THE DYNAMIC BEHAVIORS OF RBC, EPO AND OXYGEN WITH TIME DELAY

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Abstract

The process by which the red blood cells are developed is known as erythropoiesis. It is depicted that while the process involves many components, the ones are the erthrocytes themselves ant the erythropoietin hormone (EPO). The hemoglobin in the RBC absorbs the oxygen when it is flowing in the lung. The production and feedback loop in erythropoiesis consist of RBC coming from the bone marrow. A mathematical model for this process which connecting the of erythrocytes (or RBC), the EPO and The oxygen is proposed together with time delay. A bifurcation analysis is carried out to determine the ranges of parameter values that would lead to state productions of RBC. We have also shown the computer simulations of the behaviors.

Keywords: erythropoiesis, erythrocyte, bifurcation analysis, time delay

1. Introduction

The circulating tissue composed of fluid plasma and cells (red blood cells, white blood cells, platelets) is called blood. The process is called Hematopoiesis. Medical terms related to blood often begin in hemo- or hemato- (BE: haemo- and haemato-) from the Greek word for "blood". The process is called erythropoiesis while the blood cells are only red blood cells (RBC) or erythrocytes. Many components are involved in an erytropoiesis process; the erythrocytes themselves and the hormone erythropoietin (EPO) are the absolutely necessary ones. The main function of blood is to supply nutrients (oxygen, glucose) to tissues and to remove waste products (such as carbon dioxide and lactic acid). The oxygen uptaken by the hemoglobin present in the RBC also plays an important role in the regulation of the RBC production.

There are the productions and feedback loop consisting of erythrocytes which coming from the bone marrow as the result of the maturation of committed precursor stem cells into erythrocytes. The regulations of the production of the component factors in

erythropoiesis are through different feedback loops. There are several diseases such as the periodic hematopoietic diseases that are believed to arise because of abnormalities in the feedback mechanisms which regulate blood cell number [1,2,3,4]. Mathematical models have been used to learn the effects of variations in the maturation velocity and of moving boundary conditions on Hematopoiesis by [5,6].

In this paper, we wish to analyze the erythropoiesis mathematical model with considering the affect of a time delay. In section 2, our model is presented. We put the time delay into the model, and then perform Hopf bifurcation analysis; like Khan's process, and identify the suitability of our model parameters. An analysis can determine that they have the greatest effect on stability of the model in section 3. Finally, the simulation results are shown and we attempt to explain the critical day time where the erythrocyte productions go from being a steady state one to a non steady state one.

2. Mathematical Model

The rates of erythrocyte production and the hormone EPO are taken to be of the Michaelis-Menten form. The rate types are often used to describe the kinetics of pathways stimulated by growth factors [8]. For erythrocytes, the production should be small when the EPO amount present is small. When the EPO is large, the production should be large. The reverse holds for the control of EPO by the oxygen in the tissue. During periods of hypoxia, the release of EPO by the kidney should increase, while during periods of proper oxygen levels in the blood, the release of EPO should decrease. The amount of oxygen in the blood should be directly related to the number of erythrocytes in the blood unless the person is suffering from a disease that either prevents or enhances the release of the oxygen by the iron ion in the hemoglobin.

Therefore; our model for erythroposeisis is given by

$$\frac{dx}{dt} = \frac{\alpha y}{1+y} - \mu_1 x \ ; \tag{1}$$

$$\frac{dy}{dt} = \frac{kz}{1+kz} - m_2 y \ ; \tag{2}$$

and

$$\frac{dz}{dt} = gx - m_3 z \ . \tag{3}$$

where x(t) is the amount of erythrocytes or red blood cells; y(t), the amount of erythropoietin (EPO) for erythrocytes; z(t), the amount of O_2 ; The death or decay rate of each variable, $m_i, i = 1,2,3$. When the oxygen is absorbed by the tissue cells, it is removed from the blood stream. In the tissue, it is used to metabolize the nutrients to provide the needed energy for the cell to live. We denote the net birth-rate for the variables RBC, EPO, and O_2 as a , b and g , respectively.

The system described by equation (Eq. 1) to (Eq. 3) has two positive steady state $(0,0,0)$ and (x_s, y_s, z_s) where $z_s = (\gamma x_s)/\mu_3$, $y_s = k\gamma x_s/(\mu_2(k\gamma x_s + \mu_3))$, and $x_s = (k\alpha\gamma - \mu_1\mu_2\mu_3)/(k\gamma\mu_1(1+\mu_2))$. The non-vanishing steady state (x_s, y_s, z_s) interested. We applied for studying a time delay model, a linearization of the system at its steady state will produce an exponential polynomial equation.

