

## A Mathematical Age-structured Model on Aiha Using Delay Partial Differential Equations

<sup>1</sup>S. Balamuralitharan and <sup>2</sup>S.Rajasekaran

<sup>1</sup>Research Scholar/ Mathematics, B.S. Abdur Rahman University, Chennai-48/India. Department of Mathematics, Sri Ramanujar Engineering College, Chennai-48/India.

<sup>2</sup>Professor and Head, Department of Mathematics, B.S. Abdur Rahman University, Chennai-48/India.

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**Abstract:** In this paper we obtain exact global solution for the delay differential equations (DDEs) model in AIHA (Auto-immune hemolytic anemia) by an analytic approach. Three important parameters such as time  $t$ , age  $\alpha$  and rate of production  $\beta$  are involved in DDEs of cell density in a hematological disorder. Hill functions are used for solution of DDEs as they constantly fit into the data while a study on the movement of oxygen is carried out. When the erythrocyte population increases the oxygen carrying capacity of the blood will also increase but anemia will decrease. The origin of the disease anemia is unclear. Mathematical model construction is something of an art in itself and the same can be said for parameter estimation. This will open new avenues for futuristic developments.

**Key words:** Mathematical modeling, delay differential equations, ordinary and partial differential equations, red blood cell (RBC).

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### INTRODUCTION

AIHA is a decrease in normal of red blood cells (RBCs) or less than the normal quantity of hemoglobin in the blood. However, it can include decreased oxygen binding ability of each hemoglobin molecule due to deformity. Hemoglobin normally carries oxygen from the lungs to the tissues. Anemia leads to hypoxia (lack of oxygen) in organs. Since all human cells depend on oxygen for survival, various degrees of AIHA can have a wide range of clinical consequence. The three main classes of AIHA include excessive blood loss, excessive blood cell destruction and deficient RBC production. There are two major approaches: the 'kinetic' approach which involves evaluating production destruction and loss, and the 'morphologic' approach which groups AIHA by RBC size. The morphologic approach uses a quickly available and cheap lab test, since it is starting point. Some patients with AIHA have no symptoms. Others patients with AIHA may feel tiredness, fatigue, appear pale, develop palpitations and become short of breath. Any process that can disrupt the normal life span of RBC may cause AIHA. Normal life span of a RBC is typically around 120 days. RBCs are made in the bone marrow. If the MCV (mean corpuscular volume) is low ( $< 80$ ), the AIHA is categorized as microcytic anemia (low cell volume). If the MCV is in the normal range (80 - 100), it is called a normocytic anemia (normal cell volume). If the MCV is high, then it is called a macrocytic anemia (large cell volume). Generally, clinicians request complete blood counts in the first batch of blood tests in the diagnosis of an AIHA. Apart from reporting the number of RBCs by flow cytometry, this is an important tool in distinguishing between the causes of AIHA. Treatment depends on the type and cause of the hemolytic anemia. Folic acid, iron replacement, and corticosteroids may be used. In emergencies, a blood transfusion or removal of the spleen (splenectomy) may be necessary (Jean-Francois Lambert, 2010; Mackey, M.C., 2008).

It results from an abnormality of the immune system that produces auto antibodies which attack RBCs as if they were substances foreign to the body. The production of RBCs and platelets appears to be regulated by specific cytokines via negative feed back mechanisms where as granulopoiesis is perhaps more complicated and thus less clearly understood.

The growth factor (cytokine) mainly involved in the regulations of RBC production is erythropoietin (EPO). It will move increased production of primitive erythrocytes precursors partially mediated by interfering

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**Corresponding Author:** S. Balamuralitharan, Research Scholar/ Mathematics, B.S. Abdur Rahman University, Chennai-48/India. Department of Mathematics, Sri Ramanujar Engineering College, Chennai-48/India.  
E-mail: balamurali.maths@gmail.com

with apoptosis in these cells. These cells will mature and after a maturation delay produce new RBCs. Periodical hematological disorders are characterized by oscillations in the number of one or more of the circulating blood cells with periods on the order of days to months. AIHA involves oscillations in only one cell lineage. The model also contains feed back control elements (rate of apoptosis, rate of production, etc.) that regulate the release of cells from one compartment to the other. For instance, a model of RBCs could have one compartment for each recognizable stage of erythrocyte precursors. We will discuss some results using only a generic compartment. Age structured models provide a means of understanding the regulations of hematological disorder. We focus in this paper on models that use differential equations (ODE, PDE or DDE). We then show that by partial integration we can express this problem as a DDE model.

