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Hematologic Disorders and Bone Marrow–Peripheral Blood Dynamics

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Abstract. Hematologic disorders such as the myelodysplastic syndromes (MDS) are discussed. The lingering controversies related to various diseases are highlighted. A simple biomathematical model of bone marrow - peripheral blood dynamics in the normal state is proposed and used to investigate cell behavior in normal hematopoiesis from a mathematical viewpoint. Analysis of the steady state and properties of the model are used to make postulations about the phenomenon of massive apoptosis in MDS. Simulations of the model show situations in which homeostatic equilibrium can be achieved and maintained. Consequently, it is postulated that hematopoietic growth factors may possess the capabilities of preventing oscillatory dynamics and enhancing faster evolution towards homeostatic equilibrium.

Key words: hematologic disorders, mathematical model, normal hematopoiesis
AMS subject classification: 92B05, 35A24

1. Introduction

Hematologic disorders are marked by aberrations in structure or function of the blood cells or the blood-clotting mechanism. Many other diseases may be manifested in the blood and its constituents but abnormalities exhibited by red cells, white cells, platelets, and clotting factors are considered to be primary hematologic disorders and some could be malignant and others nonmalignant. Among a number of these disorders are, to mention a few; anemias that are marked by a decrease in the hemoglobin concentration, and may be due to blood loss or decreased produc-

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tion or excessive destruction of red cells, leukemias that represent a special kind of malignancy in which there is usually an uncontrolled proliferation of one or more types of leukocytes, often reflected in great increases in the white cell count of the peripheral blood, and myelodysplastic syndrome (MDS), a disease that is associated with decreased production of blood cells and used to be known as preleukemia. All these disorders tend to breach and greatly disturb the general normal functioning of the hematopoietic system. Without a doubt, hematopoiesis has remained a subject of intense study over the years because it is basically a massive process in the human body that involves various distinct cell lineages and results in the production of billions of different cell types each day. The genesis of this phenomenon is rooted in pluripotent stem cells in the bone marrow (BM) and involves a pool of totipotent stem cells that provide unipotent stem cells to the granulocytic, erythrocytic, thrombocytic and other lines. In each line, unipotent stem cells supply cells to a number of nonproliferating differentiation compartments in the BM before the release of mature neutrophils, erythrocytes, platelets, and other cell types into the blood.

Remarkable advances have been made in the detection, treatment, and management of the hematologic or hematopoietic disorders but various challenges still remain. Most of the disorders are not even as yet completely understood as is evidenced by the absence of a known cure in numerous instances along with the controversies and debates associated with various treatment approaches [8, 11, 24, 31, 35, 41, 43]. A survey of the literature shows that there have only been few attempts to mathematically model hemopoiesis and different facets of it in slightly over the past thirty years as can be found in [2, 5, 12, 13, 15, 17, 18, 26, 36, 37]. Understandably, because of the extensive nature of this phenomenon, only specific features or manifestations of it have been modeled. Even the different subsets of hematopoiesis such as granulopoiesis, lymphocytopoiesis, and thrombopoiesis, to mention a few, are by themselves massive processes that deserve intricate and extensive study and this makes the entire process of hematopoiesis, of which the above-mentioned processes constitute a part, an exhaustive and interminable area of investigation.

Our aim in this article is to contribute to deepening and enriching the understanding of the hematologic disorders and their treatment through the use of biomathematical models that give insight into their etiology and evolutionary dynamics. In doing this we elect to start our investigations by considering normal hematopoietic dynamics in the peripheral blood (PB)and BM since these compartments understandably form the overwhelming focus of research on the hematologic malignancies [1, 3, 4, 14, 19, 20, 22, 30, 31, 33–35, 39, 41]. To touch briefly on the few biomathematical contributions on normal hematopoiesis, we note that in 1978, Mackey [26] used physiological arguments to develop a time delay model that considered cell cycle dynamics in the proliferating and the resting phases. He then used the model to study the origins of aplastic anemia and periodic hematopoiesis and concluded that these disorders may be encountered as a single parameter within the stem cell population is changed. Earlier in 1975 Rubinow and Lebowitz [36] investigated a model of normal neutrophil production and control that employed first order partial differential equations in characterizing cell behavior in the resting, proliferative, reserve, and blood compartments of a normal human. Their model was based on age-time equations of the form first suggested by Scherbaum and Rasch [29] and Foerster [16] that involved cell density functions. Recently, Roeder and his co-workers [18] have also proposed a first order partial differential equation model for describing normal hematopoiesis. In this model they consider hematopoietic stem cells to be

residing in two signalling states that are proliferative and non-proliferative. They then expand the normal state model to include more model equations that are used to study the development and treatment of chronic myeloid leukemia. Our study in this discourse takes a mechanistic approach to normal hematopoiesis by looking at cell behavior in the bone marrow and peripheral blood. It is our hope that this work would add to the few existing contributions so far made to understanding hematopoiesis and its associated disorders from a biomathematical viewpoint.