3. Effect of Time Delay

3.1 The stability with time delay

There is a lag in the time the EPO acts on the pre-RBC and the fully developed erythrocyte emerge. The effects of a time delay on a mathematical model for erythropoiesis. To include the effects of time delay, we need to replace equation (Eq. 1) by

$$\frac{dx}{dt} = \frac{\alpha y(t-\tau)}{1+y(t-\tau)} - \mu_1 x \quad . \tag{4}$$

The jacobian matrix for equations (Eq. 4), (Eq. 2) and (Eq. 3) evaluated at the steady state point (x_s, y_s, z_s) is

$$\begin{bmatrix} -\mu_1 & (F(y_s)+y_sF'(y_s))e^{-\lambda\tau} & 0 \\ 0 & -\mu_2 & G(z_s)+z_sG'(z_s) \\ \gamma & 0 & -\mu_3 \end{bmatrix} \quad . \tag{5}$$

Diagonalizing the above matrix, we obtain the following characteristic equation

$$\lambda^3 + a\lambda^2 + b\lambda + c + de^{-\lambda\tau} = 0 \quad . \tag{6}$$

We now suppose that two of eigenvalues of equation (Eq. 6) are a pair of complex conjugates i.e., $\lambda(\tau) = \alpha(\tau) \pm i\omega(\tau)$. Substituting l_+ into equation (Eq. 6) and separating the real and imaginary parts, we get

$$a^2 - 3aw^2 + aa^2 - aw^2 + ba + c + e^{-at}(d\cos wt) = 0 \quad ; \tag{7}$$

$$3a^2w - w^3 + 2aaw + bw - e^{-at}(d\sin wt) = 0 \quad . \tag{8}$$

Three conditions must be meet at the critical value t_0 for a Hopf bifurcation occurring. (i) $a(t_0) = 0$, (ii) $w(t_0)^1\ 0$ and (iii) $a\phi(t_0) > 0$. To see, we first assume that the critical value defined by $\alpha(\tau_0) = 0$ exist, if the eigenvalues of the Jacobian evaluated at the steady state point (x_s, y_s, z_s) satisfy these conditions. However, we do not use this condition to find t_0. Setting $\alpha(\tau_0) = 0$ into (Eq. 7) and (Eq. 8) to have

$$-a\omega^2 + c + d\cos\omega\tau = 0 \quad ; \tag{9}$$

$$\omega^3 - b\omega + d\sin\omega\tau = 0 \quad . \tag{10}$$

Squaring the two equations and adding the squares together, we obtain

$$\omega^6 + \left(a^2 - 2b\right)\omega^4 + \left(b^2 - 2ac\right)\omega^2 + \left(c^2 - d^2\right) = 0 \quad . \tag{11}$$

Letting $s = \omega^2$, $p = a^2 - 2b$, $q = b^2 - 2ac$, and $r = c^2 - d^2$. Equation (Eq. 11) becomes the following cubic equation

$$Q(s) \equiv s^3 + ps^2 + qs + r = 0 \quad . \tag{12}$$

To find the roots of equation (Eq. 12), we introduce the following lemma 1.

Lemma 1. Condition for the existence of a cubic equation. For equation (Eq. 12)
1. If either (i) $p < 0, q \geq 0$ and $p > 3q$ or (ii) $q < 0$ and $D < 0$, then equation (Eq. 12) has positive simple roots,

where $$D = Q(e_1)(e_2) = \frac{4}{27}q^3 - \frac{1}{27}pq - \frac{2}{3}pqr + \frac{4}{27}p^3r + r^2 \tag{13}$$

with e_1 and e_2 being the two turning points of $Q(s)$ given by

$$e_1 = \left(-p - \sqrt{p^2 - 3q}\right)/3, e_2 = \left(-p + \sqrt{p^2 - 3q}\right)/3 \tag{14}$$

2. If $r \geq 0$ the necessary condition for equation (Eq. 12) to have no positive real roots are either (i) $p^2 < 3q$, (ii) $p^2 = 3q$, (iii) $p^2 - 3q > 0$ and $D > 0$, or (iv) $p^2 - 3q > 0$ and $D > 0, p > 0$ and $q > 0$.
Proof of this lemma is shown in Khan and Greenhalgh [9].

