1: $\bar{C} = 0$:

From $(4)_1$ we obtain $\bar{L}_m \left(\beta_m \ln\left(\frac{A_w}{\kappa_l + \bar{L}_m} \right) - \beta \right) = 0$. Therefore,

1. If $R(0) \leq 1$, then $\left(\beta_m \ln\left(\frac{A_w}{\kappa_l + \bar{L}_m} \right) - \beta \right) < 0$ for all $\bar{L}_m \geq 0$. Then, we necessarily have $\bar{L}_m = 0$ leading to the trivial equilibrium point

$$E_0 = (0, 0, 0, 0, 0)$$

as the only equilibrium point with no CSC. The stability properties of E_0 are determined by the roots of its characteristic equation given by

$$(z + \delta)(z + \alpha_b)(z + \eta - \beta_c)(z + \alpha_c - r(0))(z - \beta(R(0) - 1)) = 0.$$

Hence, E_0 is locally asymptotically stable if and only if $\eta > \beta_c$, $r(0) < \alpha_c$ and $R(0) < 1$. The first condition here means that over a very large time horizon the turnover rate of CSC into the non-stem malignant BM becomes greater than its rate of proliferation and renewal which may induce CSC elimination. The second condition says that the net growth rate, at the malignant cell free equilibrium, of BM healthy cells is less than zero causing elimination of healthy cells. The third condition means that the reproductive rate of malignant cells is less than one inducing elimination of the malignant population. This is similar to the case where eradication of malignancy goes along with eradication of healthy tissues as was found in Afenya et. al. [6]. The implications for treatment here is that if malignant cells are to be completely destroyed then this may have to go hand in hand with complete obliteration of healthy cells and this may not be a feasible option.

2. If $R(0) > 1$, then $L_m^0 := A_w e^{-\frac{\beta}{\beta_m}} - \kappa_l > 0$ implying that, in addition to E_0, model system (1) has another CSC free equilibrium point, namely, the biaxial equilibrium point

$$E_L := \left(0, 0, L_m^0, \frac{\beta}{\delta} L_m^0, 0\right).$$

The stability properties of E_L are determined by the roots of its characteristic equation given by

$$\begin{aligned}&(z+\delta)\left(z+\alpha_b+\tfrac{\alpha_{bd}\beta L_m^0}{\delta}\right)\left(z+\eta e^{-\frac{\tau\beta}{\delta}L_m^0}-\beta_c\right)\\&\times\left(z+\alpha_c-r\left(L_m^0\right)\right)\left(z+\beta\left(1-R\left(L_m^0\right)\right)\right)=0\end{aligned}$$

Since $\beta\left(1-R\left(L_m^0\right)\right) = \frac{\beta_m L_m^0}{\kappa_L + L_m^0} > 0$, then E_L is locally asymptotically stable if and only if $\eta > \beta_c e^{\frac{\tau\beta}{\delta}L_m^0}, r\left(L_m^0\right) < \alpha_c$, (and $R(0) > 1$ for the biological feasibility of E_L). Here, these two conditions supporting the biological feasibility of E_L show that there is an evolution of the system towards a state in which malignancy takes hold in the BM and PB, driven mostly by non-stem malignant cells with no participation from CSCs. This occurs when mutation of healthy BM cells into CSCs increases beyond a certain threshold but the turnover rate of CSCs into the non-stem malignant BM is higher than CSC proliferation and renewal leading to non-stem malignant BM cells and not CSCs being the main contributors to the malignant state. This means in an asymptotic sense that the CSC population may remain at a very low level for all time and may not necessarily contribute to complicating the malignant situation implying that treatment in this case may be a "good" option since the focus would only be on non-stem malignant cells that lack self-renewal capabilities.

3.1.2. Subcase I.2: $\bar{C} = \kappa_c\left(1 - \frac{\eta}{\beta_c} e^{\frac{-\tau\beta}{\delta}\bar{L}_m}\right)$

In this subcase we necessarily have $\bar{L}_m > \tilde{L}_m := \frac{\delta}{\tau\beta}\ln\left(\frac{\eta}{\beta_c}\right)$ for $\bar{C}$ to be positive. Substituting the expression $\bar{C} = \kappa_c\left(1 - \frac{\eta}{\beta_c} e^{\frac{-\tau\beta}{\delta}\bar{L}_m}\right)$ into equation $(4)_1$ leads to the following tri-axial equilibrium point:

$$E_{LC} := \left(0, 0, L_m^{\#}, \frac{\beta}{\delta} L_m^{\#}, C^{\#}\right)$$

where $C^{\#} := \kappa_c \left(1 - \frac{\eta}{\beta_c} e^{\frac{-\tau\beta}{\delta} L_m^{\#}}\right)$ and $L_m^{\#}$ is any root of

$$\begin{aligned} G\left(\bar{L}_m\right) = \; & \bar{L}_m \left(\beta_m \ln\left(\tfrac{A_w}{\kappa_L + \bar{L}_m}\right) - \beta\right) \\ & + \eta\kappa_c e^{-\phi T_c - \frac{\tau\beta\bar{L}_m}{\delta}} \left(1 - \tfrac{\eta}{\beta_c} e^{\frac{-\tau\beta}{\delta}\bar{L}_m}\right) \end{aligned} \tag{5}$$

in the interval $\left[\max\left(0, \tilde{L}_m\right), +\infty\right)$.

Moreover, for any $L_m^{\#} > \max\left(0, \tilde{L}_m\right)$ to be a positive root of G, it must satisfy $\beta_m \ln\left(\frac{A_w}{\kappa_l + L_m^{\#}}\right) < \beta$ implying that $L_m^{\#}$ must also be greater than L_m^0. Therefore, we restrict the investigation of the roots of G to the interval $[L_m^{\bullet}, +\infty)$ where $L_m^{\bullet} = \max\left(0, \tilde{L}_m, L_m^0\right)$.

Given that $\lim_{\bar{L}_m \to +\infty} G\left(\bar{L}_m\right) = -\infty$, we discuss the following cases:

1. If $G\left(L_m^{\bullet}\right) > 0$, then G has at least one positive root on $[L_m^{\bullet}, +\infty)$.
2. If $G\left(L_m^{\bullet}\right) < 0$, then due to $G'\left(\bar{L}_m\right) = \beta\left(H\left(\bar{L}_m\right) - \frac{\tau\eta\kappa_c}{\delta} e^{-\phi T_c - \frac{\tau\beta\bar{L}_m}{\delta}}\right)$ where $H\left(\bar{L}_m\right) := R\left(\bar{L}_m\right) - 1 + \frac{2\tau\kappa_c\eta^2}{\beta_c\delta} e^{-\phi T_c - \frac{2\tau\beta\bar{L}_m}{\delta}}$ is a decreasing function satisfying $\lim_{\bar{L}_m \to +\infty} H\left(\bar{L}_m\right) = -\infty$, we discuss the following cases:
   - **i.** If $H\left(L_m^{\bullet}\right) < 0$, then for all $\bar{L}_m > L_m^{\bullet}$ we have $H\left(\bar{L}_m\right) < 0$, implying that $G'\left(\bar{L}_m\right) < 0$. Therefore, G has no positive root on $[L_m^{\bullet}, +\infty)$.
   - **ii.** If $H\left(L_m^{\bullet}\right) > 0$, then there exists $\mathring{L}_m > L_m^{\bullet}$ such that $H\left(\mathring{L}_m\right) = 0$ and $H\left(\bar{L}_m\right) < 0$ for all $\bar{L}_m > \mathring{L}_m$. Hence, $G'\left(\bar{L}_m\right) < 0$ for all $\bar{L}_m > \mathring{L}_m$. This leads to the following subcases:
     - **a.** If $G\left(\mathring{L}_m\right) < 0$ then G has no positive root on $\left[\mathring{L}_m, +\infty\right)$.
     - **b.** If $G\left(\mathring{L}_m\right) > 0$ then G has a unique positive root on $\left[\mathring{L}_m, +\infty\right)$.

From the above investigation, we deduce the following:

1. If $R(0) < 1$ then $L_m^0 < 0$ implying that E_L is not biologically feasible and $L_m^{\bullet} = \max\left(0, \tilde{L}_m\right)$. Accordingly,
   - **i.** If $\eta \leq \beta_c$ then $\tilde{L}_m \leq 0$, implying that $L_m^{\bullet} = 0$ and $G\left(L_m^{\bullet}\right) = G(0) = \eta e^{-\phi T_c}\kappa_c\left(1 - \frac{\eta}{\beta_c}\right) > 0$. In this case G has at least one positive root $L_m^{\#}$

leading to at least one equilibrium point E_{LC}.

