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# Applications of differential Systems in the Chronic Myeloid Leukemia

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**Abstract**
Chronic myeloid leukemia accounts for 15% of all leukemia's in adults. CML progresses through three different phases (chronic, accelerated and blasted phase) and is usually diagnosed in the chronic phase. In the chronic phase of the disease, mature cells proliferate; in the accelerated phase, additional cytogenetic abnormalities appear; in the blast phase, the immature cells proliferate rapidly. In recent decades, the incidence rate of leukemia has increased slowly. From 2003 to 2012, the rate increased by 1.3% per year. Using a mathematical model represented by a system of two differential equations and the MATLAB program, we tried to simulate the behavior of leukemia for different values of the parameters in the model.

**Keywords:** Chronic Myeloid Leukemia, Ordinary Differential Equations, Mathematical models, MATLAB.

## 1. Introduction

Leukemia is when the blood has an abnormal number of white blood cells. Blood is made up of white blood cells that fight infection, red blood cells that transport blood, and platelets that help blood clot. If the body produces too many white blood cells, the other components of the blood begin to agglomerate. Chronic myeloid leukemia occurs in certain blood cells of the bone marrow[1]. A genetic change occurs in the early stages of myeloid cells - those that make up red blood cells, platelets and most white cells. Chronic myeloid leukemia cells only partially mature and, thus, the cells grow and divide and begin to accumulate in the bone marrow. After a while, leukemia cells can infiltrate other parts of the body. Many people with chronic myeloid leukemia have nonspecific symptoms at the time of diagnosis. The most common symptoms are fatigue, weakness, itching, night sweats, abdominal discomfort and weight loss[2]. An enlarged spleen (splenomegaly) is usually detected on physical examination. When the accelerated or blast phase of this form of leukemia occurs, an affected person may experience severe weight loss, high fever, bone pain, enlargement of the liver and spleen, joint pain (arthralgia), and bleeding that appears as purple discoloration spots on the skin and mucous membranes. Being a chronic form, it may take some time before symptoms start to appear. Unfortunately, chronic leukemia's are often more difficult to treat than acute leukemia's[3]. Leukemic cells begin to grow and divide. They accumulate in the bone marrow, circulate in the bloodstream and travel throughout the body. Over time, the excess of leukemic cells crowds healthy red blood cells and platelets. This can cause problems such as anemia, easy bruising, bleeding that lasts longer and a greater risk of infection. Most people with chronic myeloid leukemia remain in the chronic phase. In some cases, people who do not receive effective treatment or do not respond well to treatment go towards the accelerated or blast phase[4]. The prognosis is quite optimistic for those who are in the chronic phase and receive treatment. In the accelerated phase, survival rates vary greatly depending on the treatment. If the person responds well to the treatment, the rates are almost as good as those in the chronic phase. In general, the survival rates of those in the

blast phase are below 20%. The best chance of survival involves the use of drugs to return the person to the chronic phase and then a stem cell transplant can be attempted [5].

## 2. Materials and methods

We will introduce a mathematical model given by a two-dimensional system of differential equations to understand the transition process from normal hematopoiesis to different stages of chronic myeloid. Chronic Myeloid Leukemia progresses in three phases: chronic, accelerated and acute or blastic transformation. The differentiation of the last two phases being difficult due to similar particularities, we will refer to them as a whole, calling it an accelerated-acute phase.

The evolution of normal and leukemic cells is given by the following system [6]:

$$\begin{cases} \frac{dx}{dt} = \frac{a}{1+b_1x+b_2y}x - cx \\ \frac{dy}{dt} = \frac{A}{1+B(x+y)}y - Cy \end{cases}$$

Where:

- Term x represents the normal stem cell population,
- Term y represents the population of abnormal stem cells,
- Terms a and A represent the growth rates (due to the self-renewal process) of normal and abnormal stem cells,
- Terms c and C represent the death rates (due to differentiation, apoptosis or other elimination mechanisms) of normal and abnormal stem cells,
- Terms $b_1$, $b_2$ and B represent the parameters that describe the sensitivity of the bone marrow microenvironment,
- Terms $\frac{a}{1+b_1x+b_2y}$ and $\frac{1}{1+B(x+y)}$ quantify the impact of induced crowding in the bone marrow microenvironment, introduce competition between normal and abnormal cells, and guarantee homeostasis at the cell population level,
- We assume that for both cell populations, the growth rate is greater than the death rate: $a > c$ și $A > C$.