3.2 Critical time delay

We may denote the three positive roots of equation (Eq. 12) by $s_i, i = 1,2,3$. Then equation (Eq. 12) has three positive roots; $\omega_i = \sqrt{s_i}, i = 1,2,3$. Now, Let $\tau_0 > 0$ be the minimum value for all the values of τ which $\alpha(\tau_0) = 0$. The critical delay time can be found by substituting ω_i into equation (Eq. 10) and solving for t, we obtain

$$\tau_i^{(j)} = \left(\arcsin\left(-\left(\omega_i^3 - b\omega_i\right)/d\right) + 2(j-1)\pi\right)/\omega_i, i = 1,2,3, j = 0,1,2,... \tag{15}$$

Therefore,

$$\tau_0 = \tau_{i_0}^{(j_0)} = \min_{i=1,2,3,\, j\geq 1}\left\{\tau_i^{(j)}\right\} \quad ; \tag{16}$$

$$\omega_0 = \omega_{i_0}, \text{ and } s_0 = \omega_0^2 \quad . \tag{17}$$

4. Numerical Simulations and Conclusion

We use two methods to obtain some qualitative information about the stable solution of the system. The computer simulations for the case of $\tau = 0$ is done with a C-programming code based on the Runge Kutta order6 method. For the cases of $\tau \neq 0$, the MathLab routine for delay is used.

4.1 Estimated Parameter

The values of many of the parameters were given in Mackey-Glass [10]. From that and the other papers by Mackey, we set the dead rate for RBC (μ_1) to be closed to 1. Our bifurcation analysis requires that the dead rate of EPO must be at least a half of RBC dead rate. Since the presence of oxygen was not taken into account in the papers; Mackey and Glass 1966[10], Murray JD[11], Belair, Mackey and Mahaffy(1995)[6], and Mahaffy et al (1998,1999)[5,7]), we had to guess at the values of the parameters dealing with oxygen. In order for the for the Routh-Hurwitz condition to hold when we attempted to find the equilibrium concentration x_s , we established that the rate of removal of oxygen μ_3 had to be in the range $0 < \mu_3 < (k\alpha\gamma)/(\mu_1\mu_2)$. Setting k at various values, we determined that μ_3 should be more than 1.

4.2 Numerical Results

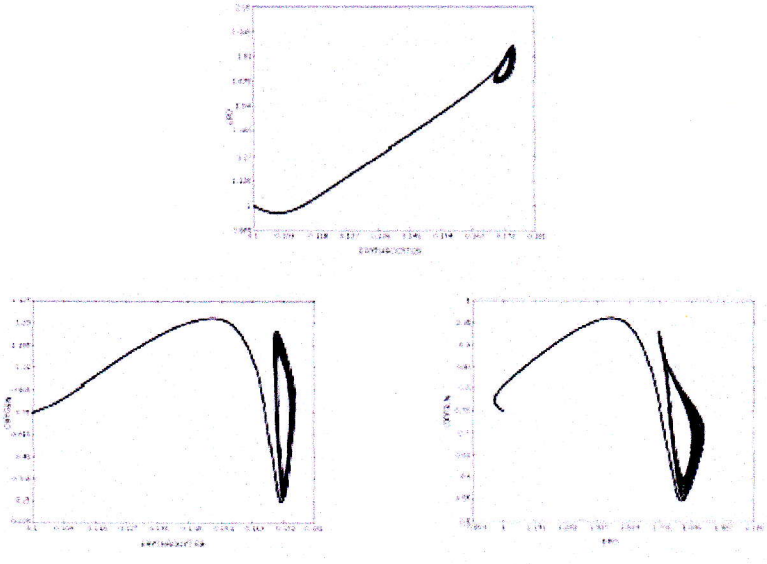
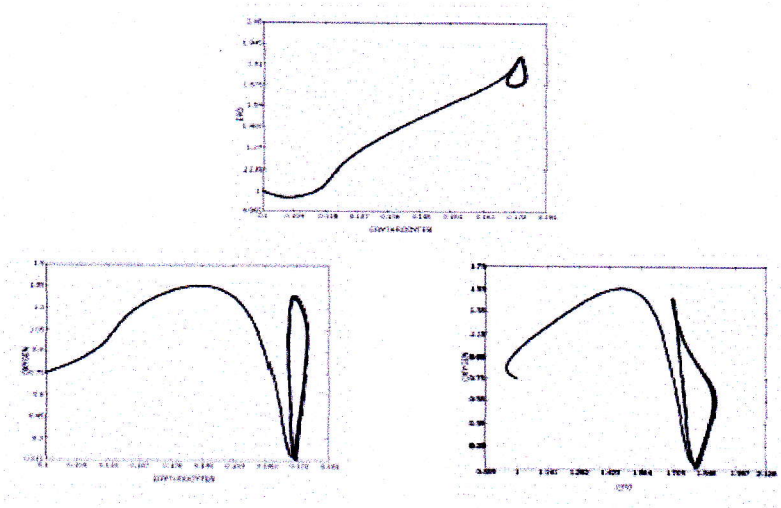
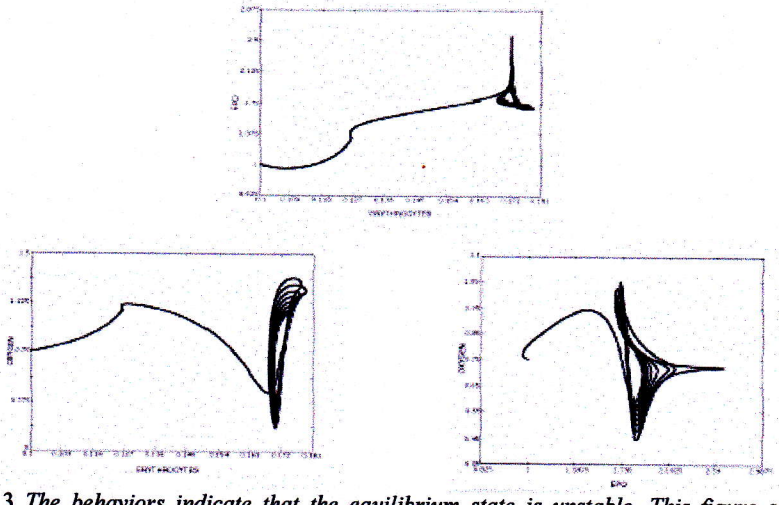