This condition means that if the turnover rate of CSC into the malignant BM, η, is less than the intrinsic growth and renewal rate of CSCs, β_c, then the CSC population can sustain its existence at a positive equilibrium level.

ii. If $\eta > \beta_c$ then $\tilde{L}_m > 0$, implying that $L_m^\bullet = \tilde{L}_m$ and $G\left(L_m^\bullet\right) = G\left(\tilde{L}_m\right) = \tilde{L}_m\left(\beta_m \ln\left(\frac{A_w}{\kappa_L + \tilde{L}_m}\right) - \beta\right)$ which is negative because $\tilde{L}_m > L_m^0$.

In this case, G has no positive root if $H\left(\tilde{L}_m\right) < 0$, and has at least one positive root if $H\left(\tilde{L}_m\right) > 0$ and $G\left(\mathring{L}_m\right) > 0$.

We note here that the condition $H\left(\tilde{L}_m\right) > 0$, expressed in terms of the carrying capacity of CSCs, is equivalent to the following condition:

$$\kappa_c > \frac{\delta e^{\phi T_c}}{2\tau\beta_c}\left(1 - R\left(\tilde{L}_m\right)\right).$$

This means that even if the turnover rate of CSCs into the non-stem malignant BM, η, exceeds the intrinsic growth and renewal rate of CSCs, β_c, CSCs are still able to establish their existence at a positive equilibrium as long as the threshold condition expressed by the inequality obtained above is satisfied.

2. If $R(0) > 1$ then $L_m^0 > 0$, implying that $L_m^\bullet = \max\left(L_m^0, \tilde{L}_m\right)$. Since $\tilde{L}_m \geq L_m^0$ if and only if $\eta \geq \beta_c e^{\frac{\tau\beta}{\delta} L_m^0}$, we discuss the following cases:

   i. If $\eta < \beta_c e^{\frac{\tau\beta}{\delta} L_m^0}$ then $G\left(L_m^\bullet\right) = G\left(L_m^0\right) = \eta\kappa_c e^{-\phi T_c - \frac{\tau\beta}{\delta} L_m^0}\left(1 - \frac{\eta}{\beta_c} e^{\frac{-\tau\beta}{\delta} L_m^0}\right) > 0$, which implies that G has a unique positive root $L_m^\#$.

   This result shows that when malignancy is established, the population of CSCs may be sustained at a positive equilibrium level if the transition rate of CSCs into the non-stem malignant BM is large enough. Furthermore, the threshold value increases exponentially with the values of malignant cells in BM at the equilibrium, L_m^0.

   ii. If $\eta \geq \beta_c e^{\frac{\tau\beta}{\delta} L_m^0}$ then $L_m^\bullet = \tilde{L}_m$ which, as in the case (**i.**) above, implies that G has no positive root if $H\left(\tilde{L}_m\right) < 0$, and has at least one positive root

if $G\left(\mathring{L}_m\right) > 0$.

This condition means that if the transition rate of CSCs into the non-stem malignant BM is too large, ($\eta \geq \beta_c e^{\frac{\tau\beta}{\delta}L_m^0}$), then CSCs can sustain their existence if their carrying capacity, κ_c, is large enough; and this comes from the relation,

$$\kappa_c > \beta_c \mathring{L}_m \left(\beta - \beta_m \ln\left(\frac{A_w}{\kappa_L + \mathring{L}_m}\right)\right) e^{\phi T_c + \frac{\tau\beta\mathring{L}_m}{\delta}} / \left(\eta\beta_c - \eta^2 e^{\frac{-\tau\beta}{\delta}\mathring{L}_m}\right).$$

The stability properties of E_{LC} are determined by the roots of its characteristic equation given by

$$\left(z + \alpha_b + \alpha_{bd}\frac{\beta}{\delta}L_m^{\#}\right)\left(z + \alpha_c - r\left(L_m^{\#}\right)\right)\left(P + Qe^{-zT_c}\right) = 0$$

where

$$P = (z+\delta)\left(z + \beta\left(1 - R\left(L_m^{\#}\right)\right)\right)\left(z + \frac{\beta_c C^{\#}}{\kappa_c}\right)$$
$$Q = \beta\eta\tau C^{\#} e^{-\phi T_c - \frac{\tau\beta}{\delta}L_m^{\#}}\left(z + 2\beta_c\frac{C^{\#}}{\kappa_c} - \beta_c\right).$$

Therefore, E_{LC} is unstable if $r\left(L_m^{\#}\right) > \alpha_c$. When $r\left(L_m^{\#}\right) < \alpha_c$, the stability of E_{LC} is determined by the following equation:

$$P + Qe^{-zT_c} = 0. \tag{6}$$

We note that equation (6) has a delay dependent parameter, we thus examine the distribution of its roots by following the methods adopted in [104].

If $T_c = 0$, then the function H is given by $H\left(\bar{L}_m\right) = R\left(\bar{L}_m\right) - 1 + \frac{2\tau\kappa_c\eta^2}{\beta_c\delta}e^{-\frac{2\tau\beta\bar{L}_m}{\delta}}$ and equation (6) reduces to

$$p_0 + p_1 z + p_2 z^2 + z^3 = 0, \tag{7}$$

where

$$\begin{cases} p_0 = \frac{\delta\beta\beta_c C^{\#}}{\kappa_c}\left(1 - R\left(L_m^{\#}\right)\right) + \beta\tau\eta\beta_c C^{\#} e^{-\frac{\tau\beta L_m^{\#}}{\delta}}\left(\frac{2C^{\#}}{\kappa_c} - 1\right) \\ p_1 = \beta\left(\frac{\beta_c C^{\#}}{\kappa_c} + \delta\right)\left(1 - R\left(L_m^{\#}\right)\right) + \frac{\delta\beta_c C^{\#}}{\kappa_c} + \beta\eta\tau C^{\#} e^{-\frac{\tau\beta L_m^{\#}}{\delta}} \\ p_2 = \beta\left(1 - R\left(L_m^{\#}\right)\right) + \delta + \frac{\beta_c C^{\#}}{\kappa_c} \end{cases}$$

We now proceed to investigate the distribution of the roots of equation (7) in the cases where E_{LC} is biologically feasible; that is when,

i. $R(0) < 1$, $\eta > \beta_c$ and $G\left(\mathring{L}_m\right) > 0$, where $\mathring{L}_m > L_m^0$ satisfies $H\left(\mathring{L}_m\right) = 0$ and $H\left(\bar{L}_m\right) < 0$ for all $\bar{L}_m > \mathring{L}_m$.

ii. $R(0) > 1$, $\eta \geq \beta_c e^{\frac{\tau\beta}{\delta}L_m^0}$, where $\mathring{L}_m > 0$ is defined as above.

iii. $R(0) > 1$ and $\eta < \beta_c e^{\frac{\tau\beta}{\delta}L_m^0}$, with L_m^0 satisfying $H\left(L_m^0\right) < 0$.

By the Routh-Hurwitz criterion [105], [106], equation (7) has no roots with positive real parts if and only if $p_0 > 0$, $p_1 > 0$, $p_2 > 0$ and $p_1 p_2 - p_0 > 0$.
It is easy to see that $p_0 > \frac{\delta\beta\beta_c C^\#}{\kappa_c}\left(1 - R\left(L_m^\#\right)\right) + 2\beta\tau\eta\beta_c C^\# e^{-\frac{\tau\beta L_m^\#}{\delta}}\left(\frac{C^\#}{\kappa_c} - 1\right) = -\frac{\delta\beta\beta_c C^\#}{\kappa_c} H\left(L_m^\#\right)$. Moreover, cases (**i.**) and (**ii.**) imply that $H\left(L_m^\#\right) < H\left(\mathring{L}_m\right) = 0$, while case (**iii.**) implies that $H\left(L_m^\#\right) < H\left(L_m^0\right) < 0$. Therefore, each of the three cases ensures that $p_0 > 0$ and $1 - R\left(L_m^\#\right) > \frac{2\tau\eta^2\kappa_c}{\beta_c\delta} e^{-\frac{2\tau\beta L_m^\#}{\delta}}$ with the latter inequality implying that p_1 and p_2 are positive.
Further, we have

$$\begin{aligned} p_1 p_2 &> \tfrac{\delta\beta\beta_c C^\#}{\kappa_c}\left(1 - R\left(L_m^\#\right)\right) + \beta\eta\tau C^\# e^{-\frac{\tau\beta L_m^\#}{\delta}} \tfrac{\beta_c C^\#}{\kappa_c} \\ &> \tfrac{\delta\beta\beta_c C^\#}{\kappa_c}\left(1 - R\left(L_m^\#\right)\right) + \beta\eta\tau\beta_c C^\# e^{-\frac{\tau\beta L_m^\#}{\delta}}\left(\tfrac{2C^\#}{\kappa_c} - 1\right) = p_0. \end{aligned}$$

