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Dynamical behavior of leukemic cells with chemotherapy in acute myeloid leukemia

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Abstract. In this paper, we consider a mathematical model for the study of the interaction between leukemia cells and chemotherapeutic drug in Acute Myeloid Leukemia (AML). In our model, there are three compartments, namely, leukemia-initiating cells, leukemics blast, and chemotherapeutic drug. Using a stability theory of differential equation, we analyze the existence and stability of the system at various equilibrium points. Furthermore, we discuss the effect of leukemia treatment by varying the values of relevant parameters. We also provide numerical simulations to illustrate the theoretical results.

1. Introduction

Acute Myeloid Leukemia (AML) is a hematologic disorder characterized by the occurrence of HSC differentiation blockade which results in the accumulation of growth a population of neoplastic or blast cells. Overproduction of white blood cells interferes with the normal process of hematopoiesis and modifies the normal mechanisms of cells differentiation, self-renewal, and proliferation [1]. Leukemogenesis in AML occurs because of its presence two classes of mutations (two-hit models), i.e., mutations that increase proliferation and cell survival and mutations that block cell differentiation and apoptosis [2].

The National Comprehensive Cancer Network (NCCN) classifies patients into three risk categories, based on the validated cytogenetics and molecular abnormalities, which are a better risk, intermediate-risk, and poor r[illegible]. The standard therapeutic strategy in a patient with AML is chemotherapy and autologous or allogeneic hematopoietic stem cell transplantation (HSCT) [3 – 7]. The main objective of those treatments is inducing remission and preventing the relapse [6]. Treatment or therapy for AML sufferers can last for several years (NCCN, 2018). This therapy consists of several stages which are classified into two, namely specific therapy and supportive therapy. Untreated AML patient results in fatal infection, bleeding or organ infiltration within weeks to months [8,9]. In recent years, despite the potential gain of HSCT, the post-transplantati[illegible]outcome remains dismal, especially those with high-risk category [9]. Currently, in order to further improve the clinical outcome of AML, the development of the new therapies has been challenging, such as cytotoxic agent, small molecule inhibitor, and targeted therapies combined with chemotherapy [10,11,12].

Mathematical modeling in hematological malignancies has several purposes. The model can provide a framework for study the leukemia genesis and treatment strategies. Through mathematical modeling, it can also explain the various aspect of leukemia, evaluate the existing therapies, or to design combination therapies and to suggest novel therapies. Several studies in the field of cancer

therapies have been discussed in [13, 14]. Recent model in leukemia therapies, especially in Chronic Myeloid Leukemia (CML) and Chronic Lymphocytic Leukemia (CLL) also has been conducted by Besse et al. [15] and Rodrigues et al. [16]. Modeling in Acute Myeloid Leukemia (AML) has been developt in Adi et al.[17], but not provide the therapies regimen.

In this paper, we will give a mathematical study of the interaction between the leukemia cells in AML with a chemotherapeutic drug. This paper is organized as follows. In Section 2, we present the mathematical model and the properties of its solutions. In Section 3, we will give an analysis of the existence and stability of equilibrium points. The numerical simulation is provided in Section 4. Finally, in Section 5, we give a discussion and conclusion.

2. Mathematical Model

2.1. The Model

In this section, we construct a mathematical model of acute myeloid leukemia cell with chemotherapy. The model consists of three populations, which are, the number of leukemia-initiating cells $L(t)$, the number of leukemics blasts $B(t)$, and the density of the chemotherapeutic drug $C(t)$.

The model is given by the following system of ordinary differential equations:

$$\begin{aligned}\frac{dL}{dt} &= r_1 L(1-p(L+B)) - aL - b_1 LC \\ \frac{dB}{dt} &= aL + r_2 B(1-p(L+B)) - dB - b_2 BC \\ \frac{dC}{dt} &= \rho - \gamma C\end{aligned} \tag{1.1}$$

with initial conditions

$$L(0) \geq 0, \quad B(0) \geq 0, \quad C(0) \geq 0. \tag{1.2}$$

The model parameters are described as follows:

r_1, r_2 : self-renewal rates of leukemia-initiating cells and leukemic blast, respectively (day $^{-1}$);

p : reciprocal carrying capacity for total leukemic cell, that is maximum size or space that leukemia–initiating cells and leukemic blast cell are allowed to occupy (cell^{-1});

a : rate of conversion of leukemia-initiating cells to leukemic blast (day $^{-1}$);

b_1, b_2 : the mortalities rates of leukemia-initiating cells and leukemic blast due to the action of the the chemotherapeutic drug, respectively (day $^{-1}$);

d : decay rate of the leukemic blast (day $^{-1}$);

ρ : the dose of the chemotherapeutic drug given (gr day $^{-1}$);

γ : the decay rate of the chemotherapeutic drug (day $^{-1}$).