## 3. Results & Discussion

The aim of the simulation using MATLAB software is to investigate the behavior of normal and abnormal stem cell populations in each of the cases: normal state, chronic state and accelerated-acute state [7]. Plots are plotted for different sets of model parameter values (a, b1, b2, c, A, B, C), for different initial values x (0), y (0) and different time intervals. The parameters used in this model depend on a large number of biophysical and biochemical mechanisms. They make it almost impossible to accurately estimate these parameters. Given that this is a qualitative analysis, parameter estimation is not essential, the relationships between the parameters being sufficient. Parameter estimation becomes essential when the model is applied for real-time predictions and on individual patients. To obtain viable results, parameter values will be established by considering other studies in the field. Thus, the number of stem cells in a healthy patient is considered to be approximately N=$2\cdot10^4$, and the growth and death rates of normal stem cells can be a=0.005 and c =0.002. The parameter $b_1$ can be estimated from the formula of N, resulting in $b_1$=$0.75\cdot10^{-4}$. We consider that the ratio $\frac{b_1}{b_2}$ is equal to 2. Thus, we obtain that $b_2$ =$0.38\cdot10^{-4}$. We also consider the value of the parameter B to be approximately half the value of $b_2$ resulting in B=$0.19\cdot10^{-4}$. The simulation will be performed for several values of the A and C parameters so that all previous relationships between the model parameters are viable. Taking these into account, the parameters will have the following values [7]:

**Table1:** Parameter values for the simulation.

| Figure | a | $b_1$ x $10^{-4}$ | $b_2$ x $10^{-4}$ | c | A | B x $10^{-4}$ | C |
|---|---|---|---|---|---|---|---|
| 4 | 0.005 | 0.75 | 0.38 | 0.002 | 0.01 | 0.19 | 0.009 |
| 5 | 0.005 | 0.75 | 0.38 | 0.002 | 0.01 | 0.19 | 0.007 |
| 6 | 0.005 | 0.75 | 0.38 | 0.002 | 0.01 | 0.19 | 0.004 |
| 7 | 0.005 | 0.75 | 0.38 | 0.002 | 0.007 | 0.19 | 0.001 |
| 8 | 0.005 | 0.75 | 0.38 | 0.002 | 0.004 | 0.19 | 0.003 |
| 9 | 0.005 | 0.75 | 0.38 | 0.002 | 0.0045 | 0.19 | 0.003 |
| 10 | 0.005 | 0.75 | 0.38 | 0.002 | 0.0045 | 0.19 | 0.0025 |
| 11 | 0.005 | 0.75 | 0.38 | 0.002 | 0.0012 | 0.19 | 0.001 |
| 12 | 0.005 | 0.75 | 0.38 | 0.002 | 0.0015 | 0.19 | 0.001 |
| 13 | 0.005 | 0.75 | 0.38 | 0.002 | 0.0025 | 0.19 | 0.001 |

The simulation will be performed for four cases, with the following relationships between parameters:

- Case one: $\begin{cases} a < A \\ c < C \\ b_1 > b_2 > B \end{cases}$
- Case two: $\begin{cases} a < A \\ c > C \\ b_1 > b_2 > B \end{cases}$
- Case three: $\begin{cases} a > A \\ c < C \\ b_1 > b_2 > B \end{cases}$
- Case four: $\begin{cases} a > A \\ c > C \\ b_1 > b_2 > B \end{cases}$

In all cases we assume that abnormal stem cells are less sensitive to environmental crowding than normal stem cells: $b_1 > b_2 > B$.