The latter inequality is due to $\frac{C^\#}{\kappa_c} - \left(\frac{2C^\#}{\kappa_c} - 1\right) = 1 - \frac{C^\#}{\kappa_c} = \frac{\eta}{\beta_c} e^{\frac{-\tau\beta}{\delta}L_m^\#} > 0$.
Thus E_{LC} is locally asymptotically stable when $T_c = 0$.
As T_c increases, the number of roots of equation (6) with positive real parts may change only if one or multiple roots cross the imaginary axis. Clearly, the number 0 is not a solution of equation (6) (otherwise $p_0 = 0$), as such, any crossing may only occur at pure imaginary roots. Without loss of generality, we can consider the possibility that $z = i\omega$, $\omega > 0$, is a solution of equation (6). Separating the real and imaginary parts in equation (6) for $z = i\omega$, we obtain

$$q_0 + q_1\omega + q_2\omega^4 + \omega^6 = 0, \tag{8}$$

where

$$\begin{cases} q_0 &= \delta^2\beta^2\left(\frac{\beta_c C^{\#}}{\kappa_c}\right)^2\left(R\left(L_m^{\#}\right)-1\right)^2 \\ &\quad -\beta^2\tau^2\eta^2\beta_c^2 C^{\#2}\left(e^{-\frac{\tau\beta L_m^{\#}}{\delta}-\phi T_c}\right)^2\left(1-\frac{2C^{\#}}{\kappa_c}\right)^2 \\ q_1 &= \left(\frac{\beta_c C^{\#}}{\kappa_c}\right)^2\left(\delta^2+\beta^2\left(R\left(L_m^{\#}\right)-1\right)^2\right) \\ &\quad +\delta^2\beta^2\left(R\left(L_m^{\#}\right)-1\right)^2-\beta^2\eta^2\tau^2 C^{\#2}\left(e^{-\frac{\tau\beta L_m^{\#}}{\delta}-\phi T_c}\right)^2 \\ q_2 &= \beta^2\left(R\left(L_m^{\#}\right)-1\right)^2+\delta^2+\left(\frac{\beta_c C^{\#}}{\kappa_c}\right)^2. \end{cases}$$

It can be shown in a similar way to the p_j's that $q_j > 0$, for $j = 0, \cdots, 3$, implying that equation (8) has no positive roots. Therefore, no stability switch occurs as T_c increases, implying that E_{LC} remains locally asymptotically stable for all T_c.
Additionally, using the following parameter values,

$$\begin{gathered} A_m\text{=1e12, } A_b\text{=1e13, } A_w\text{=1.595e14, } T_m\text{=120, } \phi\text{=0.01, } s\text{=1e-12,} \\ \alpha\text{=2.88e-3, } \alpha_m\text{=0.005, } \alpha_{md}\text{ = 1e-14, } \alpha_{bd}\text{=5e-12, } \alpha_b\text{=1e-5, } \alpha_{mr}\text{=116713, } \mu\text{=0.065,} \\ \beta\text{=0.03, } \beta_m\text{=0.00396, } \kappa_{nb}\text{ = 1.1e11, } \kappa_l\text{=8.178e10, } \kappa_{nm}\text{=1.1e11, } \delta\text{=0.1925,} \\ \beta_c\text{=0.02, } \kappa_c\text{=5e6, } \eta\text{=0.001, } \alpha_c\text{=2e-9, } T_c\text{=100, } \tau\text{=1e-5} \end{gathered} \tag{9}$$

which are chosen from Table 1 so that $R(0) > 1, \eta < \beta_c e^{\frac{\tau\beta}{\delta}L_m^0}$ and $H\left(L_m^0\right) > 0$, we can see from Figure 2 that the function $H(L_m)$ is decreasing, which implies that E_{LC} is locally asymptotically stable for all $T_c \geq 0$. This suggests that a very large time lag may exist between when CSCs evolve and when they get transformed into non-stem malignant cells and this supports the notion that such cells are slowly cycling [103] but they ultimately aid in promoting and enhancing malignancy.

3.2. Case II: $\bar{N}_m \neq 0$:

In this case,

$$\alpha\ln\left(\frac{A_m+A_b}{\kappa_{nm}+\bar{N}_m}\right)-\frac{\alpha_{mr}e^{-s\bar{L}_b}}{\kappa_{nb}+\bar{N}_b}-\alpha_{md}\bar{L}_m-\alpha_m-\alpha_c=0. \tag{10}$$

From equation $(3)_3$ we obtain,

$$\bar{N}_m=\frac{\bar{L}_m}{\alpha_m}\left(\beta-\beta_m\ln\left(\frac{A_w}{\kappa_l+\bar{L}_m}\right)\right)-\frac{\eta}{\alpha_m}e^{-\phi T_c-\frac{\tau\beta\bar{L}_m}{\delta}}\bar{C}. \tag{11}$$

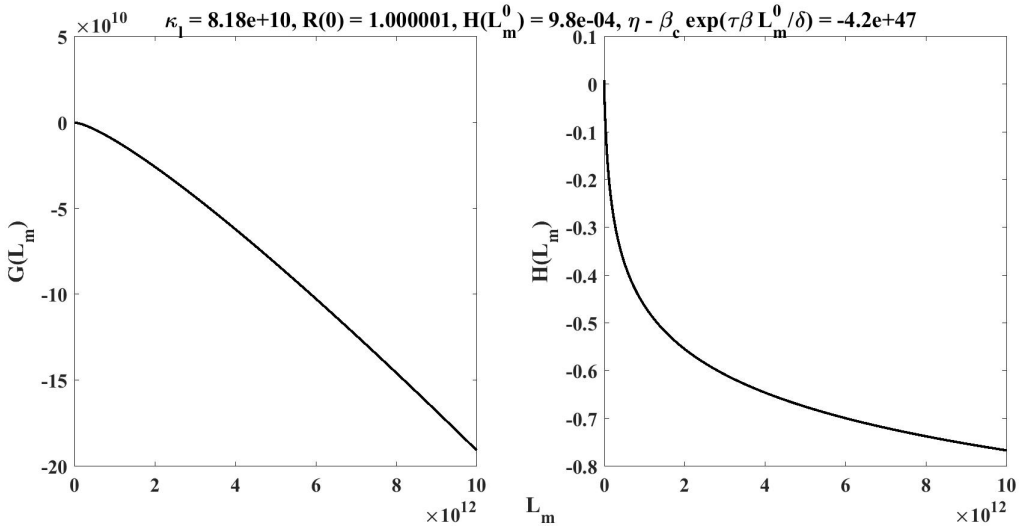

Figure 2: Profile of the functions $G(L_m)$ and $H(L_m)$ using parameters from Table 1. The monotonically decreasing nature of function $H(L_m)$ implies that steady state E_{LC} is locally asymptotically stable for all $T_c \geq 0$. The abscissa represents the increasing population of non-stem malignant cells in the BM and the ordinate represents functions $G(L_m)$ and $H(L_m)$.

Then we necessarily have $\dfrac{\bar{L}_m}{\alpha_m}\left(\beta - \beta_m \ln\left(\frac{A_w}{\kappa_l + \bar{L}_m}\right)\right) > 0$ which implies that $\bar{L}_m > L_m^0$ thus restricting the investigation of steady states to the interval $[\max(0, L_m^0), +\infty)$. Substituting equation (11) and $\bar{L}_b = \dfrac{\beta}{\delta}\bar{L}_m$ into equation $(3)_5$ leads to,

$$\bar{a}_2 \bar{C}^2 + \bar{a}_1\left(\bar{L}_m\right)\bar{C} + \bar{a}_0\left(\bar{L}_m\right) = 0 \tag{12}$$

where

$$\begin{aligned}
\bar{a}_0\left(\bar{L}_m\right) &= \frac{\alpha_c \bar{L}_m}{\alpha_m}\left(\beta_m \ln\left(\frac{A_w}{\kappa_l + \bar{L}_m}\right) - \beta\right) \\
\bar{a}_1\left(\bar{L}_m\right) &= \eta\left(1 + \frac{\alpha_c e^{-\phi T_c}}{\alpha_m}\right) e^{-\frac{\tau\beta\bar{L}_m}{\delta}} - \beta_c \\
\bar{a}_2 &= \frac{\beta_c}{\kappa_c}.
\end{aligned}$$