2.2. Properties of Solutions

For biologically meaningful of Model (1.1), it is necessary to show that all solution of the system with positive initial conditions will remain nonnegative and bounded. This will be established in the following theorem. Define the domain $D = \{(L,B,C) \in \mathbb{R}^3 : 0 < L+B \leq \frac{1}{p}, C \geq 0\}$.

Theorem 2.1. *Every solution of System (1.1) with initial conditions (1.2) exist for all* $t \in [0,T]$, *and* $L(t), B(t), C(t)$ *will remain in* D.

Proof. We know that all parameters used in the system are positive, so we can set lower bounds on each of the equations given in the model. For System (1.1) with initial conditions (1.2), we have

$$L(t) = L(0)\exp\left[\int_0^t \{r_1(1-p(L(\tau)+B(\tau))-a-b_1C(\tau)\}\,d\tau\right] \geq 0,$$

From the second equation of System (1.1), we have

$$\frac{dB}{dt} = aL + r_2B(1-p(L+B)) - dB - b_2BC \geq r_2B(1-p(L+B)) - dB - b_2BC,$$

thus we have

$$B(t) \geq B(0)\exp\left[\int_0^t \{r_2(1-p(L(\tau)+B(\tau))-d-b_2C(\tau)\}\,d\tau\right] \geq 0,$$

Finally, from the last equation of System (1.1), we have

$$C(t) = \frac{\rho}{\gamma} + \left[C(0) - \frac{\rho}{\gamma}\right]e^{-\gamma t} \geq 0.$$

Thus for all $t \in [0,T]$, $L(t), B(t), C(t)$ will be positive and remain in D. This completes the proof.

Theorem 2.2. *$L(t), B(t), C(t)$ of System (1.1) subject to initial conditions (1.2) are bounded for all $t \in [0,T]$, .*

Proof. From System (1.1), we get

$$\frac{dL}{dt} + \frac{dB}{dt} = r_1L\left(1-p(L+B)\right) + r_2B\left(1-p(L+B)\right) - b_1LC - b_1BC$$
$$\leq r\left(1-p(L+B)\right),$$

with $r = \max\{r_1, r_2\}$. Now, let $Z(t) = L(t) + B(t)$, thus we have $\frac{dZ}{dt} = \frac{dL}{dt} + \frac{dB}{dt} \leq r\left(1-p(L+B)\right) = r\left(1-pZ\right)$. From the Comparison Theory [18], we get $\limsup_{t\to\infty} Z(t) \leq \frac{1}{p}$. Thus, $(L+B)(t)$ is bounded, so $L(t)$ and $B(t)$ are bounded.

Furthermore, from the third equation of System (1.1), we get $C(t) = \frac{\rho}{\gamma} + \left[C(0) - \frac{\rho}{\gamma}\right]e^{-\gamma t}$, so we have $\limsup_{t\to\infty} C(t) \leq \frac{\rho}{\gamma}$. Hence $C(t)$ is bounded. This completes the proof.

3. Existence and Stability of Equilibria

The System (1.1) has the following equilibrium points

(i). Leukemia free equilibrium, $E_0 = (0,0,\frac{\rho}{\gamma})$,

(ii) Leukemic blast persistent equilibrium, $E_1 = \left(0, \frac{r_2\gamma - b_2\rho - a\gamma}{pr_2\gamma}, \frac{\rho}{\gamma}\right)$,

(iii) Coexisting equilibrium, $E^* = \left(L^*, B^*, C^*\right)$, where

$$L^* = \frac{1}{pr_1\gamma}\left(\left(\frac{a(a\gamma + b_1\rho - r_1\gamma)}{a\gamma(r_1-r_2) + \rho(b_2r_1 - b_1r_2) + dr_1\gamma}\right) - (a\gamma + b_1\rho - r_1\gamma)\right), \quad B^* = \frac{a(r_1\gamma - a\gamma - b_1\rho)}{p\left(a\gamma(r_1-r_2) + \rho(b_2r_1 - b_1r_2) + dr_1\gamma\right)},$$

and $C^* = \frac{\rho}{\gamma}$.