**Mathematical Modeling:**

Let  $x(t, \alpha, \beta)$  be the cell density at time  $t$ , age  $\alpha$  and rate of production  $\beta$  in a generic compartment (Basak Karpuz, Özkan Öcalan, 2010; Changyou Wang, 2010; Gani Tr. Stamov, 2010; Lianhua He, 2010; Xiaohua Ding, 2010; Zhenbin Fan, 2010). We assume that cells disappear (die) at a rate  $\gamma(t)$ . We also assume that the cells in the compartments  $\alpha$  &  $\beta$  with a velocities  $V(t)$  &  $U(t)$  and that a cell enters a compartment at  $\beta=0$  and exit this compartment at  $\beta = \tau$ . We assume that  $x(t, \alpha, \beta)$  satisfies the following time-age-Erythrocyte population equation:

$$\frac{\delta x}{\delta t} + V(t) \frac{\delta x}{\delta \alpha} + U(t) \frac{\delta x}{\delta \beta} = -\gamma(t) x, \quad t > 0, \alpha, \beta \in [0, \tau] \tag{1}$$

With boundary condition:

$$x(t, \alpha, 0) = \psi(t) \tag{2}$$

and initial condition

$$x(0, \alpha, \beta) = \varphi(E) \tag{3}$$

$$\int_0^\tau \frac{\delta x(t, \alpha, \beta)}{\delta t} d\beta + \int_0^\tau V(t) \frac{\delta x(t, \alpha, \beta)}{\delta \alpha} d\beta + \int_0^\tau U(t) \frac{\delta x(t, \alpha, \beta)}{\delta \beta} d\beta = -\int_0^\tau \gamma(t)x(t, \alpha, \beta) d\beta$$

$$\frac{dx}{dt} + V(t) [x(t, \alpha, \tau) - x(t, \alpha, 0)] + U(t) [x(t, \alpha, \tau) - x(t, \alpha, 0)] = -\gamma(t) X(t).$$

$$\frac{dx}{dt} + [V(t) + U(t)] [x(t, \alpha, \tau) - x(t, \alpha, 0)] = -\gamma(t)X(t) \tag{4}$$

Where  $X(t)$  is the total number of cells.

$$X(t) = \int_0^\tau x(t, \alpha, \beta) d\beta$$

We can substitute the B.C  $x(t, \alpha, 0) = \psi(t)$

$$(4) \Rightarrow \frac{dx}{dt} = [V(t) + U(t)] [\psi(t) - x(t, \alpha, \tau)] - \gamma(t) X(t) \tag{5}$$

Let  $x(s) = x(t(s), \alpha(s), \beta(s))$

$$\frac{dx}{ds} = \frac{\delta x}{\delta t} \frac{dt}{ds} + \frac{\delta x}{\delta \alpha} \frac{d\alpha}{ds} + \frac{\delta x}{\delta \beta} \frac{d\beta}{ds} - \gamma(t)x \tag{6}$$

This defines a set of four ODEs for  $t > 0$  and  $\alpha, \beta \in [0, \tau]$  as follows.

$$\frac{dt}{ds} = 1 \Rightarrow t(s) = t(0) + s \tag{7}$$

$$\frac{d\alpha}{ds} = V(t) \Rightarrow \alpha(s) = \alpha(0) + \int_0^s V(w)dw \tag{8}$$

$$\frac{d\beta}{ds} = U(t) \Rightarrow \beta(s) = \beta(0) + \int_0^s U(w)dw \tag{9}$$

$$\frac{dx}{ds} = -\gamma(t)x \Rightarrow x(s) = x(0) \exp -\int_0^s \gamma(t(w), \alpha(w), \beta(w)) \tag{10}$$

Denote by C the curve emanating from the point  $(t, \alpha, \beta) = (0, 0, 0)$ , and separating the  $t$ - $\alpha$  &  $t$ - $\beta$  plane into three distinct regions  $R_1$  &  $R_2$ . The curve C is defined by

$$C = \{(t, \alpha, \beta) / t(s) = s, \alpha(s) = \int_0^s V(w)dw \text{ and } \beta(s) = \int_0^s U(w)dw \text{ for } s \in [0, s_T]\} \tag{11}$$