One can see that $\bar{a}_0\left(\bar{L}_m\right) < 0$, implying that equation (12) has a unique positive solution given by

$$\bar{C} = \frac{-\bar{a}_1\left(\bar{L}_m\right) + \sqrt{\bar{a}_1^2\left(\bar{L}_m\right) - 4\bar{a}_0\left(\bar{L}_m\right)\bar{a}_2}}{2\bar{a}_2} := \bar{C}\left(\bar{L}_m\right) \tag{13}$$

We note here that by an implicit differentiation of equation (12) with respect to L_m, we obtain

$$\bar{C}'\left(\bar{L}_m\right) = -\frac{\bar{a}_1'\left(\bar{L}_m\right)\bar{C}\left(\bar{L}_m\right) + \bar{a}_0'\left(\bar{L}_m\right)}{\left(2\bar{a}_2\bar{C} + \bar{a}_1\left(\bar{L}_m\right)\right)} = -\frac{\bar{a}_1'\left(\bar{L}_m\right)\bar{C}^2\left(\bar{L}_m\right) + \bar{a}_0'\left(\bar{L}_m\right)C\left(\bar{L}_m\right)}{\bar{a}_2\bar{C}^2\left(\bar{L}_m\right) - a_0\left(\bar{L}_m\right)}$$

Since $\bar{a}_0\left(\bar{L}_m\right) < 0, \bar{a}_2 > 0, \bar{a}_1'\left(\bar{L}_m\right) = -\frac{\tau\beta\eta}{\delta}\left(1 + \frac{\alpha_c e^{-\phi T_c}}{\alpha_m}\right)e^{-\frac{\tau\beta\bar{L}_m}{\delta}} < 0$ and $\bar{a}_0'\left(\bar{L}_m\right) = \frac{\alpha_c\beta}{\alpha_m}\left(R\left(\bar{L}_m\right) - 1\right) < \frac{\alpha_c\beta}{\alpha_m}\left(R\left(L_m^0\right) - 1\right) < 0$, then $\bar{C}'\left(\bar{L}_m\right) > 0$ and the function $\bar{L}_m \to \bar{C}\left(\bar{L}_m\right)$ is increasing on $[L_m^0, +\infty)$.

These results suggest that there is a direct functional relationship that exists between CSCs and non-stem malignant cells. We observe from the expression $\bar{L}_m \to \bar{C}\left(\bar{L}_m\right)$ that an increasing population of non-stem malignant BM cells leads to an increase in the CSC population. The calculations show that non-stem malignant cells increase exponentially the threshold values that support and enhance CSC population levels. We must ask at this juncture whether this functional relationship described above works in converse fashion. That is, do increases in CSC population levels lead to increases in the population levels of non-stem malignant cells? Indeed, to satisfy our curiosity in trying to answer this question, we most importantly find out that by means of the inverse function theorem [107] it is easy to obtain from the above result that the function $\bar{C} \to \bar{L}_m\left(\bar{C}\right)$ is increasing. This demonstrates that increases in CSC population levels lead to increases in non-stem malignant BM cell population levels with the calculations showing that an expanded equilibrium state for BM blast cells is possible. Model calculations thus suggest that the emergence of the CSC population in the BM, no matter how small, confers a mutual relationship on the CSCs and the non-stem malignant cells and this may complicate the existing malignant situation that may pose challenges to treatment. Therefore, predictions from the model confirm observations that have been made about the maintenance of cancer by the CSC population [9].

Proceeding further, we see that substituting equation (13) once more into equation

$(3)_3$, implies that

$$\bar{N}_m = \frac{\bar{L}_m}{\alpha_m}\left(\beta - \beta_m \ln\left(\frac{A_w}{\kappa_l + \bar{L}_m}\right)\right) - \frac{\eta}{\alpha_m} e^{-\phi T_c - \frac{\tau\beta\bar{L}_m}{\delta}} \bar{C}\left(\bar{L}_m\right) := \bar{N}_m\left(\bar{L}_m\right) \tag{14}$$

Equations (14) and $(3)_2$ imply that

$$\bar{N}_b = \frac{1}{2}\left[-\kappa_{nb} + \sqrt{\kappa_{nb}^2 + \frac{4\delta\alpha_{mr} e^{-\mu T_m - \frac{s\beta\bar{L}_m}{\delta}}}{\delta\alpha_b + \alpha_{bd}\beta\bar{L}_m} \bar{N}_m\left(\bar{L}_m\right)}\right] := \bar{N}_b\left(\bar{L}_m\right). \tag{15}$$

Finally, substituting equations (13)-(15) into equation (10) implies that,

$$\chi\left(\bar{L}_m\right) := \alpha \ln\left(\frac{A_m + A_b}{\kappa_{nm} + \bar{N}_m\left(\bar{L}_m\right)}\right) - \alpha_m - \alpha_c - \frac{\alpha_{mr} e^{-\frac{s\beta\bar{L}_m}{\delta}}}{\kappa_{nb} + \bar{N}_b\left(\bar{L}_m\right)} - \alpha_{md}\bar{L}_m = 0.$$

Moreover, $\lim\limits_{\bar{L}_m \to +\infty} \frac{\eta e^{-\phi T_c - \frac{\tau\beta\bar{L}_m}{\delta}}}{\alpha_m} \bar{C}\left(\bar{L}_m\right) = \lim\limits_{\bar{L}_m \to +\infty} \frac{\eta\sqrt{-4\bar{a}_0\left(\bar{L}_m\right)\bar{a}_2 e^{-2\phi T_c - 2\frac{\tau\beta\bar{L}_m}{\delta}}}}{2\bar{a}_2\alpha_m} = 0$ and $\lim\limits_{\bar{L}_m \to \infty} \bar{N}_m\left(\bar{L}_m\right) = +\infty$. Hence, $\lim\limits_{\bar{L}_m \to \infty} \bar{N}_b\left(\bar{L}_m\right) = +\infty$ and $\lim\limits_{\bar{L}_m \to \infty} \chi\left(\bar{L}_m\right) = -\infty$. Also, equation $(3)_3$ implies that $\bar{N}_m(0) = \bar{N}_m\left(L_m^0\right) = 0$ and $\bar{C}(0) = \bar{C}\left(L_m^0\right) = 0$. Therefore, $\bar{N}_b(0) = \bar{N}_b\left(L_m^0\right) = 0$ implying that $\chi(0) = r(0) - \alpha_c$ and $\chi\left(L_m^0\right) = r\left(L_m^0\right) - \alpha_c$. Hence, we discuss the following cases:

1. If $r(0) > \alpha_c$, then E_0 is unstable. Moreover,

   i. If $R(0) < 1$ then $L_m^0 < 0$, which implies that $\max\left(0, L_m^0\right) = 0$. Since $\chi(0) = r(0) - \alpha_c > 0$, then $\chi\left(\bar{L}_m\right)$ has at least one root $L_m^* > 0$.

   ii. If $R(0) > 1$ then $L_m^0 > 0$. If in addition $r\left(L_m^0\right) > \alpha_c$, then $\chi\left(L_m^0\right) = r\left(L_m^0\right) - \alpha_c > 0$ and $\chi\left(\bar{L}_m\right)$ has at least one positive root $L_m^* > L_m^0$.

2. If $r(0) < \alpha_c$, $R(0) > 1$ (implying that $L_m^0 > 0$) and $r\left(L_m^0\right) > \alpha_c$, then $\chi\left(L_m^0\right) = r\left(L_m^0\right) - \alpha_c > 0$ which implies that $\chi\left(\bar{L}_m\right)$ has at least one root $L_m^* > L_m^0$.

For each positive root L_m^*, we can easily see that $\bar{N}_m\left(L_m^*\right) > 0$ and $\bar{C}\left(L_m^*\right) > 0$. Moreover, for the set of parameter values given in (9), we found that $\bar{N}_b\left(L_m^*\right) > 0$ implying that model system (1) has at least one interior equilibrium given by,

$$E^* = \left(\bar{N}_m\left(L_m^*\right), \bar{N}\left(L_m^*\right), L_m^*, \frac{\beta L_m^*}{\delta}, \bar{C}\left(L_m^*\right)\right)$$

where $\bar{C}\left(L_m^*\right)$, $\bar{N}_m\left(L_m^*\right)$ and $\bar{N}_b\left(L_m^*\right)$ are described in equations (13), (14) and (15) respectively.