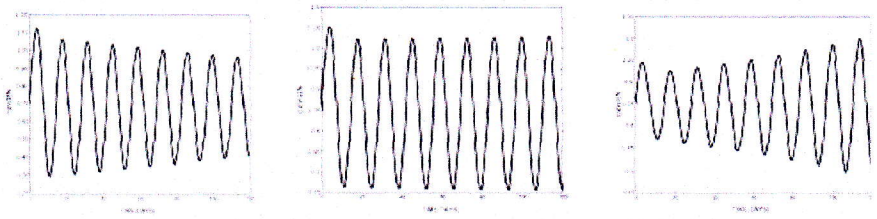
Fig. 1 *shows numerical solutions of the model. (Eq. 2-4) (*$t = 1.245 < t_0 = 6.85207$*) The parameters used are as follows:* $m_1 = 0.945, m_2 = 0.4725,\ a = 0.25, k = 6.7636,$ $m_3 = 1.32025,\ x_s = 0.1705, y_s = 1.81403, z_s = 0.88698$. *The trajectories show on 2D phase plane. The motion spirals toward the steady state.*



Fg. 2 *2D Plots of EPO and others. The numerical solutions are stable. The values of the parameters are the same as Fg. 1 except* $t = t_0 = 6.85207$. *The trajectory is a limit cycle.*



Fg. 3 *The behaviors indicate that the equilibrium state is unstable. This figure shows numerical solutions of the system model (Eq.2-4). The parameters are the same as Fg. 1 except* $t = 8 > t_0 = 6.85207$.



Fg.4 *Changing in the oxygen as time involves. The numerical solutions of the model (Eq.2-4) are the case* $t = 1.245, 6.85207, 8$ *respectively. The graphs depict that the trajectories are periodic oscillation, tending to the steady state and unstable, respectively.*

5. Conclusion

In this paper, we have proposed a mathematical model involving a set of nonlinear equations for the production and regulation of red blood cells. The model contains an effective delay in the effect of the hormone, EPO on the production of erythrocyctes by the stem cells in the bone marrow. The time delay is included to simulate the dynamics of the maturation steps needed to transform a precursor stem cell into a fully functional RBC. Included in our model is the role of oxygen in the production of the EPO by the liver/kidney. The amount of RBC in the blood stream does not directly determine the amount of EPO that is produced by the kidney/liver. The amount of EPO produced is related to the amount of oxygen absorbed by certain tissues in the kidney/liver. Since the oxygen is carried to the tissue by the hemoglobin in the RBC, the amount of EPO produced is indirectly related to the amount of RBC in the blood stream. The inclusion of the dynamics of the oxygen in our model for erythroproiesis completes the feedback loop required for the regulation of the erythrocytes production. The dynamics of the oxygen could be ignored is we put in another time delay into the equations. The amount of EPO produced at time t would depend on the amount of RBC at time $t-\tau_2$ (τ_2, being the time for the EPO producing tissue to produce additional EPO in response to the lack of oxygen). We find that there is an optimal turn-around time (Eq. 16) for all components in this complicated system.

Acknowledgements

The authors would like to thank Prof. Dr. Ahnond Bunyaratvej (Institute of Science and Technology for Research and Development, Mahidol University, Nakhon Pathom) for helpful taking some data in his laboratory.

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