2. Model Design and Analysis

By relying on information from the literature regarding hematopoiesis [6, 10, 13, 25–28, 38–40] and drawing upon investigations related to a representative hematologic disorder such as MDS [1, 3, 4, 14, 19, 22, 30, 32, 33, 34], it is appropriate to consider a model that comprises two broad compartments - a BM compartment and a peripheral blood (PB) compartment. Since the BM is said to be surprisingly uniform [39], it will be assumed to a reasonable first approximation that the cells in this tissue are homogeneously distributed. This assumption is stretched to the PB compartment. The assumption of homogeneity of the PB could be considered to be a good one if it is reasoned that cell behavior in this compartment may not be drastically different from what happens in the BM. However, since the PB itself contains various types of cells, a loss of this assumption may lead to considering the PB within a space-time framework, this is left for our future investigations. It is known that cells in the BM spend some time maturing [6, 10, 38] in this tissue before entering the blood to perform various functions during hemopoiesis. This means that a time lag due to cell maturation exists during the movement of cells from the BM compartment to the PB. Also in existence is a feedback mechanism through which cells in the BM are instructed to reproduce to account for shortfalls in the cell population of the PB compartment when situations that entail such developments arise. A schematic description of hemopoietic function is shown in Figure 1.

An interpretation of this description that yields the model can be stated in words as follows:

[Rate of Change of the BM Cell Population] = [Growth Rate of Marrow Cells] - [Rate of BM Cell Apoptosis] - [Release Rate of BM Cells to the Blood].
[Rate of Change of the Blood Cell Population] = [Rate of Influx into and Turnover of Cells in the PB] - [Rate of Efflux of Cells out of the PB].

We note that the rate of influx into and turnover of cells in the PB encompass the rate at which BM cells are released into this compartment that may include PB to BM feedback signalling [6]. The efflux rate of cells out of the PB include the rate of cell loss or cell disappearance [6] out of this compartment. In mathematical terms we obtain the following system of equations:

$$\dot{M} = \alpha_m(M) - \alpha_{md}M - \alpha_m(M(t - T_m), B) \tag{2.1}$$

$$\dot{B} = \alpha_m(M(t - T_m), B) - \alpha_{bd}B \tag{2.2}$$

where the parameters and variables in the equations above are described as follows: $\alpha_m(M)$ = state-dependent growth rate of the BM cells per unit time, $\alpha_m(M(t-T_m), B)$ = release rate of

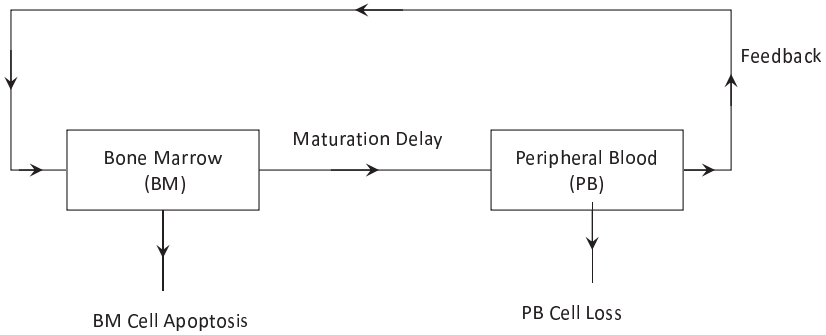

Figure 1: Schematic description of growth and development of cells in the bone marrow and peripheral blood.

cells from the BM into the PB that also includes feedback from the PB to the BM, α_{md} = fractional apoptotic rate of BM cells per unit time, α_{bd} = fractional rate of PB cell loss per unit time, T_m = transit time of cells in the BM due to maturation, $M = M(t)$ = population of BM cells/liter at time t, and $B = B(t)$ = population of PB cells/liter at time t.