The remaining cases, namely,

1. $R(0) > 1$ and $r(L_m^0) < \alpha_c$
2. $R(0) < 1$ and $r(0) < \alpha_c$

are investigated numerically. In the first case we have $\max\left(0, L_m^0\right) = L_m^0$ with $\chi\left(L_m^0\right) = r\left(L_m^0\right) - \alpha_c < 0$, while the second case implies that $\max\left(0, L_m^0\right) = 0$ with $\chi\left(0\right) = r\left(0\right) - \alpha_c < 0$. Here we use the same parameter values given in (9) except for κ_l and α_m which are chosen so that conditions 1 and 2 directly above are satisfied. The values of κ_l and α_m along with the corresponding values of the threshold parameters R and r are presented on top of Figure 3, where it can be seen that the corresponding $\chi\left(\bar{L}_m\right)$ is decreasing and thus has no positive roots in the two cases stated above.

We note here that analyzing the stability of E^* would entail investigation of the roots of a transcendental equation with delay-dependent parameters and unknown parameters (due to the unknown expressions of E^*) which proves to be difficult to examine analytically. Using parameter values from Table 1, we find that system (1) has at least one interior equilibrium point E^*. Further, a numerical investigation of the roots of the characteristic equation of E^* suggests that $r\left(0\right) = \alpha_c$ engenders a transcritical bifurcation.

In a nutshell, the analytical assessments of model system (1) reveal that the model produces four steady states that are; a) the trivial equilibrium state E_0 that signifies a situation in which elimination of the malignant cells go simultaneously along with destruction of healthy tissue in the BM and PB, b)the biaxial steady state E_L that depicts a state in which non-stem malignant cells in the BM and PB dominate the entire system at the expense of healthy cells, c) the triaxial equilibrium point E_{LC} that describes a situation in which the CSCs join in aiding and coexisting with non-stem malignant cells in the BM and PB to suppress and dominate the entire system to the disadvantage of healthy cells, and finally, d) the steady state E^* that

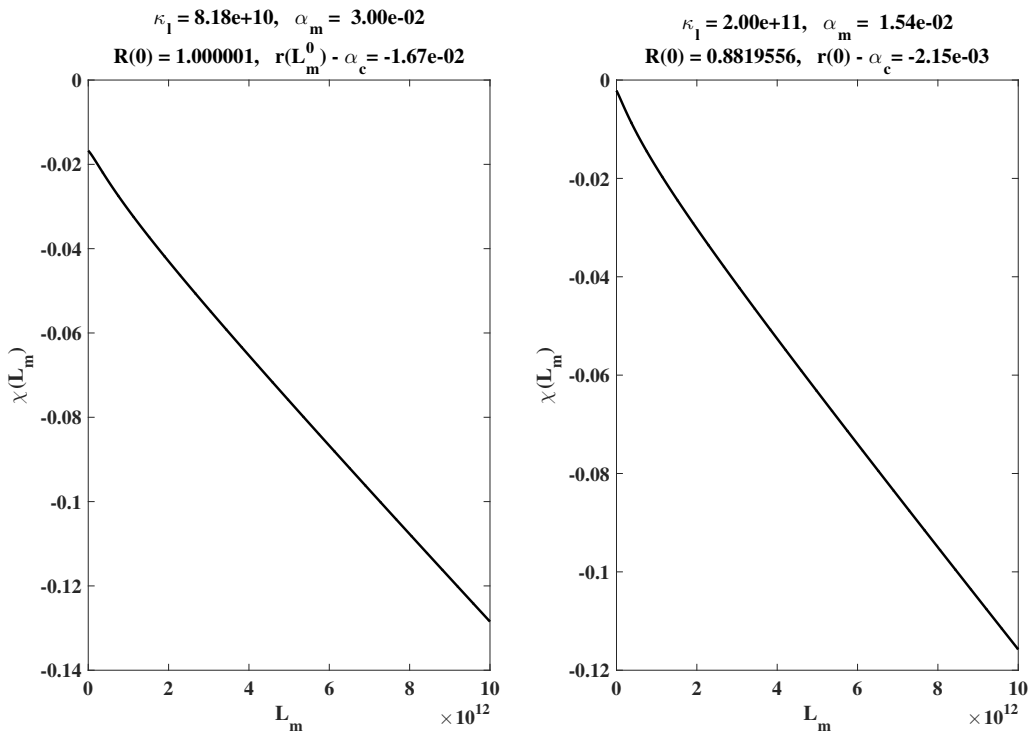

Figure 3: Profile of the decreasing function $\chi(L_m)$ using parameters from Table 1. The abscissa represents the increasing population of non-stem malignant cells in the BM and the ordinate represents function $\chi(L_m)$.

shows the possibility of coexistence of the CSCs and the non-stem malignant cells in the BM and PB with the healthy cells. The stability properties of these steady states as analyzed above do show circumstances in which they could remain stable or breakdown. Essentially, the majority of the emerging steady states show that healthy cells remain at a disadvantage so long as non-stem malignant cells and CSCs are present.

4. Model Simulations

In this section, we introduce Table 1 that presents various parameter values that are deduced and inferred from the scientific literature and from which values were obtained for the simulations and illustrations in Figures 2 and 3. We must point out that difficulties arise in obtaining appropriate model parameters because of in-

consistencies that sometimes occur when accessing clinical and experimental data [108]. As a result, the parameters in Table 1 are either numerically estimated from published results presented in existing data from the cited literature, obtained or extracted from experimental measurements, or are appropriately chosen in line with the roles they played during the model analysis regarding cell kinetics. Within the framework of accommodating and correcting for the inconsistencies arising from various data sources as mentioned earlier, the extracted parameter values are bracketed over various ranges as can be observed in the table (Table 1).

In addition to the simulations indicated in Figures 2 and 3, we proceed to show model simulations that seek to confirm our analytical findings in what follows. On the strength of the analyses conducted in the previous section, we identified parameters κ_l, α_m, and α_c as crucial to the propagation of malignancy and numerically sort to hold κ_l and α_m fixed while studying model behavior when α_c took on different values inside and outside its stated range. As already pointed out, within the context of the difficulties related to obtaining data, the simulation experiments that involve different sets of parameters are considered to be equivalent to experiments that include different disease situations in human hosts.

In Figure 4, over a relatively large time horizon of 10,000 hours, we observe evolution towards the trivial steady state, a state that signifies the demise of the host should no interventions to arrest the situation take place. Under similar but slightly different parameter conditions, model simulations in Figures 5 and 6 show BM and PB normal and malignant cells evolving over very large (10,000 hours) time horizons either towards the steady state of coexistence (see Fig. 5 where the mutation rate α_m is slightly reduced) or towards the steady state that reveals heavily diminished healthy cells in these compartments (see Fig. 6 where the parameter κ_1 is slightly reduced). Essentially, in all the cases depicted in the simulations, it can be observed that the presence of malignant cells in the BM and PB leads to a pattern of decrease among the healthy cells while the malignant cells may rise but settle at levels that dominate the viable healthy population. In the case of the CSCs that we consider separately, we observe under various parameter conditions

Table 1: Parameter Values and Definitions

Symbol	**Values(Units)**	**Basis**	**Definition**
α	[0.002, 0.149] (/hour)	[109]	growth or renewal rate of healthy BM cells
α_m	[0.0013, 0.0154] (/hour)	[94]	probabilistic rate of healthy BM cell mutation into malignant cell
α_{md}	$[1.0e-14, 5.0e-06]$	[52], [55]	degree of inhibition of healthy BM cells by malignant cells
α_{bd}	$[1.0e-14, 5.0e-06]$	[52], [55]	degree of inhibition of healthy PB cells by malignant cells
α_b	[0.00001, 0.0083] (/hour)	[97], [110]	death rate of healthy PB cells
β	[0.0065, 0.0565] (/hour)	[98]	release rate of BM blasts into the PB
T_m	[96, 144] (hours)	[111], [112]	transit time of healthy BM cells
T_c	[576, 1440] (hours)		time lag for CSC conversion to BM blasts
β_m	0.00396 ± 0.04825 (/hour)	[100]	growth rate of BM blasts
α_{mr}	$[9.0e+02, 1.23e+05]$ (/hour)	[52], [113]	maximal release rate of mature BM cells to the PB
α_c	$[1.0e-07, 1.0e-03]$ (/hour)		probabilistic rate of healthy BM cell mutation into CSC
A_m	$[1.0e+10, 5.88e+13]$ (cells/liter)	[114], [115]	maximum allowable number of healthy BM cells
A_b	$[1.0e+12, 1.0e+13]$ (cells/liter)	[59], [114]	maximum allowable number of healthy PB cells
A_w	$[6.0e+12, 3.688e+14]$ (cells/liter)	[59], [100], [112]	maximum allowable number of healthy and malignant cells
N_{mc}	$[1.0e+10, 5.0e+11]$ (cells/liter)	[52]	threshold level of healthy BM cells
κ_c	$[3.0e+04, 1.0e+06]$ (cells/liter)		CSC carrying capacity
β_c	$[0.0001, 0.05]$ (/hour)		growth or renewal rate of CSCs
δ	[0.001, 0.2] (/hour)	[100], [112]	death rate of PB blasts
s	$[1.0e-13, 1.0e-12]$ (liters/cell)		volume growth rate of malignant cells in PB after T_m
τ	$[1.0e-13, 1.0e-12]$ (liters/cell)		volume growth rate of malignant cells in PB after T_c
μ	[0.02, 0.11] (/hour)	[98]	arrival rate of healthy BM cells in PB
ϕ	[0.002, 0.02] (/hour)		arrival rate of CSCs in BM
η	[0.0001, 0.05] (/hour)		transition rate of CSCs into non-stem BM
κ_{nm}	$[1.0e+10, 5.0e+11]$ (cells/liter)		threshold population level of healthy BM cells
κ_{nb}	$[1.0e+10, 5.0e+11]$ (cells/liter)		threshold population level of healthy PB cells
κ_l	$[1.0e+10, 5.0e+11]$ (cells/liter)		threshold population level of malignant BM cells

