International Journal of Statistics and Applied Mathematics 2023; 8(2): 75-82

ISSN: 2456-1452
Maths 2023; 8(2): 75-82

https://www.mathsjournal.com
Received: 03-01-2023
Accepted: 04-02-2023

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Mathematical modelling of acute myeloid Leukaemia with dynamics of accidental cell death

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DOI: https://doi.org/10.22271/maths.2023.v8.i2b.955

Abstract
Recent mathematical models have been developed for the Acute myeloid Leukaemia and myeloproliferative disorder. In this paper system of the ODE is modelled. With the help of the mathematical model we proposed necrotic core which develops in the progression of the disease where the cell is subjected to the accidental death that leads to inflammation.

Keywords: Necrosis, myeloproliferative neoplasm, ODE

1. Introduction
Myeloproliferative disorder is a lethal disease of bone marrow which leads to the growth and uncontrollable production of the stem cells in the blood stream. The particular types of hematological malignancy in Acute Myeloid leukemia. Acute Myeloid Leukemia (AML) comes under the classification of disorder of Myeloproliferative Neoplasm (MPNs). From the Biological point of view the origin starts in the bone marrow. Stem cells or hematopoietic stem cells (HSC) prevail inside into the bone marrow microenvironment where all the types of blood cell are formed. HSC turns out into differentiated progenitor cells. Mutation is the main cause for the leukemic cell and also can occur in the section of HSC cells and turned into malignancy. The reason leukemia happens as the outcome of the differentiated cells of the healthy cells including infection [1]. Cancer stem cell hypothesis, suggests that healthy stem cells turned out into differentiated and this is the main cause of malignancy and its uncontrolled growth [2, 3]. There are few other types of disorders for instance, chronic myeloid leukemia (CML) also obtain from the same theoretical process. CML is a lethal disease under myeloproliferative disorder the origination from a stem cell clone and acquire the Philadelphia-chromosome expressing the BCR-ABL gene [4, 5]. Furthermore WHO highlights their distinguish properties and classification of myeloid neoplasm and acute leukemia [6] From the biological and molecular point of view, the development of AML is various step progressing by tumor cells of multiple genomic alterations and it effects in cellular various parameters [7, 8].
Under the process of Genomic Alternation in AML the activation of programmed cell occur and death it involved various stages in the development, in long-term viable of multicellular organisms [9, 10]. Programmed cell death or Suicidal cell such as Apoptosis and Accidental death like Necrosis are the most common modality of cell death, which can identified by terms of morphological and biochemical properties [11-14]. Apoptosis, for instance, usually involved with setup of a cytokine-dependent regulatory proteases, or caspases family [15-18], although it is significant that cell death mode may occur in caspase independent manner with involved catalytically distinct proteases. Accidental cell death signified the "stage of dying", a high cell damage arises generate by external stimuli (drugs, infection, mechanical trauma), developed the random degradation of the whole cell, with disruption of plasma membrane. Necrotic core is formed in accidental cell death process, dissimilar from Programmed Cell Death (PCD) [19].

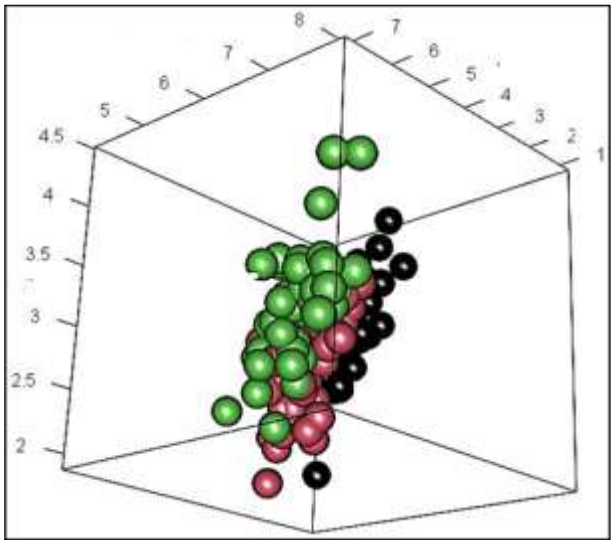

Fig 1: In 3D structure of cell Green color represents the healthy cell, red color represents differentiated cells, black colour represents mutated cells