Due to feedback mechanisms during normal hematopoietic function, it is reasonable to assume that the growth rate of cells in the BM will be small when the population of cells is close to a large finite value and will go through a process of rapid increase when this population is at a relatively low level. This suggests the exhibition of Gompertz-type growth kinetics or growth kinetics of sigmoidal kind. Thus, among various choices of growth functions, the Gompertz growth function was selected as the most appropriate candidate for the state-dependent quantity $\alpha_m(M)$ in the form $\alpha_m(M) = \alpha_m \log \frac{A}{M}$, based on our previous work [12, 13], where α_m = intrinsic growth rate of BM cells per unit time and A = marrow carrying capacity or the maximum allowable number of cells/liter in the BM. It can be observed that as $M \to A$, $\alpha_m(M) \to 0$. Another impact on hemopoietic function arises from the release of cells from the BM to the PB and from the feedback from the PB to the BM when the population of cells in the blood compartment is above or below a certain level. Using the work of Mackey and Glass [25] and Mackey [26] as bases, we assume that the release and feedback processes could be captured by candidate functions expressed by the quantity $\alpha_m(M(t-T_m), B)$ and consider one function of the form $\alpha_m(M(t-T_m), B) = \frac{a\alpha_{mr}M(t-T_m)}{a+B}$ where a and α_{mr} are constants with a playing the role of a "shape" parameter and α_{mr} being the maximal rate of release of mature marrow cells to the blood based on feedback. Putting all these together, the updated versions of equations (2.1) and (2.2) become:

$$\dot{M} = \alpha_m(\log \frac{A}{M})M - \frac{a\alpha_{mr}M(t-T_m)}{a+B} - \alpha_{md}M \tag{2.3}$$

$$\dot{B} = \frac{a\alpha_{mr}M(t-T_m)}{a+B} - \alpha_{bd}B \tag{2.4}$$

with $M(0) = M_0$, $B(0) = B_0$, and $M(t) = M_c$ when $-T_m \leq t < 0$ where M_c is the critical homeostatic level of cells per liter in the BM. It is important to remark that before the time of maturation is reached, cells evolving in the BM may exhibit a history of maintaining a population level that does not adversely affect hemopoietic function and this population level could be assumed to be the critical homeostatic level of cells in the marrow.

To facilitate effective analysis of the model system above, we introduce appropriate scaling that yields:

$$\frac{dx}{d\tau} = -x(\tau) + \mu + \frac{\beta}{1+y(\tau)}\exp[-x(\tau) + x(\tau - \tau_m)] \tag{2.5}$$

$$\frac{dy}{d\tau} = -\nu y(\tau) + \frac{\gamma}{1+y(\tau)}\exp[-x(\tau - \tau_m)] \tag{2.6}$$

with $x(0) = x_0, y(0) = y_0$, and $y(t) = y_c$ when $-T \leq t < 0$, where $x(\tau) = \log\frac{A}{M}$, $y(\tau) = B/a$, $\tau = \alpha_m t$, $\tau_m = \alpha_m t$, $T = \alpha_m T_m$, $\beta = \alpha_{mr}/\alpha_m$, $\gamma = \alpha_{mr}A/a\alpha_m$, $\mu = \alpha_{md}/\alpha_m$, and $\nu = \alpha_{bd}/\alpha_m$.

The steady states of system (2.5)–(2.6) are in the forms $(\overline{x}, \overline{y})$ and their numerical values have to be obtained from the equations:

$$\overline{x} = \mu + \frac{\beta}{1+\overline{y}} \tag{2.7}$$

$$\nu\overline{y}(1+\overline{y}) = \gamma\exp[-(\mu + \frac{\beta}{1+\overline{y}})] \tag{2.8}$$