The equilibrium E_0 always exists, while equilibrium E_1 is biologically admissible if and only if $r_2\gamma > b_2\rho + a\gamma$. For the existence of E^* we have the following theorem.

Theorem 3.1. *Let* $Q = r_1\gamma - a\gamma - b_1\rho$ *and* $R = a\gamma(r_1 - r_2) + \rho(b_2 r_1 - b_1 r_2) + dr_1\gamma$. *The equilibrium* E^* *exists if* $Q > 0, R > 0$, *and* $R > a$.

Proof. Equilibrium point exists if all component if positive. First, E^* will exist if the leukemic blast, B^* positive. Two cases will happen,i.e. if $r_1\gamma - a\gamma - b_1\rho > 0$, then we must have $a\gamma(r_1 - r_2) + \rho(b_2 r_1 - b_1 r_2) + dr_1\gamma > 0$. Whereas if $r_1\gamma - a\gamma - b_1\rho < 0$, then $a\gamma(r_1 - r_2) + \rho(b_2 r_1 - b_1 r_2) + dr_1\gamma < 0$. On the other hand, the leukemia-initiating cells L^* also must be positive. Therefore, L^* will be positive if $\left(\frac{a(a\gamma + b_1\rho - r_1\gamma)}{a\gamma(r_1 - r_2) + \rho(b_2 r_1 - b_1 r_2) + dr_1\gamma}\right) - (a\gamma + b_1\rho - r_1\gamma) > 0$. Hence, the equilibrium point E^* exists if (i). $Q > 0, R > 0$, *and* $R > a$ or (ii). $Q < 0$, $R < 0$, *and* $R > a$ is proved. However, since the value of the parameter a is nonnegative, then the condition $R < 0$ and $R > a$ is impossible. Thus we conclude that E^* exists if $Q > 0, R > 0$, and $R > a$.

Next, we will study the stability of the equilibrium points. To discuss the local stability of equilibrium points, we need to compute the eigenvalues of the Jacobian matrix of System (1.1) in the equilibrium point. The Jacobian matrix of the system (1.1) is given by

$$J(E) = \begin{pmatrix} r_1 - 2r_1 pL - r_1 pB - a - b_1 C & -r_1 pL & -b_1 L \\ a - r_2 pB & r_2 - r_2 pL - 2r_2 pB - d - b_2 C & -b_2 B \\ 0 & 0 & -\gamma \end{pmatrix} \tag{1.3}$$

Theorem 3.2. *The equilibrium point* E_0 *is locally asymptotically stable if* $r_1\gamma < a\gamma + b_1\rho$ *and* $r_2\gamma < d\gamma + b_2\rho$.

Proof. The Jacobian matrix at E_0 is

$$J(E_0) = \begin{pmatrix} r_1 - a - b_1\frac{\rho}{\gamma} & 0 & 0 \\ a & r_2 - d - b_2\frac{\rho}{\gamma} & 0 \\ 0 & 0 & -\gamma \end{pmatrix}.$$

Therefore, the eigenvalues of the characteristic equation $J(E_0)$ are $\lambda_1 = r_1 - a - b_1\frac{\rho}{\gamma} = \frac{r_1\gamma - a\gamma - b_1\rho}{\gamma}$, $\lambda_2 = r_2 - d - b_2\frac{\rho}{\gamma} = \frac{r_2\gamma - d\gamma - b_2\rho}{\gamma}$, and $\lambda_3 = -\gamma$. It is clear that the eigenvalue λ_3 is negative. Then, E_0 is stable if the eigenvalue λ_1 and λ_2 are both negative, that is $r_1\gamma < a\gamma + b_1\rho$ *and* $r_2\gamma < d\gamma + b_2\rho$.

Note that, the equilibrium E_0 stable if and only if E_1 and E^* do not exist. In this case, both leukemic-initiating cells and leukemia blast cells annihilated and it means that the chemotherapy is successful.