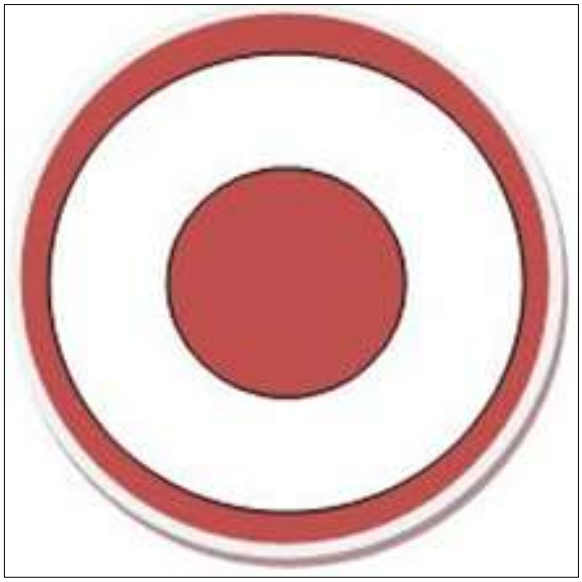

Fig 2: In figure it shows the cells undergoing accidental death the inner circle shows the necrotic core because of the deficiency of nutrients and outer layer shows the cell membrane which is swelling because of the inflammation and other factors

One of the major differences between Programmed Cell Death (Apoptosis) and Accidental Cell Death (Necrosis) is the rise of the inflammatory response. The intracellular material release undergoes into the extracellular environment in the formation of the necrotic core and hence it triggered inflammation [19]. Necrosis is the main reason for decline in plasma membrane integrity, perturbation of calcium homeostasis, general degradation by lysosomal hydrolases and induction of the inflammatory response. According to Greenspan [20]. 'The necrotic core remain constant due to growth retardation throughout in the process of cancer. In the proposed model we have coupled necrosis in the existing model to see its effect rise and fall during the tenure. The objective of this study is to review the effect of the accidental Cell Death in AML. The purpose of the study is to investigate the effect of necrosis in haematological malignancy like AML. We propose that effect of necrotic core is constant throughout the procedure and it does not change into entire procedure. As the hypothesis of stem cell the growth retardation is the main cause of forming necrotic core, which leads necrosis. When the cancerous cells die due to the lack of decisive nutrients, it rise the development of necrotic core also when each and every cells including cancerous cells receive acquire sufficient nutrients the consumption of a nutrients falls towards the center of a node, due to the law of exponential growth retardation as resultant cell breaks and applied pressure or force in nutrients like glucose starts break towards necrotic core. This process arise necrosis due to the lack of crucial nutrients. The accidental death of cells does not follow the same procedure of apoptotic pathway, but rather they promote the activation stage in various receptors as outcomes in the deprivation in volume of cell [20]. If necrosis is left untreated it start decompose the cellular structure of a cell towards death. This information may help mathematicians and physicians to understand the mechanics for transition states of necrotic core effect in hematological malignancy and metastasis. Based on above theory it described the relationship between the AML and necrotic core. In this method we describe the proliferation from stem cells turned up into differentiated to mature cells in the presence of inflammation with immune response in accidental death of cell.