Where the values of  $s_T$  corresponds to the value of  $s$  required to reach  $a = E = \tau$ , thus  $s_T$  must satisfy

$$\tau = \int_0^{s_T} V(w)dw \text{ \& } \tau = \int_0^{s_T} U(w)dw \tag{12}$$

the solution  $x(t, \alpha, \beta)$  takes a different from depending on whether it lies in region  $R_1$  or  $R_2$ . Recall that the general solution is given by (10)

$$x(s) = x(0) \exp -\int_0^s \gamma(t(w), \alpha(w), \beta(w))$$

therefore, we need to find an expression for  $x(0)$  and  $s$  as a function of  $\alpha, \beta$  &  $t$  in order to obtain the expression

$$x(t, \alpha, \beta) = x(t(s), \alpha(s), \beta(s)) \tag{13}$$

recall also that we are interested in the value  $x(t, \alpha, \tau)$

If  $(t(0), \alpha(0), \beta(0)) \in R_1$ , then we have  $t(s) = s$  and  $\beta(s) = \beta(0) + \int_0^s U(w)dw$  with  $0 < \beta(0) < \tau$ . Using the initial condition (3)

$$x(0) = \varphi(E - \int_0^t U(w)dw) \tag{14}$$

$$x(t, \alpha, \tau) = \varphi(E - \int_0^t U(w)dw) \exp (-\int_0^t \gamma(w)dw)$$

If  $(t(0), \alpha(0), \beta(0)) \in R_2$ , then we have  $\beta(0) = 0$  and thus  $\beta(s) = \int_0^s U(w)dw$  and  $t(s) = t(0) + s$ . Hence using the BC (2)

$$\Rightarrow x(0) = \varphi(t - s) \tag{15}$$

$$\beta(s) = \int_0^s U(w)dw = \int_0^s U(t(0) + w)dw = \int_{t(0)}^{t(0)+s} U(\sigma)d\sigma \tag{16}$$

Let us define by T the time needed for the  $\beta$  variable to go from 0 to  $\tau$

$$\tau = \int_0^T U(w)dw = \int_{t-T}^t U(w)dw \tag{17}$$

$$x(t, \alpha, \tau) = \varphi(t - s) \exp(-\int_0^T \gamma(w)dw) \tag{18}$$

The method of characteristics the solution  $x(t, \alpha, \tau)$  is

$$x(t, \alpha, \tau) = \varphi(t - \int_0^t U(w)dw) \exp(-\int_0^t \gamma(w)dw) \text{ if } (t, \beta) \in R_1 = \psi(t - T) \exp(-\int_0^T \gamma(w)dw) \text{ if } (t, \beta) \in R_2 \quad (19)$$

$$x(t, \alpha, \tau) = \psi(t - T) \exp(-\int_0^T \gamma(w)dw)$$

Substituting in eqn. (5)

$$\frac{dx}{dt} = [V(t) + U(t)] [\psi(t) - \psi(t - T) \exp(-\int_0^T \gamma(w)dw)] - (t)X(t) \quad (20)$$

Eqn. (21) reduces to

$$\frac{dx}{dt} = [V(t) + U(t)] [\psi(t) - \psi(t - T) e^{-\gamma T}] - \gamma X(t), \quad (21)$$

( $\gamma$  is a constant)

In addition, if the erythrocyte population velocity is constant ( $U(t) = U$ ), we have that  $T$  satisfies

$$\tau = \int_{t-T}^t U dw = UT \quad (22)$$

$T = \tau / U$ , hence if  $\gamma$  and  $U$  are constant, we obtain the following DDEs with constant delay

$$\frac{dx}{dt} = [V(t) + U(t)] [\psi(t) - \psi(t - T) e^{-\gamma \tau / U}] - \gamma X(t), \quad (23)$$

**Periodic Aiha Modeling:**

Let  $p(t, \alpha, \beta)$  be the population of precursor cells at time  $t$ , age  $\alpha$  and rate of production  $\beta$ . let  $V(R)$  &  $U(R)$  be the velocities of rate of production & maturation, which may depend on the hormone (EPO) concentration. If  $N(R)$  is the number of cells recruited into the reproduce precursor population, and then the entry of new precursor cells into the structured model will satisfy the boundary condition,

$$(V(R)+U(R))p(t,\alpha,0)=N(R) \quad (24)$$

**Boundary Condition Rate Cells Exchange:**

$$(V(R) + U(R)) p(t, \alpha, \beta) = E m(t, \alpha, 0) \quad (25)$$

Let the birth rate for reproducing precursor cells be  $\beta$  and  $\alpha$  represent the death rate through apoptosis.