In case I, the growth and death rates of normal stem cells are much lower than the growth and death rates of leukemic stem cells. Figure 1 shows the time behavior (t = 3,000 days) of the two cell populations for the parameter values

provided by Table 1, values corresponding to the normal hematopoietic state [7]. The population of normal stem cells, x(t), represented in the graph by the blue color, tends towards the value d, and the population of abnormal stem cells, y(t), represented by the red color, tends towards 0.

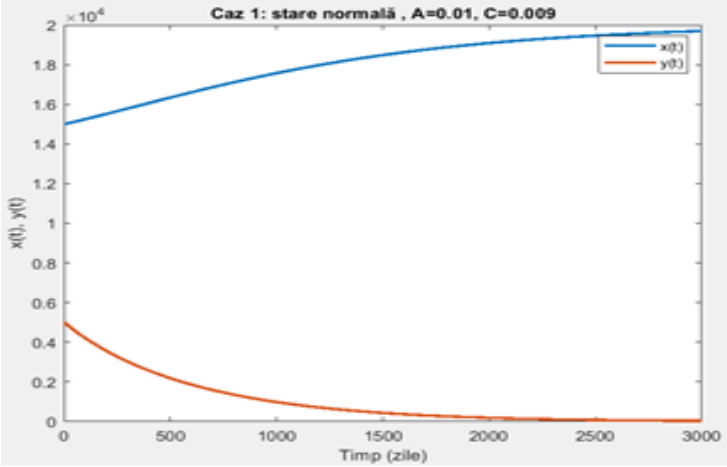


**Fig.1:** Behavior of normal and leukemic stem cell populations in case I - normal state (initial conditions: x(0)=1.5$\cdot 10^4$ and y(0)=5$\cdot 10^3$)

Figure 2 shows the time behavior (t = 25,000 days) of the two cell populations for values corresponding to the chronic state.

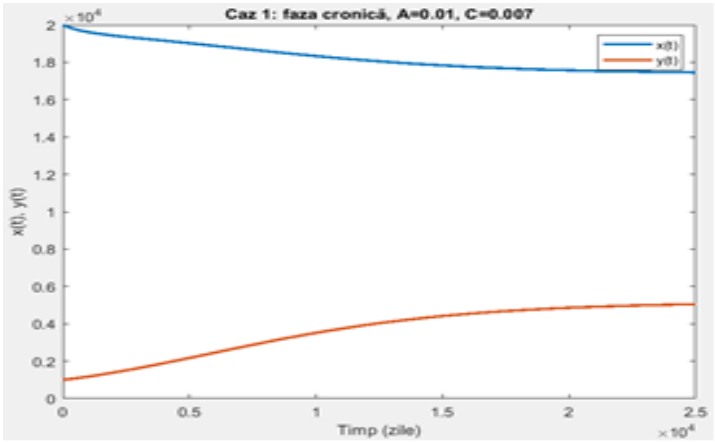


**Fig. 2:** Behavior of normal and leukemic stem cell populations in case I - chronic phase (initial conditions: x(0)=2$\cdot 10^4$ and y(0)=$10^3$)

Finally, Figure 3 shows the time behavior (t = 8,000 days) of the two cell populations for the values leading to the accelerated-acute state. In this phase, compared to the normal state, the population of normal cells tends towards 0, while the population of leukemic cells tends towards the D value.