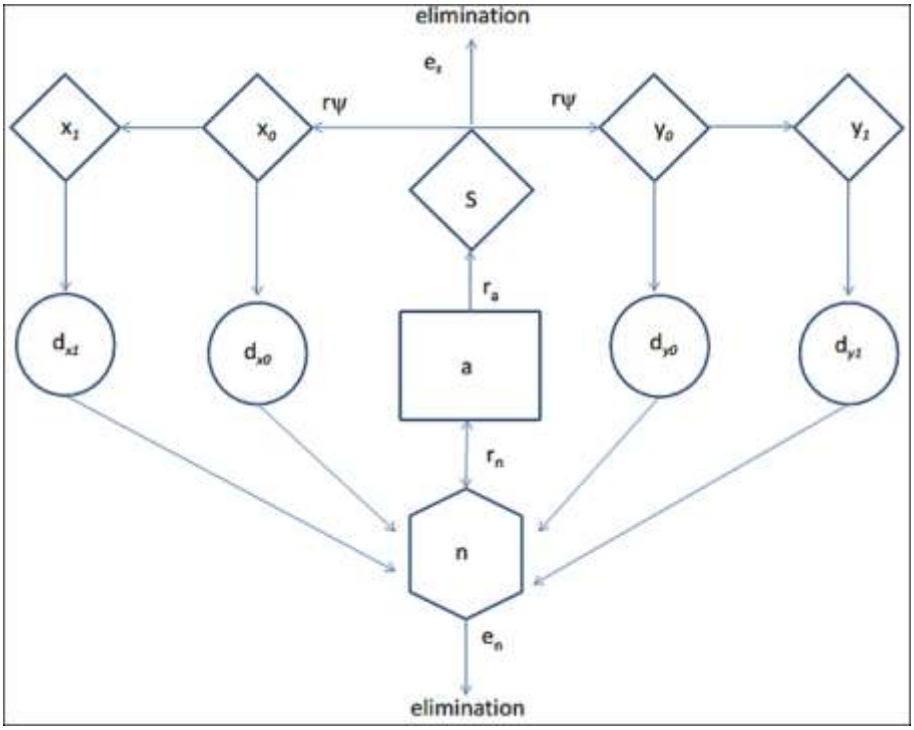

Fig 3: Model represents the three boxes1 in centre compartments s(immune response), a (dead cells), n (necrotic core) and boxes of x_0, x_1, y_0, y_1 in terms of healthy stem cells, differentiated cells, mutated cells, mature cells respectively. The arrow represents the flow towards compartments. dx_0, dx_1, dy_0, dy_1 are the no of dead cells from each compartments

2. Model

In this paper we are going to focus on the effect of necrotic core in the progression of AML. In our model we are going to implicit the dynamics of the accidental death in which a necrotic core is developed before the cell dies with inflammatory response and the infection is developed. As the outcome of the model shows, the total amount of dead cells gives a rise of inflammation. Regardless the nature of complexity, the model allows the possible relevant quantities to show the behavior of necrosis in AML. Basically, the architecture of the model depends on the four sections i.e. hematopoietic stem cells (HSC), hematopoietic mature cells (HMC), the MPN-mutated stem cells (MPN SC) and the MPN mature cells (MPN MC). The cells are signified by x_0, x_1, y_0 and y_1 respectively, The healthy stem cell spread into the disorder of malignant proliferation. Hypothesis suggest about stem cell (SC) may in three ways;

- Symmetric self-renewal.
- Asymmetric self-renewal.
- Symmetric differentiation.

The multistep process in progenitor cells plays the important role for stem cells to produce mature cells. The stem cells will form number of mature cells by factor B_i which is the rate of self-renewal in stem cells and malignant cell and the continuum sequence of the progenitor cells is regardless in specified way [21]. The dynamics of the mathematical modeling will be presented by linear ordinary differential equations by using conservation laws. The product rate of A_x and A_y will Amplifies for stem cells and malignant cells. The Amplified self-renewal rate for healthy stem cells and mature cells are r_x, r_y respectively. The marked change with the rate of a_x for healthy stem cells whereas a_y is the marked change for malignant cell. The accidental cells may die with decrease rate and mature cells may die with increase rate. The overall death rates for the healthy stem cells, differentiated cells, mutated cells, mature cells are dx_0, dx_1, dy_0, dy_1 respectively. The rate of mutation and the amplification factor introduced by Dingli and Michor from here we take the model describe duplicates structure for the model describe for $A = 1$ [22]. Furthermore, Anderson et all proposed the same model by applied inflammation [36]. The mutation rate r_m is not considered about describes probability undergoes into the mutation of malignant Stem Cell (MPN SC), this states that the single mutation r_m is not considered as the probability and related expected mutation is characterized in Poisson process [23]. The study characterize the probability of cell mutation is around 10^{-7} year/cell in hematological malignancy [24]. Nevertheless, all mutated cell were not malignant only malignant mutated cells were found in their nucleic acids of the DNA, which is the reason to occur AML with mutations. Another factor to give up rise of AML is exposure to uv lights, drug like benzene, smoking of cigarette, tobacco, and certain drugs and chemicals increase the risk [25-27]. The initial stages of mutation, we assume that healthy stem cells present in steady state with the zero-mutation rate or mutation rate is zero the initial condition proposed for model. Mutation rate does not affect with the model outcomes. The general equation for the model we take the difference rate of each compartment with the rate of elimination that gives the appropriate validation of our model with the respective manner of time. The leftover of a cell is surrounded by phagocytic cells, (e.g. neutrophils and macrophages) whenever cells die the inflammatory cytokines were free [28-30]. The necrotic