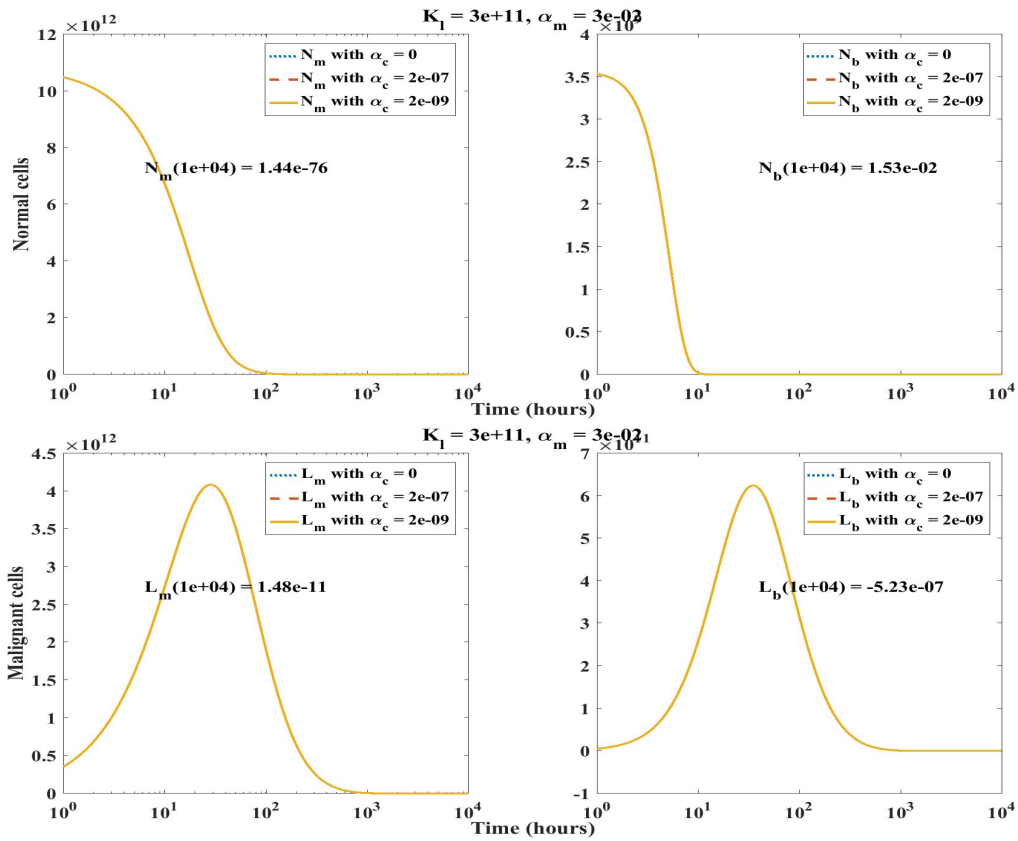

Figure 4: Simulations showing the evolution of the malignant and healthy populations in the BM and PB towards the trivial steady state E_0. In the top two graphs, healthy BM and PB cells fall to low levels upon the emergence of malignant non-stem cells that rise to high levels but fall to low levels due to possible unavailability of nutrients for supporting their continued growth over a large time horizon of 10,000 hours as shown in the bottom two graphs. The parameters κ_l (denoted here in uppercase) and α_m are held fixed while different values of α_c are considered. The visually distinct solid curves for the value $\alpha_c = 2e-09$ are shown.

for parameters κ_l, α_m, and α_c in Figure 7 that their population level rises over a moderate time window of 600 hours and peaks for very large time horizons as conversions take place from this compartment to the non-stem compartment. In Figure 8 the simulations reveal that a functional relationship exists between the non-stem malignant population in the BM and the equilibrium state of the CSCs that suggests that these two, albeit malignant populations, enhance the existence of each other. We note that this confirmatory evidence from the simulations gives adequate credence to our earlier analytical finding that the very presence of CSCs enhances and stimulates the entire malignant architecture.

5. Discussion and Concluding Remarks

From a survey of the literature, we observe that of the few existing CSC-driven mathematical models, the one proposed by Stiehl and Marciniak-Czochra [75] is most relevant to our studies, as we noted earlier, since it addresses the CSC concept within the blood system as we attempt to do in this discourse. It is instructive to note that despite the entirely different approaches adopted in our model and the model in [75], similar model predictions are obtained in certain circumstances. Stiehl and Marciniak-Czochra [75] describe cell activity in multiple healthy and diseased cell compartments with interaction among the cells described by a nonlinear coupled signal. In our model, discrete time delays inherent in the cell cycle that may be unavoidable are introduced, cell-cell interactions in the BM and PB are quantified by mass action type terms, and asymptotic bounds on cells in the BM and PB appear. The resulting steady states of our model and the Stiehl-Marciniak-Czochra model show coexistence of healthy and malignant cells in certain scenarios that may describe preleukemic states such as the myelodysplastic syndromes and they also show the pure diseased states. Obviously because of how the nonlinearities and other factors play out in the two different models, different model predictions are expected in certain circumstances. For example, the resulting biaxial steady state in our model captures the dominance of non-stem malignant cells over healthy cells without the participation of CSCs while the triaxial steady state which is similar to

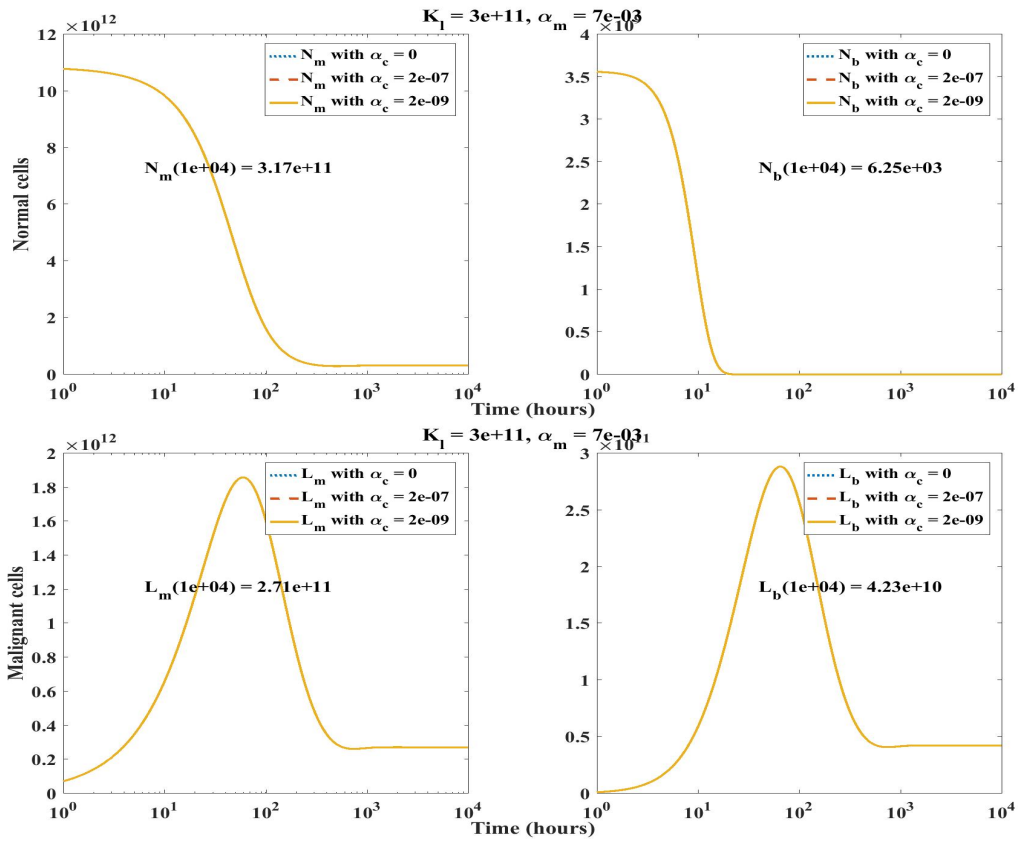

Figure 5: Simulations depicting evolution of the malignant and healthy populations in the BM and PB towards the steady state of coexistence E^*. In the top two graphs, healthy BM and PB cells fall to low levels upon the emergence of non-stem malignant cells that rise to high levels but settle at levels that ensure their dominance in the PB over a large time horizon of 10,000 hours as shown in the bottom two graphs. The parameters κ_l (denoted here in uppercase) and α_m are held fixed while different values of α_c are considered. The visually distinct solid curves for the value $\alpha_c = 2e-09$ are shown.