Let  $D(\mu - \bar{\mu})$  be the density of the distribution of maturity levels of the cells when released into the circulation blood,  $\bar{\mu}$  where represents the mean age of mature precursor cells.

$$\int_0^{\mu_1} D(\mu - \bar{\mu}) d\mu = 1 \ \& \ \int_0^{\mu_2} D(\mu - \bar{\mu}) d\mu = 1$$

The disappearance rate function is given by:

$$D(\mu) = \frac{D(\mu - \bar{\mu})}{\int_{\mu}^{\mu_1} D(x - \bar{\mu}) dx + \int_{\mu}^{\mu_2} D(x - \bar{\mu}) dx} \quad (26)$$

With these condition the age structured model for the population of precursor cells with  $t > 0$ ,  $0 < \mu < \mu_1$  and  $0 < \mu < \mu_2$  satisfies:

$$\frac{\delta P}{\delta t} + V \otimes \frac{\delta P}{\delta \mu_1} + U(R) \frac{\delta P}{\delta \mu_2} = (V(R) + U(R)) [\beta(\mu, R) p - \delta(\mu, R) p - D(\mu) p]. \tag{27}$$

Let  $m(t, \alpha, 0)$  be the population of mature non-reproducing cells at  $r$  and age  $\alpha$ . From the disappearance rate function, the boundary condition for cells entering the mature population is given by

$$E m(t, \alpha, 0) = V(R) \int_0^{\mu_1} D(\mu - \bar{\mu}) p(t, \mu) d\mu + U(R) \int_0^{\mu_2} D(\mu - \bar{\mu}) p(t, \mu) d\mu \tag{28}$$

where the maturity levels  $\mu_1$  and  $\mu_2$  represents the maximum age for a cell reaching maturity. We assumed that destruction of RBC occurs by active removal of the old cells. From a modeling point of view, this results in a moving boundary condition with the age of the oldest RBC,  $(t)$  varying in  $t$ . The boundary condition is then given by

$$(E - \frac{\delta \theta}{\delta t}) m(t, \theta) = F \tag{29}$$

where  $F$  is the fixed RBC removal rate. If  $\gamma(\theta)$  is the death rate of mature cells, then the partial differential equation describing  $m(t, \theta)$  is given by:

$$\frac{\delta m}{\delta t} + E \frac{\delta m}{\delta \theta} = -E \gamma(\theta) m, t > 0, \theta > 0, \tag{30}$$

The total population of mature cells function is given by:

$$\int_0^{\theta(t)} m(t, \theta) d\theta \tag{31}$$

The differential equation for  $R$  (red blood cells production) is thus:

$$\frac{dR}{dt} = \frac{\beta}{1 + KM^\gamma} - kR \tag{32}$$

Where  $k$  is the decay constant for the hormone and the rate of production  $\beta$  is given by a monotone decreasing Hill function. The given equation is linear in  $R$ .

$$\frac{dR}{dt} + kR = \frac{\beta}{1 + KM^\gamma} \tag{33}$$

IF (integrating factor)  $e^{\int k dt} = e^{kt}$

$$\begin{aligned} Re^{kt} &= \int \frac{\beta}{1 + KM^\gamma} e^{kt} dt + C \\ &= \frac{\beta}{(1 + KM^\gamma)K} e^{kt} + C \\ R &= \frac{\beta}{(1 + KM^\gamma)K} + C_1 \end{aligned} \tag{34}$$

where  $C_1$  is the integrating constant for the red blood cells production. This is modeled by using a monotone decreasing Hill function for the production rate  $\beta$ . They assumed constant maturing velocity and were then able to reduce their model to a threshold-type DDE with two constants delays (Honglian You, Rong Yuan, 2010; José, P.C. dos Santos, 2010; José M. Arrieta, 2010; Mackey, M., A. Rudnicki, 2008; Pue-on, P., 2010; Ruhollah Jahanipour, 2010; Zhenbin Fan, Gang Li, 2010).