core of accidental cell death triggered the self-renewal rate of stem cells with immune response. For the analysis and hypothesis, we assume, (n) for necrosis and (a) for dead cells and (s) immune response with rate constant expressed by r_s per dead cell whereas, es is the rate of eliminated in cells. The characteristics properties of AML showed in low time-scale years property and whereas, on the other hand inflammatory immune processes required rapid on time, for instance in term of hours, day scale. The number of die cells were derived by $d_{x0}.x_0 + d_{y0}.y_0 + d_{x1}.x_1 + d_{y1}.y_1$ per time, n is the necrosis, r_n is rate of the necrotic core and e_n is the elimination rate of necrosis in dead cells. It is prominent that the mutation rate [31] of AML is affected by inflammation process as well [32]. In contrast to, we also proposed the imatinib therapy for AML, we proposed these were taken to be proportionally with the inflammatory level, yet the level fixed at constant levels so does the inflammation, the study represent the amount of inflammatory cytokines showed high and trigger the AML and various step from controlled through the initial stages of cancer i.e.ET, PV, to the advanced stage of cancer or well known as myelofibrosis (PMF) [33, 34]. The complete analysis of mathematical equations and default parameters values were used in model is described in Table in Appendix. The following expression for AML necrotic core model

$$\dot{x}_0 = (B_1 s - d x_0 - a_x) x_0 - r_m s x_0$$

Where B_1 is the self-renewal rate of HSC with hill function and the initial condition is $x_0(0) = x_{0i}$

$\dot{x}_1 = a_x x_0 - d_{x_1} x_1$ and the initial condition $x_1(0) = x_{1i}$

$\dot{y}_0 = (B_2 s - d y_0 - a_y) y_0 + r_m s x_0$ the initial condition $y_0(0) = y_{0i}$

$\dot{y}_1 = a_y y_0 - d_{y_1} y_1$ $y_1(0) = y_{1i}$

$\dot{n} = d_{x0} x_0 + d_{x_1} x_1 + d_{y_0} y_0 + d_{y_1} y_1 - e_n n a$ $n(0) = n_i$

$\dot{a} = r_n n - r_s a$ $a(0) = a_i$

$\dot{s} = r_s a - e_s s + I$ $s(0) = s_i$

Here in the above set of ODE

$$B_1 = r_x \varphi_x \quad B_2 = r_y \varphi_y$$

$$\varphi_x(x_0, y_0) = \frac{1}{1 + (c_{xx} x_0 + c_{xy} y_0)^2}, \quad \varphi_y(x_0, y_0) = \frac{1}{1 + (c_{yx} x_0 + c_{yy} y_0)^2}$$

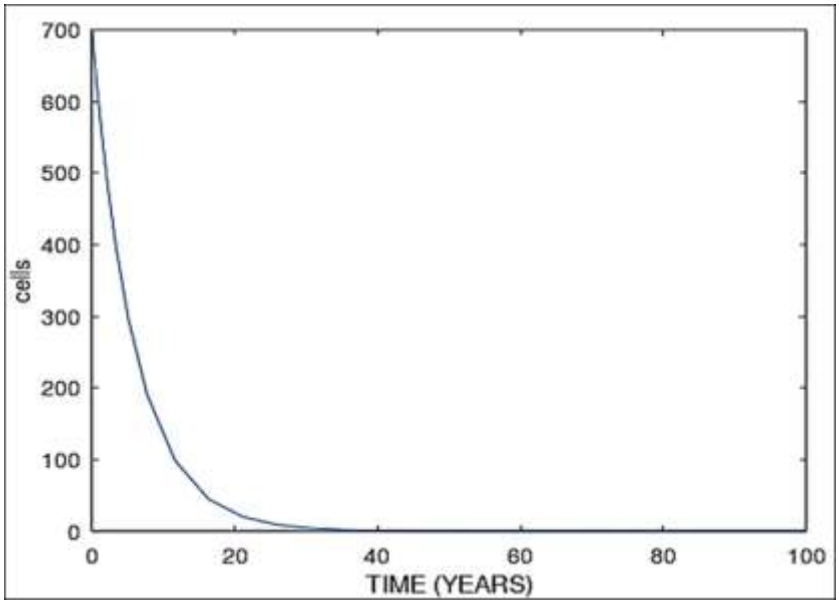

Fig (a)