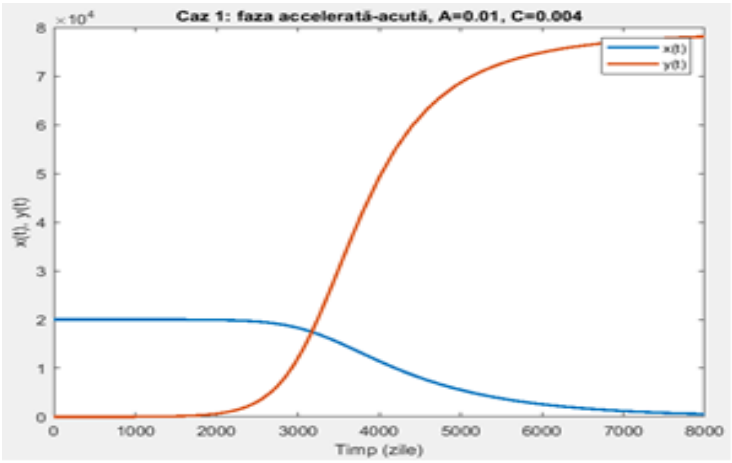


**Fig. 3:** Behavior of normal and leukemic stem cell populations in case I - accelerated-acute phase (initial conditions: x(0)=2$\cdot 10^4$ and y(0)=1)

In case II, the growth rate of normal stem cells is lower than the growth rate of abnormal stem cells, and the death rate of the normal cell population is higher than the death rate of the abnormal cell population [7]. Therefore, only the accelerated-acute state is possible. Figure 4 shows the time behavior (t = 6,000 days) of the two cell populations, and it can be seen that the normal cell population tends to 0, while the leukemic cell population tends to D

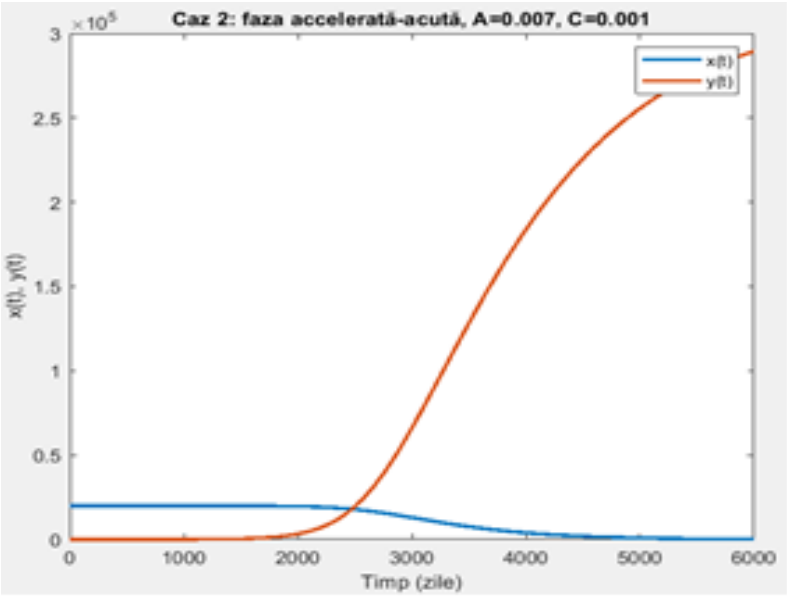


**Fig. 4:** Behavior of normal and leukemic stem cell populations in case II - accelerated-acute phase (initial conditions: x(0)=2 $\cdot 10^4$ *104 and y(0)=1)

In case III, the growth rate of normal stem cells is higher than the growth rate of abnormal stem cells, and the death rate of normal stem cells is lower than the death rate of abnormal stem cells. Figure 5 shows the behavior over time (t = 25,000 days) of the two cell populations, the parameter values corresponding to the normal hematopoietic state. The normal cell population tends toward the d value, while the abnormal cell population tends toward 0.