Stability properties of the system are then obtained from the equation:

$$\lambda^2+\lambda(1+\nu+\frac{\beta}{1+\overline{y}}+\frac{\gamma\exp[-\overline{x}]}{(1+\overline{y})^2})+\nu+\frac{\beta\nu}{1+\overline{y}}+\frac{\beta\gamma\exp[-\overline{x}]}{(1+\overline{y})^3} = [\lambda+\nu+\frac{2\gamma\exp[-\overline{x}]}{(1+\overline{y})^2}]\frac{\beta\exp[-\lambda\tau_m]}{(1+\overline{y})} \tag{2.9}$$

where λ represents the eigenvalues of the system. We note from equations (2.7) and (2.8) that when $\overline{y}$ is close to zero and a high proliferation of marrow cells occurs the marrow population will stay close to its carrying capacity apparently to offset the blood cell loss. When $\overline{y}$ is large then $\overline{x}$ will be close to μ and in this case the marrow cell population may not be at its maximum level but may stay at a level that ensures normality. If massive apoptosis occurs in the marrow compared to the level of cell production in this organ, the quantity μ will be large in comparison to other quantities assuming they are held fixed. Under these circumstances $\overline{x}$ will be large and this means the marrow population will be depleted. From the equations, a depletion of the marrow population will lead to a dipping of $\overline{y}$ and for that matter the blood cell population to a low level. This analysis, therefore, suggests that in the steady state situation:

Table 1: **Parameters and Constants**

Parameter/Constant	Value/Range of Values (Units)	Data Based on:
α_m	[0.01275, 0.149] (/hour)	Parker et. al. [20]
α_{mr}	[0.009, 0.03] (/hour)	Assumed
α_{md}	[0.0014, 0.0054] (/hour)	Shimazaki et. al.[22]
a	$[10^{11}, 2.4 \times 10^{11}]$ (cells/liter)	Mackey et. al. [25]
T_m	[96, 144] (hours)	Lord et. al. [6]
A	$[10^{10}, 5.88 \times 10^{11}]$ (cells/liter)	Hara et. al. [21]
		Schrier [39]
α_{bd}	[0.0083, 0.1] (/hour)	Dale et. al. [10]
		Glass et. al. [23]
M_c	$[5 \times 10^9, 5 \times 10^{10}]$ (cells/liter)	Assumed

1. When the blood cell population is at a low level, there may be increased production of marrow cells due to increased marrow cell proliferation so as to compensate for the shortfall and this may cause the marrow cell population to stay close to its carrying capacity so as to guarantee normal functioning homeostatic mechanisms.

2. A semblance of normal activity proceeds when the marrow and blood cell populations are at reasonable homeostatic levels.

3. When a high level of apoptosis occurs in the marrow, the depletion of marrow cells leads to a dipping of the blood cell population towards low levels and this may signify a movement into a disease state.

To capture a full profile of the dynamics we now move to numerical work in the next section.

3. Parameter Estimates and Results from Model Simulations

We obtained values for some of the model parameters and constants from the existing literature but some of the parameter values had to be chosen arbitrarily because it was difficult to find clinical or experimental information on them. Table 1 shows a summary of the estimated or inferred ranges of values of the various model parameters and constants. The table also indicates the sources of data upon which the estimates were based.

The following specifically determined values from the table below were employed in solving equations (2.7)–(2.9) numerically: $\alpha_m = 0.04675, \alpha_{mr} = 0.024, \alpha_{md} = 0.0017, \alpha_{bd} = 0.05, a = 2.37 \times 10^{11}, T_m = 100, A = 10^{11}$. These produced the values $\nu = 1.07, \gamma = 0.2166, \mu = 0.0364, \beta = 0.5134, \tau_m = 4.675$. These values in turn yielded a leading numerical eigenvalue of

$\lambda = -0.1709$ from equation (2.9) that suggests system stability, and also yielded the nondimensional steady state values $\overline{x} = 0.4986$ and $\overline{y} = 0.11069$ that resulted in the following values for the steady state population level of cells in the marrow and blood respectively: $M = 6.0738 \times 10^{10}$ and $B = 2.6236 \times 10^{10}$. The data in the table were also employed in the simulations of model system (2.3)-(2.4) to obtain BM and PB cell dynamics for certain values of the maturation delay, as is shown in the figures below. From the data, the normal range for the maturation cycle T_m is between 96-144 hours and Figure 2 shows the evolution of BM and PB cells when T_m assumes values in this range. Figure 3 shows the behavior of cells when the maturation time is relatively shorter than normal, a situation that can be likened to what occurs when hematopoietic growth factors are added to stimulate hemopoietic activity. It could be observed from Figure 2 that the BM and PB cells evolve in a shortlived oscillatory fashion towards a stable homeostatic level over time during normal hematopoietic activity. In comparison, no oscillation occurs in Figure 3 indicating that homeostatic equilibrium is achieved faster in this case with a shorter than normal maturation delay. This observation is consistent with findings from clinical investigations [6, 10, 38, 40], which reveal that recombinant hematopoietic growth factors produce the effects of shortening the normal BM transit time. In Figure 4 a semblance of oscillation in cell numbers is observed for values of the maturation delay that are far above the upper bound for the normal maturation interval but the system appears to settle around certain values for the populations as time grows. In Figure 4, a dip in the plateau for marrow cells and a rise in the plateau for PB cells can be observed. This may be due to the bone marrow-peripheral blood interchange that goes on over time. In such a case, when low levels of PB cells occur, the marrow sends cells to this compartment to compensate for the decrease leading to a decrease in the BM population. For values of the maturation delay in its normal range, an increase in the release rate of cells from the marrow to the blood causes oscillations to occur in the cell numbers as can be observed in Figure 5 but the oscillations proceed with decreasing amplitudes towards the end of the profile. We observe from all the figures that the BM population dominates the PB population. One exception is seen in figure 5 where the PB population overshoots the BM population.