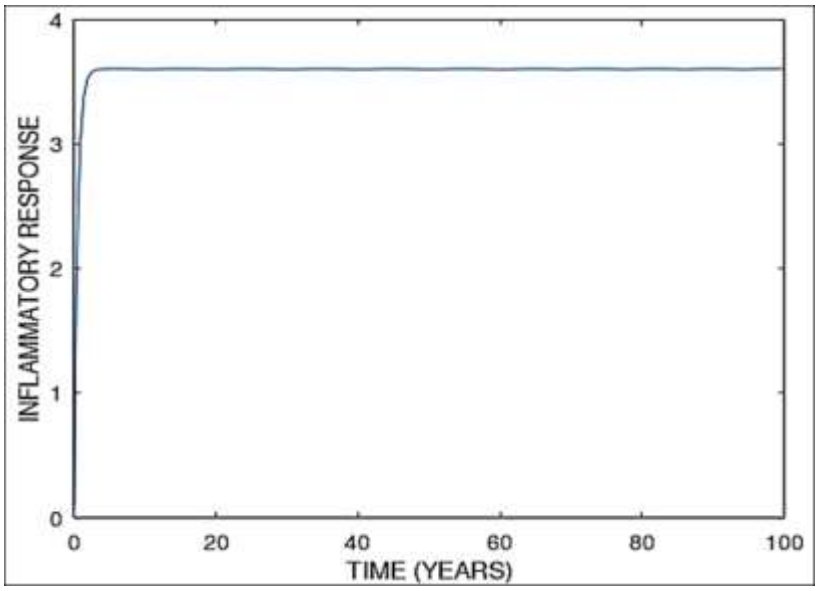

Fig (b)

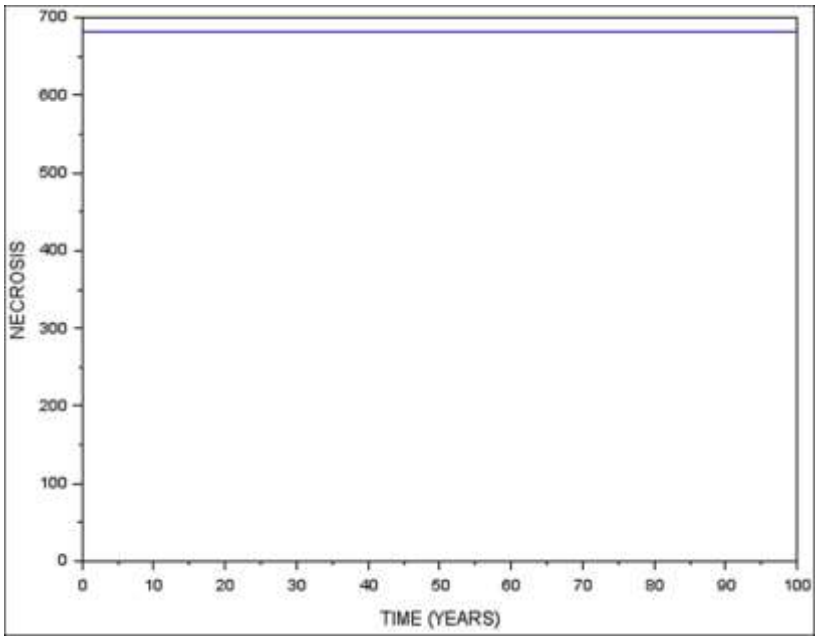

Fig (c)

Fig 4: Graph represents (a) for dead cells, (b) graph shows the effect of inflammation in tenure period (c)graph shows the affect of necrosis in AML disease predicted curves versus time

3. Results and Discussion

In conclusion, we have applied mathematical modeling with the concept of necrotic core and inflammation a closing linked to the develop of AML. We have place on account the effect of necrotic core in the present model is constant throughout the procedure, which seen the reference to the theory of necrosis that it does not affect much in the process of development of the disease, whereas the inflammation increase exponentially in tenure of the disease which is very much in the graphical representation. Hence, we conclude that mathematical modeling if done properly the whole complex process can be modeled appropriately, there are still many parameters which have not been explode till now, by using mathematical modeling a more complex but accurate model can be framed out.

4. Conclusion

We have shown in our paper that necrotic core can be included, in the modeling of hematological malignancy with impact of inflammation and by making ODE model. We have also shown that it doesn't change with the parameter although it is almost unchanged throughout the whole program.