Theorema 3.3. *The equilibrium point* E_1 *is locally asymptotically stable if* $r_1 < \frac{(a\gamma + \rho b_1)}{(a\gamma + \rho b_2)} r_2$ *and* $r_2 + d - \frac{b_2\rho}{\gamma} > 2a$.

$$J(E)=\begin{pmatrix} r_1-r_1p\left(\frac{r_2\gamma-b_2\rho-a\gamma}{pr_2\gamma}\right)-a-b_1\frac{\rho}{\gamma} & 0 & 0 \\ a-r_2p\left(\frac{r_2\gamma-b_2\rho-a\gamma}{pr_2\gamma}\right) & r_2-2r_2p\left(\frac{r_2\gamma-b_2\rho-a\gamma}{pr_2\gamma}\right)-d-b_2\frac{\rho}{\gamma} & -b_2\left(\frac{r_2\gamma-b_2\rho-a\gamma}{pr_2\gamma}\right) \\ 0 & 0 & -\gamma \end{pmatrix}.$$

The eigenvalues $J(E_1)$ are $\lambda_1=\frac{1}{r_2\gamma}\left(a\gamma(r_1-r_2)+\rho(b_2r_1-b_1r_2)\right)$, $\lambda_2=\frac{1}{\gamma}\left((r_2\gamma-b_2\rho-d\gamma)-2(r_2\gamma-b_2\rho-a\gamma)\right)$, and $\lambda_3=-\gamma$. Thus, E_1 is a stable equilibrium point if $\left(a\gamma(r_1-r_2)+\rho(b_2r_1-b_1r_2)\right)<0$ or $r_1<\frac{(a\gamma+\rho b_1)}{(a\gamma+\rho b_2)}r_2$ and $(r_2\gamma-b_2\rho-d\gamma)-2(r_2\gamma-b_2\rho-a\gamma)<0$ or $r_2+d-\frac{b_2\rho}{\gamma}>2a$. This completes the proof.

In this case, the leukemia-initiating cells do not exist and the leukemic blast cells exist, which means that after administration of the chemotherapeutic drug, all leukemia-initiating cell annihilated but leukemic blast still exists. Hence, stability E_1 is not useful for chemotherapy regimen.

Theorema 3.4. *Let* $Q=r_1\gamma-a\gamma-b_1\rho$, $R=a\gamma(r_1-r_2)+\rho(b_2r_1-b_1r_2)+dr_1\gamma$, *and* $S=r_2\gamma-d\gamma-b_2\rho$. *The equilibrium point* E^* *is locally asymptotically stable if* $R+ar_1\gamma-2a<0$ *and* $S<\frac{r_2R}{r_1Q}(a-R-2ar_1\gamma)<0$.

Proof. The eigenvalues of the Jacobian matrix of the system (1.1) at E^* are

$$\lambda_1=r_1-\frac{2}{\gamma}\left(\frac{a(a\gamma+b_1\rho-r_1\gamma)}{a\gamma(r_1-r_2)+\rho(b_2r_1-b_1r_2)+dr_1\gamma}-(a\gamma+b_1\rho-r_1\gamma)\right)+\frac{r_1a(a\gamma+b_1\rho-r_1\gamma)}{a\gamma(r_1-r_2)+\rho(b_2r_1-b_1r_2)+dr_1\gamma}-a-\frac{b_1\rho}{\gamma},$$

$$\lambda_2=r_2-\frac{r_2}{r_1\gamma}\left(\frac{a(a\gamma+b_1\rho-r_1\gamma)}{a\gamma(r_1-r_2)+\rho(b_2r_1-b_1r_2)+dr_1\gamma}-(a\gamma+b_1\rho-r_1\gamma)\right)+\frac{2r_2a(a\gamma+b_1\rho-r_1\gamma)}{a\gamma(r_1-r_2)+\rho(b_2r_1-b_1r_2)+dr_1\gamma}-d-\frac{b_2\rho}{\gamma},$$

and $\lambda_3=-\gamma$.

After simple calculation, we find $\lambda_1=\frac{Q}{\gamma R}(ar_1\gamma-R-2a)$ and $\lambda_2=\frac{1}{\gamma}\left(S-\frac{r_2Q}{r_1R}(a-R-2ar_1\gamma)\right)$. We have λ_3 negative, thus E^* is locally asymptotically stable if λ_2 and λ_3 are both negative. Because Q and R are positive, then $\lambda_1<0$ whenever $ar_1\gamma-R-2a<0$ and $\lambda_2<0$ whenever $S<\frac{r_2Q}{r_1R}(a-R-2ar_1\gamma)<0$.

4. Simulation Results

In this section, we provide some numerical simulations to support the analytical results. We do the simulation for three cases of equilibrium points. For this reason, we choose the related parameter values that meet the conditions of stability of the equilibrium points in the previous section.