**Results:**

This model is constructed using a monotone decreasing Hill function. Here we consider the parameters that are a function of red blood cells age and rate of production. These parameters describe a simplified production and our aim is to accelerate RBC spread. The moving boundary for these regions are determined

by investigating all possible combinations of initial conditions and then further analyzing the areas of interest with multiple works of the model. AIHA leads to an abnormally high destruction rate of the RBCs (erythrocytes). Symptomatic treatment can be given by blood transfusion, if there is marked anemia [Antibody attaching to RBCs (Direct or indirect Coombs test), May be associated with thrombocytopenia (Evan's syndrome), Idiopathic, drugs, infection, Treatment (treat underlying cause, steroids)]. In severe immune-related hemolytic anemia, steroid therapy is sometimes necessary. The RBCs population will be increased and so will be the oxygen carrying capacity of the blood. EPO (Erythropoietin) mediates a negative feed back such that a increase in the number of erythrocytes leads to an decrease in erythrocyte production. EPO production adjusts to the demand of oxygen in the body such that if there is a decrease in the oxygen levels in tissues, there will be an increase in EPO levels. This scenario provides the power of mathematical models as the novel epidemic simulation and visualization techniques. From figure 1, we can clearly see where the mean age of mature precursor cells and the total populations of mature cells are situated, as well as identify the place of RBC production. In such a situation the increase of rate of production  $\beta$  plays less and has the same effect on the spread of the AIHA disease (Ana Llea, 2010; Bélair, J., 2008; Murray, J.D., 2002).

#### **Discussion:**

We performed a linear stability analysis of this model and showed that a supercritical Hopf bifurcation occurs when the death rate of circulating RBC is increased above a certain critical value. This transition from Restrain to stable oscillation would characteristics the onset of periodic AIHA and account for the experimentally observed characteristics of AIHA. They developed an age-structured model that incorporates the fact that the population of precursor cell matures at differing rates depending on the EPO concentration, which itself varies according to the amount of oxygen carried in blood. Next, we present the equations of this extended age-structured model for hematopoiesis that includes apoptosis and active degradation of the oldest mature cells. Recent research suggests the replacement dose of iron, at least in the elderly with iron deficiency, may be as little as 15 mg per day of elemental iron. An experiment done in a group of 130 anemia patients showed a 98% increase in iron count when using an iron supplement with an average of 100 mg of iron. Women who develop iron deficiency anemia in mid-pregnancy can be effectively treated with low doses of iron (20–40 mg per day). The lower dose is effective and produces fewer gastrointestinal complaints. Iron deficiency protects against infection by creating an unfavorable environment for bacterial growth. Nevertheless, while iron deficiency might lessen infections by certain pathogenic diseases, it also leads to a reduction in resistance to other strains of viral or bacterial infections, such as *Salmonella typhimurium* or *Entamoeba histolytica*. The reader will, no doubt, also realize that each model has its positive and negative aspects. A mathematical analysis might then be hard to under-take and the conclusions may only be based on numerical experiments which many, including us, find less than satisfactory. On the other hand, a simple model may be easier to analyze and mathematical analysis can give more insights into the dynamical properties or the underlying system, but it may oversimplify and fail to capture some important features of the reality. So, as mathematical model construction is something of an art in itself the same can be said for parameter estimation (Catherine Foley, 2008; Mahaffy, J., 2008).

#### **Conclusion:**

We have discussed the origin of periodic AIHA by considering the age  $\alpha$  and rate of production  $\beta$  in age structured model with the hope of capturing the physiological reality of death rate in circulating blood cells. Due to this, RBC's are divided into two stages. In the age structured model, we can easily find out the RBC production. If RBC increases, there is no AIHA and if RBC decreases, they are infected by AIHA. We present the mathematical approaches that are useful for modeling in hematology. We discuss the normal aspects of the regulation and production of blood cells as well as the basic characteristic of some periodic hematological disorders. The origin of the disease is unclear. Moving boundary conditions are enabled to forecast the rate of production in AIHA. Symptoms for AIHA can easily be detected & treatment can be started at an early state.

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