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Appendix

The model is originally presented by Dingli Michor [22], whereas the extended phase represents our natural extension. The basic model without the effect of necrotic core and inflammatory. The original equation of the model [22].

$$\overset{*}{x}_0 = [r_x\phi - d_0]x_0 \text{ , } x(0) = x_{0i}, [x_0 = HSC], \quad \ldots (1)$$

$$\overset{*}{x}_1 = a_x x_0 - a_1 x_1 \quad x_1(0) = x_{1i}, [x_1 = HMC], \quad \ldots (2)$$

$$\overset{*}{y}_0 = [r_y\phi - d_0]y_0 \quad y(0) = y_{0i} \; [y_0 = MPNSC] \quad \ldots (3)$$

$$\dot{y}_1 = a_y y_0 - d_1 y_1 \; y_1(0) = y_{1i}, [y_1 = MPNMC], \quad \ldots (4)$$

Where x_{0i}, x_{1i}, y_{0i}, and y_{1i} denotes HSC (Hematopoietic Stem Cell), HMC (Hematopoietic Mature Cell), MPN SC, MPN MC respective cells.

$$\dot{x}_0 = (B_1 s - dx_0 - a_x)x_0 - r_m s x_0 \quad x_0(0) = x_{0i} \; [x_0 = HSC], \quad \ldots (5)$$

$$\dot{x}_1 = a_x x_0 - d_{x_1} x_1 \quad x_1(0) = x_{1i} \; [x_1 = HMC], \quad \ldots (6)$$

$$\dot{y}_0 = (B_2 s - d y_0 - a_y)y_0 + r_m s x_0$$

$$\dot{y}_1 = a_y y_0 - d_{y_1} y_1 \qquad y_0(0) = y_{0i} \; [y_0(0) = MPNSC] \quad \ldots (7)$$

$$y_1(0) = y_{1i} \; [y_1(0) = MPNMC] \quad \ldots (8)$$

$$\dot{n} = d_{x0}x_0 + d_{x_1}x_1 + d_{y_0}y_0 + d_{y_1}y_1 - e_n n a \quad n(0) = n_i \; [n(0) = necroticcore] \quad \ldots (9)$$

$$\dot{a} = r_n n - r_s a \qquad a(0) = a_i \quad a(0) = deadcells$$

$$\dot{s} = r_s a - e_s s + I \quad s(0) = s_i \quad s(0) = \inf \; lammation \quad \ldots (10, 11)$$

Where,

$$\varphi_x(x_0, y_0) = \frac{1}{1 + (c_{xx}x_0 + c_{xy}y_0)^2}, \; \varphi_y(x_0, y_0) = \frac{1}{1 + (c_{yx}x_0 + c_{yy}y_0)^2}$$

For healthy steady state we choose parameter values for equations at t=0. We have taken values from Stiehl *et al.* [35], Dingli & Michor [22]

Table 1

Parameter	Value	Unit	Parameter	Value	Unit	Parameter	Value	Unit
r_x	8.7*10^4	day^{-1}	r_y	1.3*10^-3	day^{-1}	e_n	2	day^{-1}
a_x	1.1*10^–5	day^{-1}	a_y	a_x	day^{-1}	r_s	3*10^-4	day^{-1}
A_x	4.7*10^13	day^{-1}	A_y	A_x	day^{-1}	r_n	3*10^-4	day^{-1}
dx_0	2*10^–3	day^{-1}	dy_0	dx_0	day^{-1}	n	0.1030	day^{-1}
dx_1	129	day^{-1}	dy_1	129	day^{-1}	I	7	day
c_{xx}	7.5*10^-5	-	c_{yx}	c_{xx}	-	r_m	0	day^{-1}
e_s	2	day^{-1}	e_a	2*10^9	day^{-1}	c_{yy}	c_{xx}	-

Where,

r_x = Self-renewal rate of healthy stem cell.

a_x = Proliferation rate of stem cells.

A_x = Amplification rate of produced mature cells.

dx_0 = dead rate of stem cell (HSC).

dx_1 = Dead rate of HMC.

c_{xx} = Factor rate of healthy stem cell for self-renewal.

c_{yx} = Factor rate of mature cells for self-renewal.

r_y = Self-renewal rate of MPN SC.

a_y = Proliferation rate of MPN SC.

Ay = Amplification factor rate of produced MPN MC.

dx_0 = Dead rate of MPN SC.

dy_1 = Dead rate of MPN MC.

c_{YY} = Factor rate of MPN SC for own self renewal.

e_s = Elimination rate of cytokines.

r_s = Rate by which the dead cells of phagocyte cells.

e_a = Elimination rate of dead cells per cytokine cells.

r_m = Rate of mutation.

n = Necrotic core.

r_n = Rate of necrotic core.

e_n = Elimination rate of necrotic core.