Case I, *Leukemia free equilibrium point*.

In this case, we choose the set of parameter values

$$r_1=0.4, p=0.000000005, a=0.001, b_1=0.05, r_2=0.2, b_2=0.01, d=0.04\rho=0.003, \gamma=0.01. \quad (1.4)$$

With this parameter values, we have a leukemia-free equilibrium point $E_0=(0,0,0.3)$, and the system (1.1) meets the conditions of Theorem 3.2. Hence, the equilibrium point E_0 is locally

asymptotically stable. Figure 1 shows the evolution of leukemia-initiating cells and the leukemic blast cells, whereas Figure 2 shows that this equilibrium point is asymptotically stable.

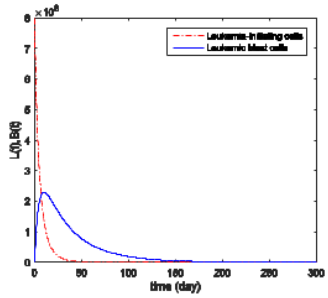

Figure 1. The time evolution leukemia-initiating and leukemic blast cell starting near the equilibrium point E_0

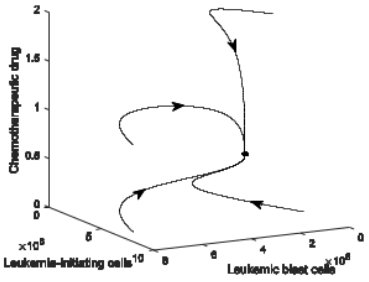

Figure 2. Phase solution indicates that with the parameter value (1.4), the equilibrium point E_0 is locally asymptotic stable.

Case 2, *Leukemia blast persistent equilibrium point*.
In this case, we choose the set of parameter values

$$r_1 = 0.04, p = 0.000000005, a = 0.01, b_1 = 0.05, r_2 = 0.2, b_2 = 0.01, d = 0.04, \rho = 0.003, \gamma = 0.01. \quad (1.5)$$

With this parameter values, the system (1.1) meets the conditions of Theorem 3.3 and we have leukemic blast persistent equilibrium point $E_1 = (0, 1.57000000 \times 10^8, 0.3)$, which is locally asymptotically stable. In Figure 3, we show the evolution of leukemia-initiating cells and the leukemic blast cells, whereas Figure 4 shows that the equilibrium point E_1 is locally asymptotically stable. Figure 3 top-right show that the leukemia-initiating cell has no oscillation, while Figure 3 bottom-right shows that the leukemic blast has an oscillation near the equilibrium point.

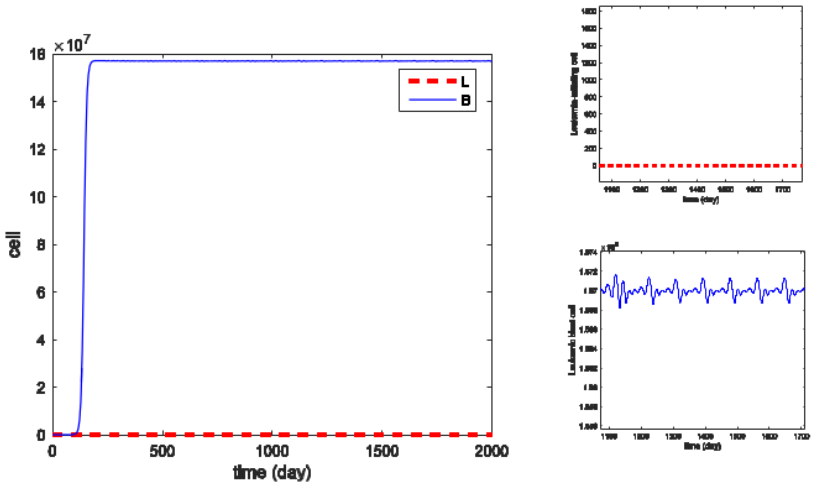

Figure 3. The time evolution leukemia-initiating and leukemic blast cell starting near the equilibrium point E_1

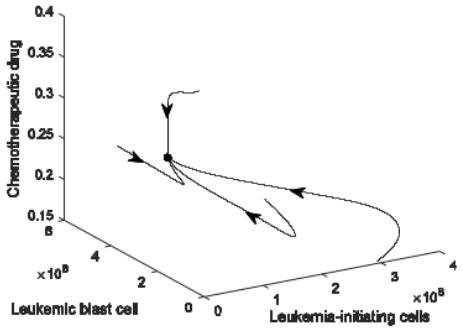

Figure 4. Phase solution indicates that with the parameter value (1.5), the equilibrium point E_1 is locally asymptotic stable.