4. Discussion and Concluding Remarks

Analysis and simulations of the model show that in normal functioning mode, the hematopoietic system evolves towards a stable state in which feedback mechanisms play an important role. The negative eigenvalues and the steady state values of the cell populations obtained from the numerical calculations tend to support the evolution of the system towards a stable state. The behavior displayed in Figure 5 in the case where oscillations occur, even though in a decaying fashion, suggests that the feedback mechanisms may play a critical role in guaranteeing homeostatic equilibrium. The analysis in the steady state situation showed that there is an inability of the hematopoietic system to function normally when large scale apoptosis occurs in the bone marrow as has been shown to be the case in the myelodysplastic syndromes in a number of clinical investigations [1, 3, 4, 22, 33]. Therefore, we may at this point suggest that the model predictions support the clinical inves-

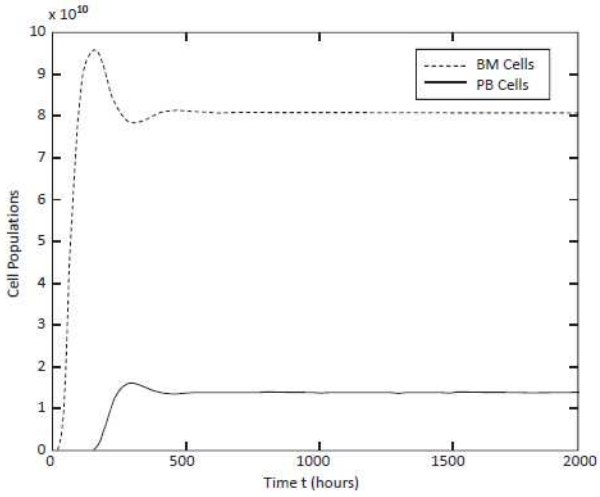

Figure 2: Evolution of cells in the bone marrow and peripheral blood towards homeostatic equilibrium when the maturation cycle time is within normal range with $T_m = 100$ hours.

tigations that have found massive BM apoptosis to be a major factor in contributing to ineffective hemopoiesis in MDS. The simulations do lend support to the analytical predictions of the model and show that cells in the BM and blood evolve towards homeostatically stable levels after going through very brief oscillations during the normal maturation cycle of the bone marrow, as is exemplified by Figures. 2-4.This suggests that a normally functioning hemopoietic system will obey various conditions or rules and mechanisms that guarantee cell function and production and may get into situations of abnormality when these rules and mechanisms are violated, as may be the case in many disease states. Figure 3 provides a graphic demonstration of the effects of shortening the normal cycle of maturation, as is the case when growth factors are introduced [6, 10, 38, 40]. It could be observed that oscillations do not occur as the system evolves towards homeostatic equilibrium in this case. Thus it may be appropriate to remark that growth factors may prevent oscillatory dynamics and enhance a speedier achievement of stable states during normal hemopoietic development. We must mention that the achievement of homeostatic equilibrium remains attainable even when the maturation cycle time is relatively longer than normal as could be observed from Figure 4. This means that the hemopoietic system is capable of maintaining a normally functioning state even beyond the well-known maturation cycle and thus possesses the properties of "bioversatility." By "bioversatility" we mean the hemopoietic system possesses extensive capabilities of adapting to situations that threaten its very existence.