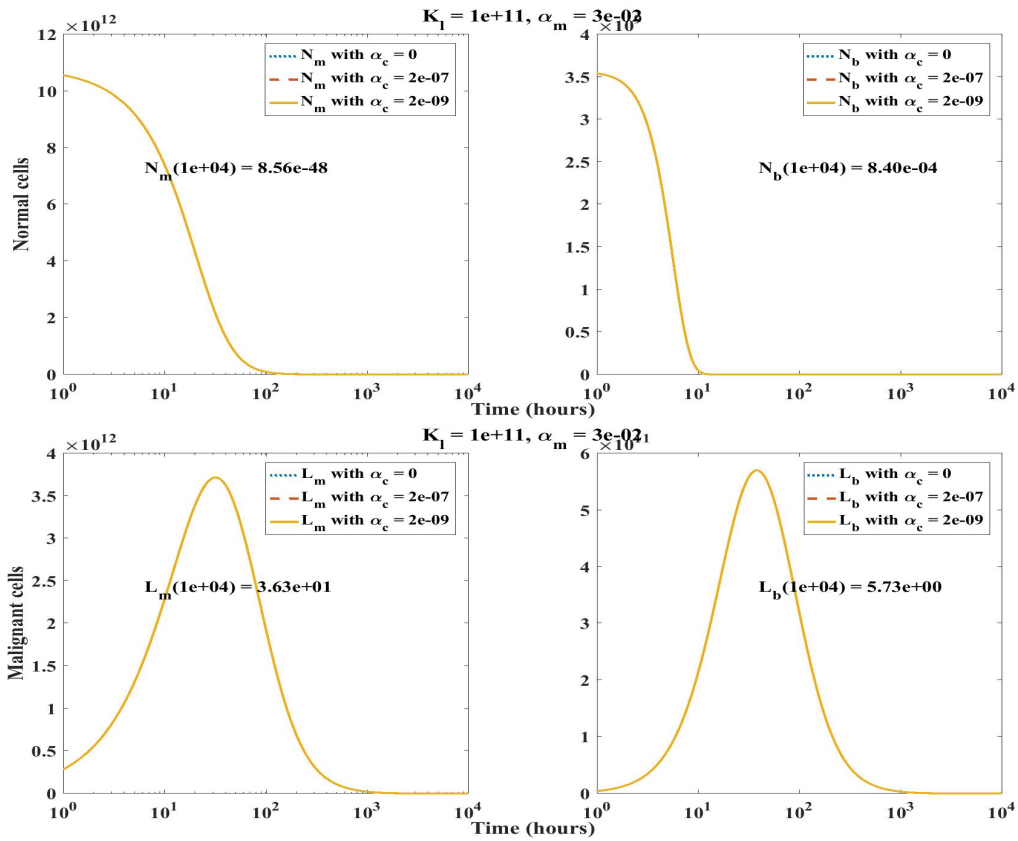

Figure 6: Simulations showing the evolution of malignant and healthy populations in the BM and PB towards the biaxial equilibrium E_L in which healthy cells face extinction. In the top two graphs, healthy BM and PB cells fall to low levels upon the emergence of non-stem malignant cells that rise to high levels but settle at levels that may render them still viable despite possible unavailability of nutrients to sustain their growth over a large time horizon of 10,000 hours as shown in the bottom two graphs. The parameters κ_l (denoted here in uppercase) and α_m are held fixed while different values of α_c are considered. The visually distinct solid curves for the value $\alpha_c = 2e-09$ are shown.

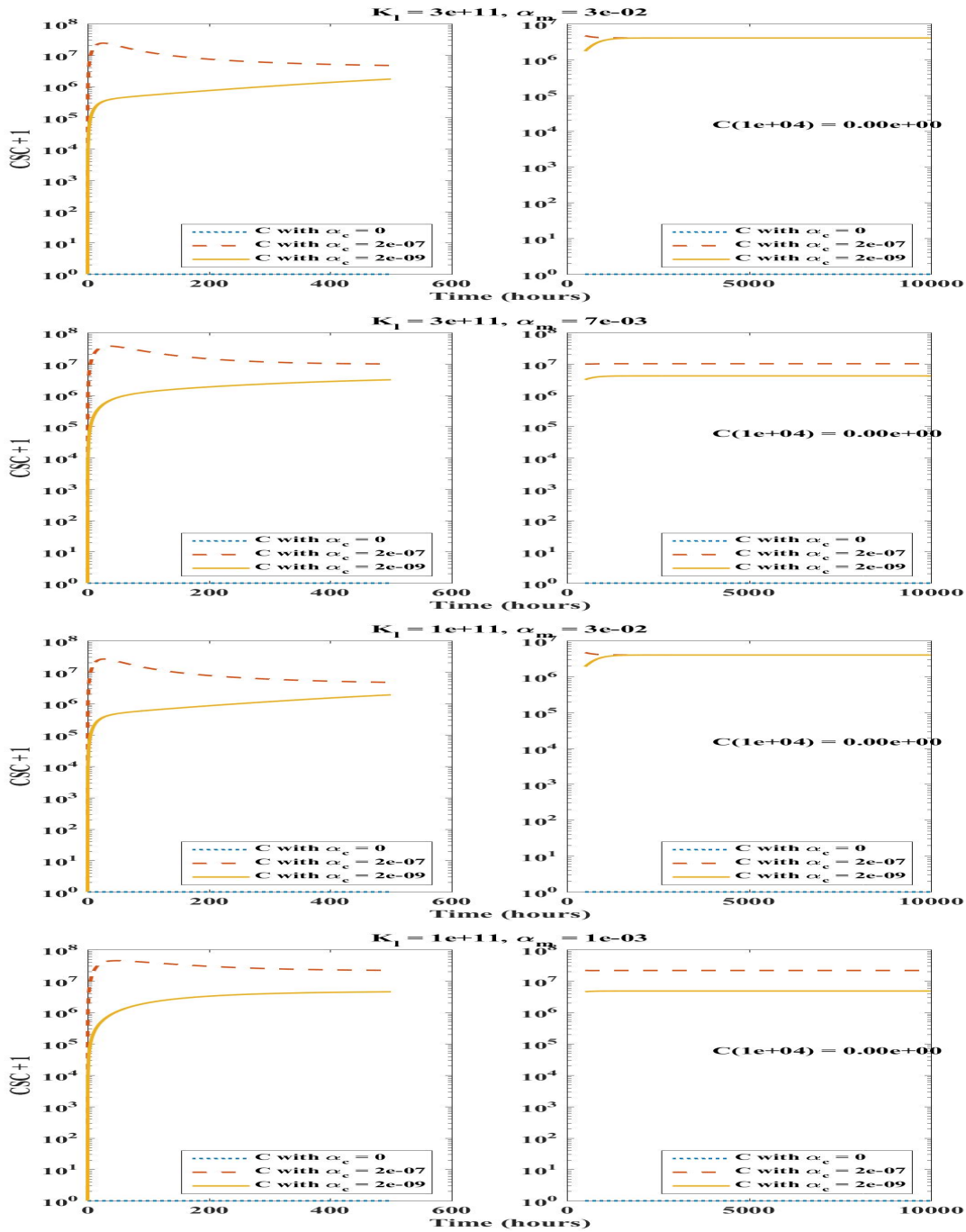

Figure 7: Simulations depicting evolution of the CSC population over moderate (left panel) and very large (right panel) time horizons. A semi-log plot of CSC + 1 is used here for ease of notation. For different fixed values of κ_l (denoted in uppercase) and α_m, the CSC population tends to rise and peak at certain levels. The visually distinct solid curves for the values $\alpha_c = 2e-07$ and $\alpha_c = 2e-09$ are shown.