Case 3, *Coexisting equilibrium point*.
In this case coexistence of all population, we choose the set of parameter values

$$r_1 = 0.04, p = 0.000000005, a = 0.1, b_1 = 0.05, r_2 = 0.02, b_2 = 0.01, d = 0.04, \rho = 0.003, \gamma = 0.01. \quad (1.6)$$

With this parameter values, the system (1.1) meets the conditions of Theorem 3.4 and we have coexisting equilibrium point $E^* = (1.866666667 \times 10^8, 5.333333333 \times 10^6, 0.30)$, which is locally asymptotically stable. In Figure 5, show the evolution of leukemia-initiating cells and the leukemic blast cells, whereas Figure 6 shows that the equilibrium point E^* is locally asymptotically stable. Figure 5-right show that both the leukemic blast and the leukemia-initiating cell have an

oscillation near the equilibrium point. In this case, we can say that the administration of the chemotherapeutic drug has a failure to destroy both the leukemia-initiating cells and the leukemic cells.

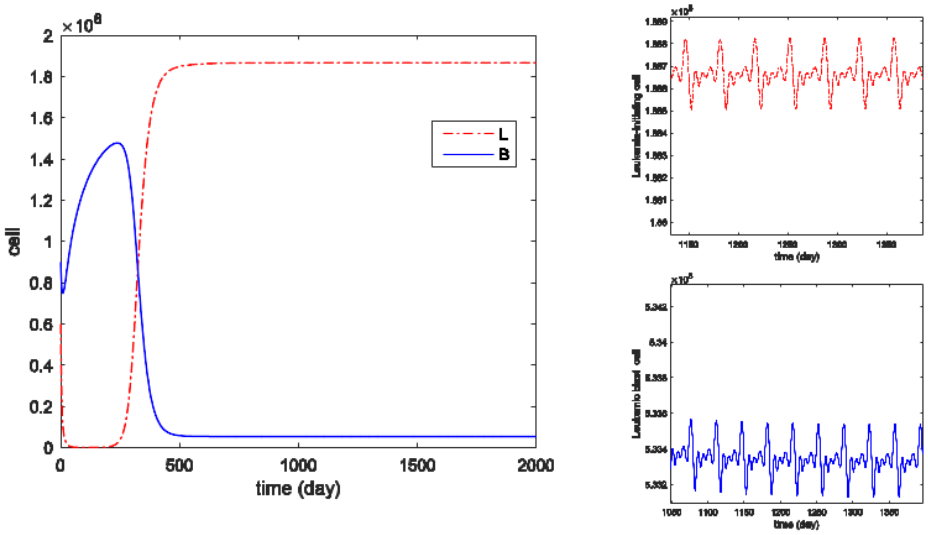

Figure 5. The time evolution leukemia-initiating and leukemic blast cell starting near the equilibrium point E^*

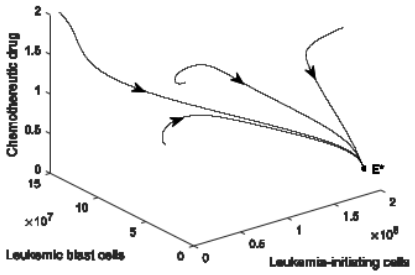

Figure 6. Phase solution indicates that with the parameter value (1.6), the equilibrium point E^* is locally asymptotic stable.

Finally, in Figure 7, we provide numerical simulation by using the set of parameter values (1.7) with the various value of the dose of the chemotherapeutic drug, ρ from 0.003 to 0.2.

$$r_1 = 0.04, p = 0.000000005, a = 0.1, b_1 = 0.05, r_2 = 0.02, b_2 = 0.01, d = 0.04, \gamma = 0.01. \quad (1.7)$$