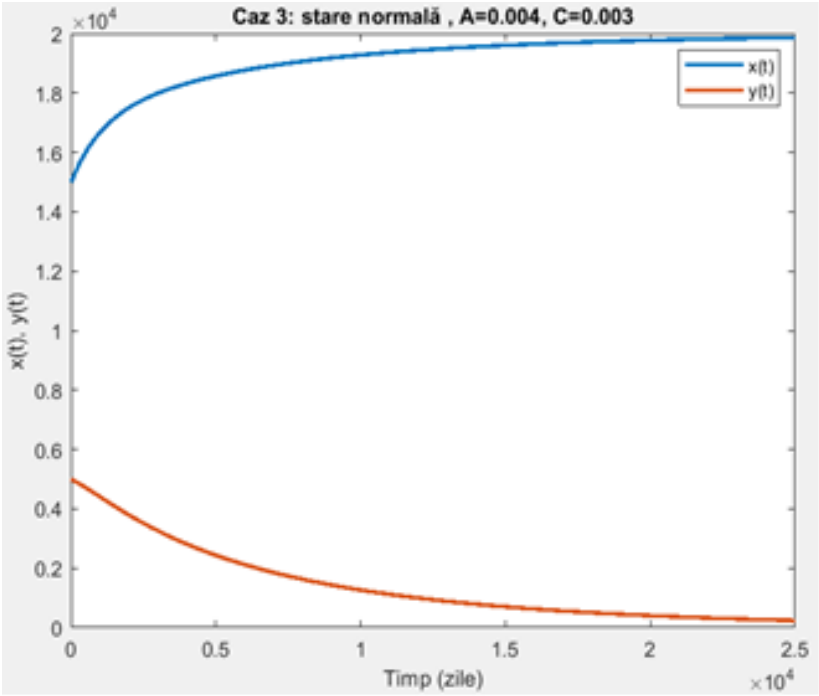


**Fig.5:** Behavior of normal and leukemic stem cell populations in case III - normal state (initial conditions: x(0)=1.5 $\cdot 10^4$ and y(0)=5 $\cdot 10^3$)

Figure 6 shows the behavior over time (t = 25,000 days) of the two cell populations, the parameter values corresponding to the chronic state.

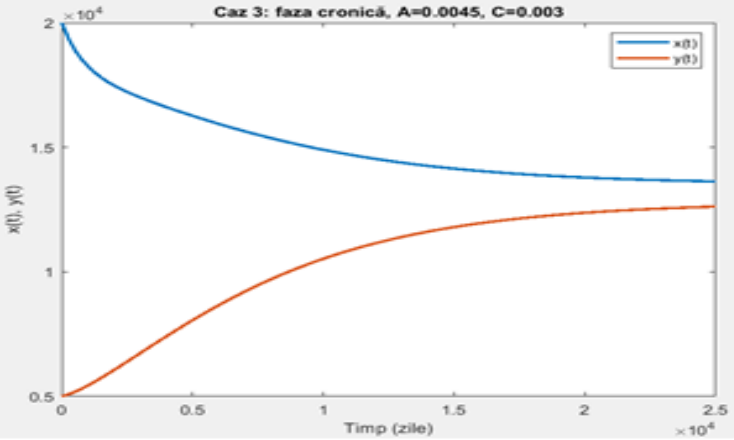


**Fig.6:** Behavior of normal and leukemic stem cell populations in case III - chronic phase (initial conditions: x(0)=2$\cdot 10^4$ and y(0)=5$\cdot 10^3$)

Figure 7 shows the time behavior (t = 40,000 days) of the two cell populations, the parameter values corresponding to the accelerated-acute state. The normal stem cell population tends toward 0, while the leukemic stem cell population tends toward D.