In conclusion it could be noted from the analysis and simulations that among other things the model predicts the following: 1) Development of a situation (that is a possible disease state) in which difficulties arise in sustaining normal hemopoiesis when a high level of apoptosis occurs in the marrow. This is in line with clinical observations of ineffective hematopoiesis related to the effects of massive apoptosis in the myelodysplastic syndromes. 2) Virtual nonexistence of oscillations in the bone marrow and blood cell populations when the maturation cycle is shorter than

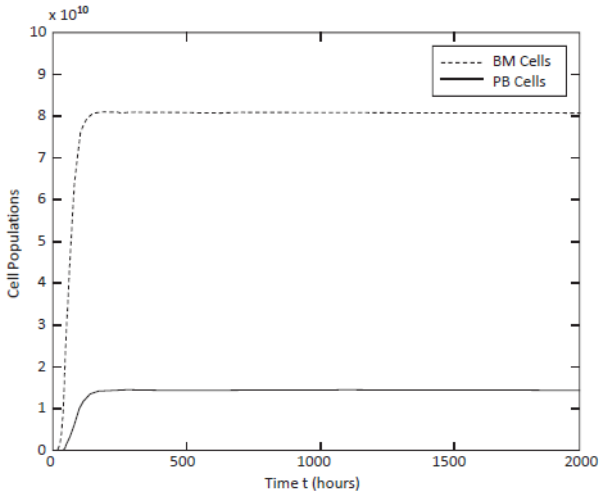

Figure 3: Evolution of cells in the bone marrow and peripheral blood towards homeostatic equilibrium when the maturation cycle time is relatively shorter than normal (here $T_m = 50$ hours).

normal. 3) Evolution of BM and blood cells towards stable homeostatic levels during the normal maturation cycle and for some reasonable period beyond this cycle. During such an evolutionary process, the BM population always dominates the PB population in order for homeostatic stability to be maintained. 4) An increase in oscillations in the BM and blood cell populations that provide signals of chaotic dynamics when an increased rate of release of cells to the peripheral blood occurs possibly due to events related to feedback mechanisms. We will conduct a detailed investigation of such dynamics and the development of the disease state in a sequel to this article.

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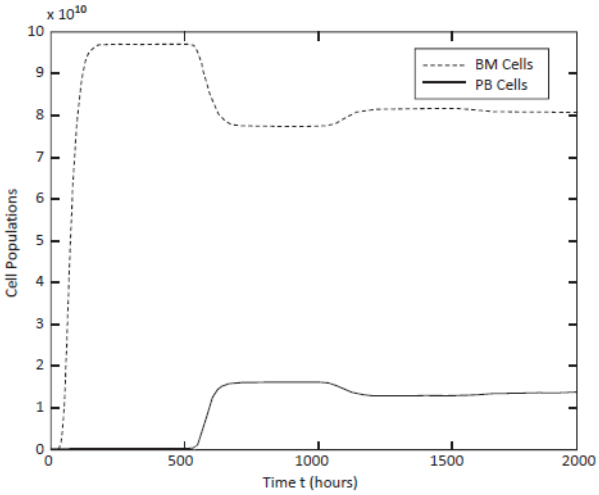

Figure 4: Evolution of cells in the bone marrow and peripheral blood towards homeostatic equilibrium when the maturation cycle time is relatively longer than normal ($T_m = 200$ hours).

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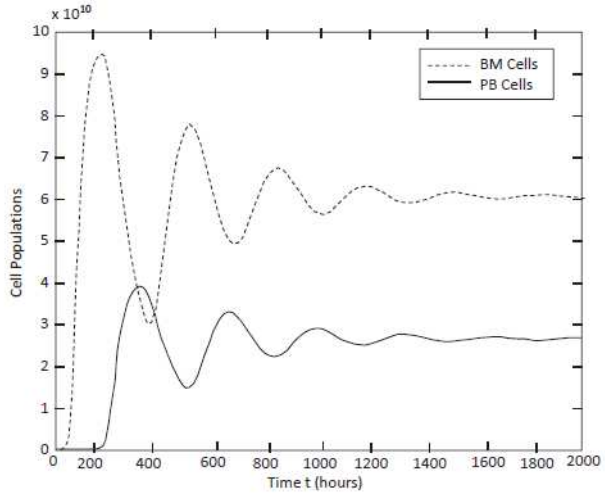

Figure 5: Propagation of decaying oscillations in cell numbers when the release rate of marrow cells increases beyond 0.03/hour due to an event.

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