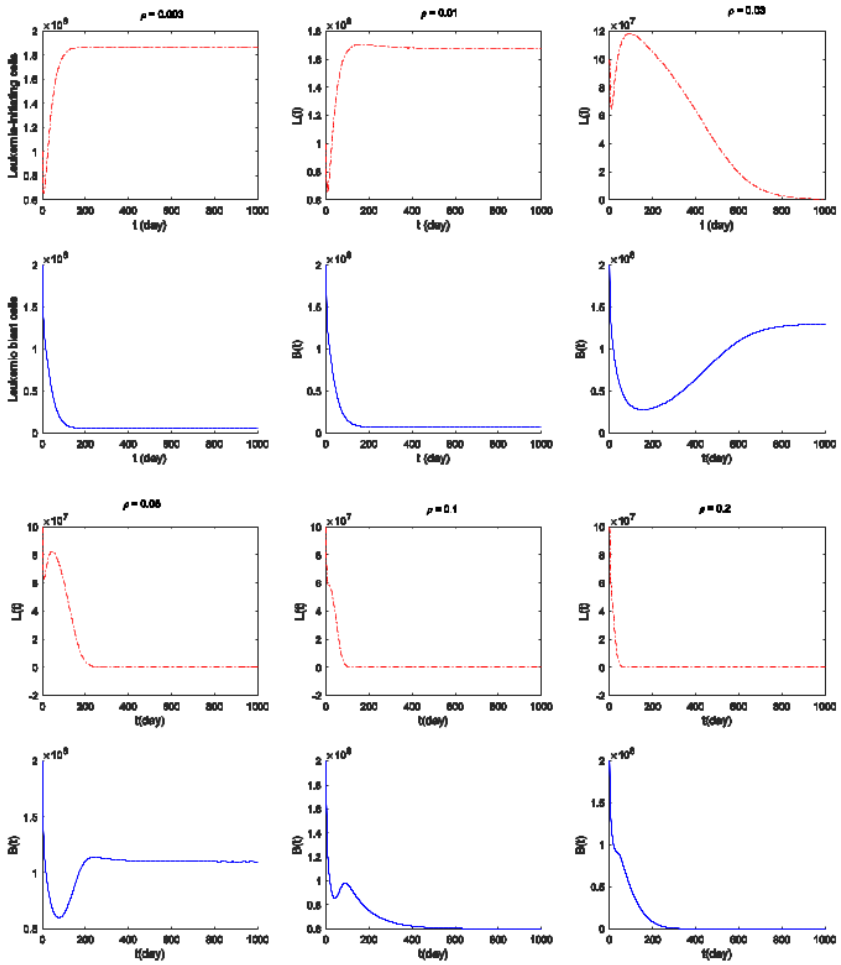

Figure 7. Dynamic of Leukemia-initiating cells and leukemic blast cell with varying values of ρ .

In a medical point of view, the dose of the chemotherapeutic drug varies according to the type of drug and the condition of patient. In the numerical simulation in Figure 7, we give the dose of chemotherapy in the range of 0.003 g (or 3 mg) to 200 mg, which is medically possible. The greater the dose of chemotherapy, although it will mathematically increase the success of chemotherapy, medically it can be very dangerous.

5. Discussion and conclusion

In this paper, we have developed a mathematical model that describes the interactions between the leukemia-initiating cell, leukemic blast cell and chemotherapeutic drug in Acute Myeloid Leukemia. Furthermore, we have discussed system behavior by analyzing the existence and stability of the equilibrium solutions of our system. We also provide numerical simulation to verified the analytical results. From the graphical representation we can get an estimate of chemotherapeutic drugs that can be given to leukemia patients. In a medical point of view, of course, we do hope that every initial

condition will tend to a disease free equilibrium. Analytically we have found the relationship between the chemotherapeutic drug administration and both the leukemia-intitating cell and leukemic blast cells, which represented by $r_1\gamma < a\gamma + b_1\rho$ and $r_2\gamma < d\gamma + b_2\rho$, respectively. Medically, its mean that if the chemotherapeutic drugs more durable than both the leukemia-intitating cell and leukemic blast cells then the disease free equilibrium will be stable. In other word, the AML patient will be cured. Otherwise, the AML disease will persist.

In this paper, the model is only based on one treatment regimen, i.e. treatment by chemotherapy. Although the model is rather simple but may give insight into some of the consequences of medical policies. We note that, not of all the parameter values used in this model based on the clinical data that can be obtained from some medical literature. It could be very useful for determining the range of the various parameter involved. In the future work, it can be considered to incorporate the delay differential equation, a periodic function of chemotherapeutic dose. Chemotherapy, immunotherapy, targeted therapy may also be considered.

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