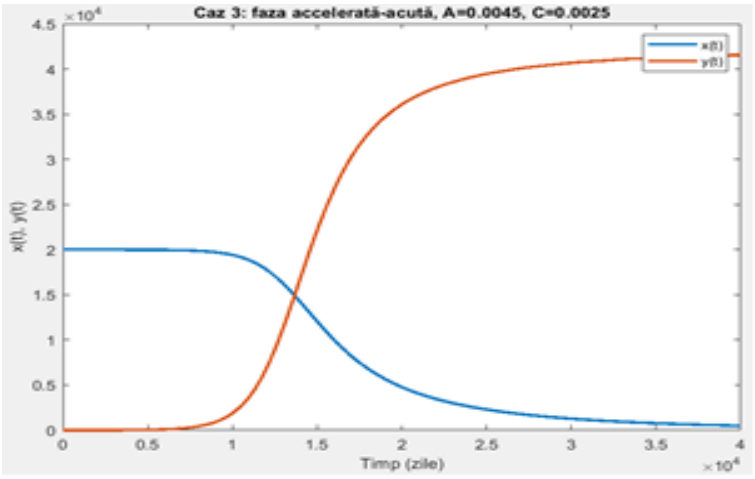


**Fig.7:** Behavior of normal and leukemic stem cell populations in case III - accelerated-acute phase (initial conditions: x(0)=2$\cdot 10^4$ *104 and y(0)=1)

In case IV, which is the last case shown, the growth rate of normal stem cells is higher than the growth rate of abnormal stem cells, and the death rate of normal stem cells is higher than the death rate of abnormal stem cells [7]. Figure 8 shows the behavior over time (t = 25,000 days) of the two cell populations, the parameter values corresponding to the normal hematopoietic state (D < d). The normal cell population tends toward the d value, while the abnormal cell population tends toward 0.

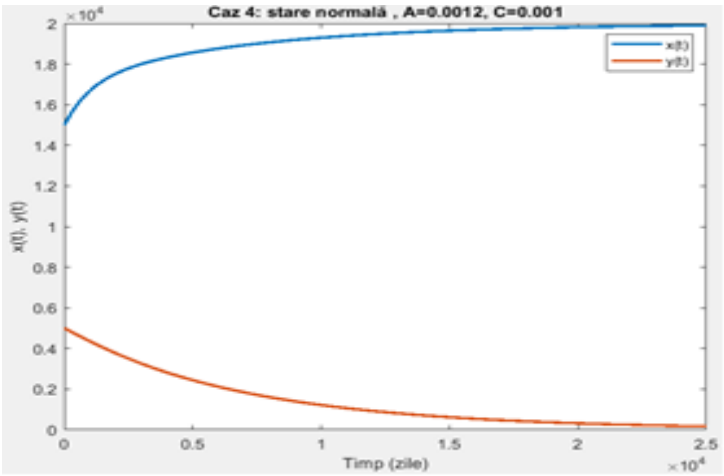


**Fig.8:** Behavior of normal and leukemic stem cell populations in case IV - normal state (initial conditions: x(0)=1.5$\cdot 10^4$ and y(0)=5$\cdot 10^3$)

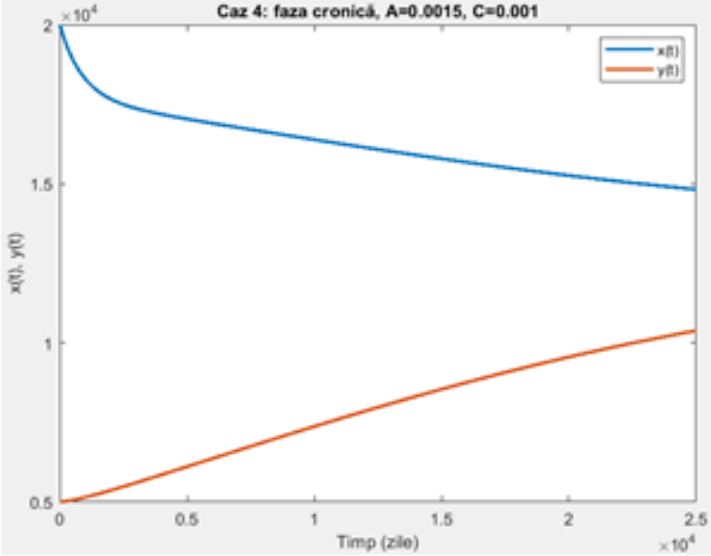


**Fig. 9:** Behavior of normal and leukemic stem cell populations in case IV - chronic phase (initial conditions: x(0)= $2 \cdot 10^4$ and y(0)= $5 \cdot 10^3$ )

Figure 9 shows the behavior over time (t = 25,000 days) of the two cell populations, the parameter values corresponding to the chronic state.