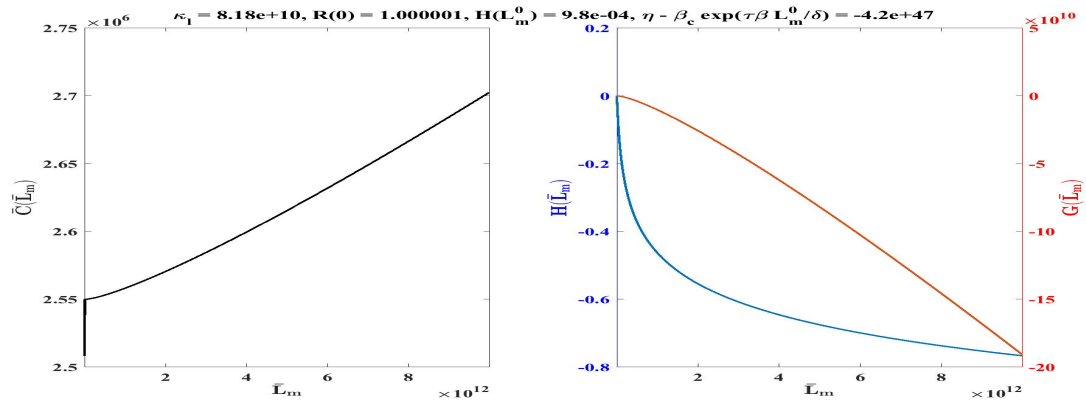

Figure 8: Simulations illustrating the functional relationship between the steady state level of CSCs and the equilibrium population of non-stem BM malignant cells, as seen in the left panel. The right panel shows the decreasing functions H and G as shifts occur in the non-stem BM malignant population.

what is obtained in [75] describes the evolution of a pure malignant state that also includes CSCs.

Bringing together all the notable results we have obtained from our model analyses and simulations, the following paint a comprehensive picture of model evolution and behavior when CSCs emerge in association with providing further mathematical-scientific foundations that undergird the developing CSC theory.

1) The model predictions seek to buttress the findings in [6] and other works such as those in [75] that suggest that malignant domination of the entire bone marrow - peripheral blood architecture occurs once malignancy evolves. Model predictions show that this is achieved through the evolution towards steady states in which any semblance of cell normality, portrayed through the presence of healthy cells, is ultimately rendered nonexistent.
2) Model analyses and simulations, as seen through Eqns. (10) - (13) in subsection 3.2, show that the emergence of CSCs lends support to an environment in which the non-stem malignant population in the BM evolves towards an expanded equilibrium state. Such an anomalous situation in turn tends to enhance the equilibrium state of the CSC population. In such circumstances, the

CSC population, no matter how small, may be serving as a major driver of malignancy.

3) The model predicts the evolution of four steady states; the trivial steady state, E_0, in which no normal or malignant cells are ultimately present, the biaxial equilibrium, E_L, that shows complete dominance by the non-stem malignant populations in the BM and PB, the triaxial equilibrium, E_{LC}, that reveals dominance by the CSC population and the non-stem malignant populations in the BM and PB, and the steady state of coexistence, E^*, the interior equilibrium.
4) Model analysis reveals that the triaxial steady state, which quantifies malignant dominance in the BM and PB by non-stem malignant cells and CSCs, remains stable and does not break down under conditions where a large time lag exists for the emergence and conversion of CSCs into non-stem malignant cells. This may provide the underpinning for regarding the CSCs as the main agents propelling malignant propagation and the main instigators of relapses after remissions are achieved [8–11]. Additionally, the existence of such a large time lag may suggest that CSCs may possess the capabilities of hiding their effects for a long period of time.
5) Model calculations reveal that malignancy may take hold in the BM and PB when mutation of healthy BM cells into CSCs increases beyond a certain threshold but the turnover of CSCs into the malignant BM is higher than CSC proliferation leading to CSC conversion into non-stem malignant cells. Under such circumstances, cells may move rapidly through the CSC compartment and the CSC population may maintain asymptotically low numbers that correspond to the biaxial equilibrium.
6) Model results tend to support the findings in [6] that once the hematopoietic system evolves towards a malignant state, such a state becomes irreversible in the absence of treatment and the effort needed to completely disrupt this state may entail the total eradication of all cells including the healthy ones and this undoubtedly suggests the enormous challenges confronting cancer treatment.
7) Maintenance of a positive equilibrium level of CSCs depends on the relationship

between the release rate of CSCs to the non-stem malignant BM, the intrinsic growth rate of CSCs, and the CSC carrying capacity and this reflects the influence of the BM micro-environment in CSC propagation.

8) The model-suggested functional relationship that exists between CSCs and non-stem malignant cells may indicate that as long as non-stem malignant cells exist in the BM, CSCs may emerge and act to enhance and support malignant growth. Conversely, existence of CSCs enhances the propagation of non-stem malignant cells. Existence of this functional relationship may support the finding in [2] that shifts in the equilibrium states may critically influence clinical outcomes and lead to more CSC-rich tumors. Essentially, these cell entities serve to reinforce the survival of each other and result in the anomalous enhancement of the CSC population.

9) The complexities inherent in the model manipulations suggest that the emergence of the CSC population presents with very serious complications of the already existing evolutionary malignant dynamics that as can be observed affects the equilibrium state of the entire malignant system. This suggests that the CSC population is very crucial and critical in propagating malignancy to a very large extent, as has been found in a number of cancers ([8], [16], [30]).

At this juncture, it stands to reason that the body of evidence that has accumulated in the literature so far about CSCs undoubtedly points to their identification as perhaps one of the major culprits, if not the major culprit, driving cancer propagation and development possibly at the microscopic level before detection, at diagnosis, and during treatment and our work here supports this line of thought. As we have already noted, CSCs are adjudged to be some of the main protagonists in hastening the termination of remissions, causing treatment failure, and instigating relapses. Despite the accumulated evidence about these cells so far, we believe more work still needs to be done in thoroughly understanding how these cells behave and act within the bone marrow-peripheral blood milieu.

The work we have done here is an attempt, albeit from a theoretical and phenomenological standpoint, to investigate and provide biologically driven mathemat-

ical underpinnings for the CSC theory. Admittedly, we must say that such work in association with other mathematical modeling endeavors in this area remains a challenging task in its very self because of the relatively low availability of definitive CSC data at this time and this highlights the novelty of our model and CSC-driven models such as the Stiehl-Marciniak-Czochra model [75]. What we have basically done is to, at a relatively preliminary stage, draw from available biomedical information on the CSC hypothesis and employ prior existing ideas such as those propounded by Clarkson [7] about cancer development, to develop an expanded mathematical model that we believe provides certain insights and scientific bases that lend credence to the existence and evolution of CSCs.

We must emphasize at this point that the study of time delays in biological systems has always been a nontrivial undertaking but such studies do open up windows through which certain underlying dynamics could be uncovered. In Adimy et. al. [116] for example a single distributed time delay was introduced into a system of two nonlinear ODEs that corresponded with the duration of the cell cycle and oscillations in some periodic hematological diseases were studied. Crauste [117] studied the single discrete delay in the Mackey model [113] highlighting the cell cycle duration in a system of two nonlinear ODEs. From such perspectives, the new insightful value of our work here lies in the ability of the model to show how two naturally occurring discrete delays inherent in the cell cycle that cannot be ignored participate in and largely complicate model dynamics and their analyses in the presence of an emerging population of CSCs reflected in a coupled nonlinear system of five ODEs. The model also uncovers the structural relationship that exists between non-stem malignant cells and CSCs, a relationship that may drive propagation towards CSC abundance over time [2]. This suggests that attempts to eliminate or control malignancy through treatment may not be successful by only focusing on one cell entity and leaving the other. This structural relationship between non-stem malignant cells and CSCs may have to be completely disrupted at the same time that these cell entities are identified and attacked and this constitutes part of our future modeling tasks as we employ the model to study various treatment strategies.

In our search and quest for more knowledge about an enigmatic disease such as cancer in general and CSCs in particular we must acknowledge that a number of questions remain and new ones constantly arise that must be consistently addressed. Within our modeling frameworks alone, some of these questions border on; the types of interactions that arise between healthy cells, CSCs, and non-stem malignant cells and behaviors that evolve when such interactions propagate. Other questions include how CSCs and non-stem malignant cells, taken together, may behave in the presence of various forms of treatment protocols. Addressing such questions form the focus of our future investigations. We must say at this final juncture that it appears that extensive studies of the BM may hold important clues to thoroughly understanding malignancy and CSCs for a long time to come. In this respect, we hope to continue our investigations by looking at various viewpoints and approaches in the modeling of cancer and its treatment.

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