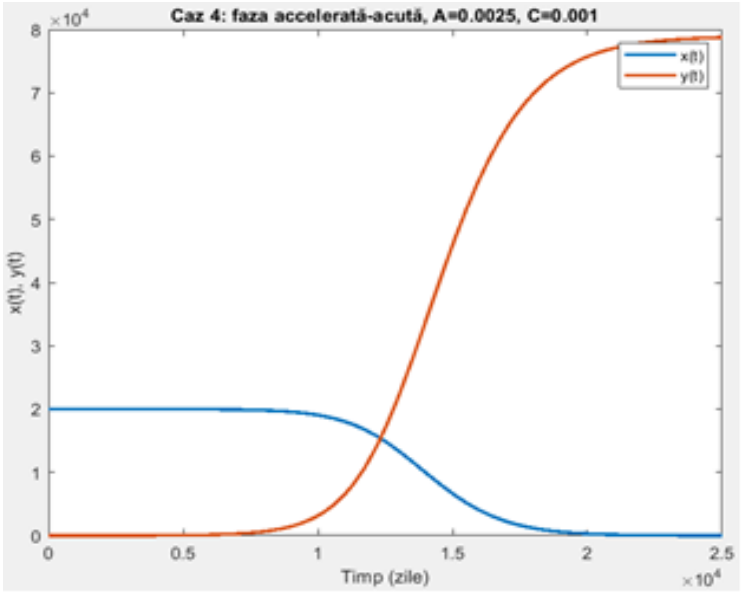


**Fig.10:** Behavior of normal and leukemic stem cell populations in case IV - accelerated-acute phase (initial conditions: x(0)= $2 \cdot 10^4$ and y(0)=1)

Finally, Figure 10 shows the behavior over time (t = 25,000 days) of the two cell populations, the parameter values corresponding to the accelerated-acute state. The normal stem cell population tends toward 0, while the leukemic stem cell population tends toward the D value.

## 4. Conclusions

Through the presented mathematical model, it was possible to analyze some elements and characteristics of both normal and leukemic stem cells, which can be useful for the mathematical modeling of leukemic pathology and for future research. From the analysis of the first case, in which abnormal stem cells have a higher growth rate than normal stem cells (two times higher), it is observed that the evolution of leukemic pathology is dependent on the ratio given by the mortality rates of normal and leukemic stem cells . Therefore, at a death rate of leukemic cells four times that of normal cells, the disease progressed and led to the disappearance of leukemic cells. The analysis of the second case confirms our previously mentioned conclusion, according to which the disease progresses to the accelerated-acute phase of Chronic Myeloid Leukemia in the absence of a death rate of leukemic stem cells several times higher than the death rate of normal stem cells. This case demonstrates the importance of the microenvironment in the evolution of the disease and implicitly in the choice of treatment. Thus, if treatments fail to decrease the proliferation rate or increase the death rate of leukemic stem cells, the microenvironment is considered the only remaining therapeutic target available. It is also noted that the accelerated-acute phase of chronic myeloid leukemia developed approximately six years after the appearance of

the first leukemic stem cell, if no changes occur in the initial parameters.

By analyzing cases III and IV, in which the growth rate of leukemic stem cells is lower than that of normal stem cells, it is demonstrated that chronic myeloid leukemia can occur and move between its three stages. The disease follows a similar course to that observed in case I, but is characterized by a longer evolutionary time interval, probably caused by the slow proliferation rate of hematopoietic stem cells. In general, these cases with a slow progression of the disease are rare and occur in elderly people . In conclusion, mathematical models applied in the biomedical field can reveal basic aspects, which through future research in correlation with medical practice, can discover improved treatments of leukemia or other pathologies.

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