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A Mathematical Model for Erythroid Regulation

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Abstract: - A mathematical model connecting the dynamics of the essential components in this process; the erythrocytes (RBC), the hormone erythropoietin (EPO) and the oxygen is proposed. A time delay is included to simulate the dynamics of the maturation steps. A bifurcation analysis is performed to determine the ranges of parameter values. The effects of the time delay are seen in the simulated production of the erythrocytes as the delay time is increased past the critical value.

Key-Words: - Erythropoiesis, Nonlinear autonomous equation, Delay, Hopf bifurcation, Critical delay time.

1 Introduction

Erythropoiesis is a three step process by which erythrocytes (red blood cells (RBC)) are developed. The main role of the RBC is to transport oxygen from the lungs to the tissues. The RBC's also have a role in regulating the process itself. The main regulator of the production of RBC is the hormone, erythropoietin (EPO). The regulator of the EPO is the lack of oxygen. The amount of oxygen reaching the kidney producing the EPO depends on the RBC in circulation. The production of RBC is controlled by a positive feedback loop involving the EPO. The production of the EPO is controlled by a negative feedback loop involving the oxygen. The role of oxygen in the control of erythropoiesis is only now being recognized.

In the first model of hematopoiesis, Mackey and Glass[1] used a single differential equation containing a time delay. Mackey *et al.*, [2-5] extended the mathematical description of erythropoiesis by introducing an additional equation to describe the dynamics of the EPO**.** They did not include a role for oxygen. In this paper, we wish to study the effects of a time delay on our mathematical model for erythropoiesis which includes an explicit role for oxygen in the physiological control of erythropoiesis.

2 Problem Formulation

We are interested in real systems which are best represented by a mathematical model consisting of three nonlinear autonomous first order differential equations having both a positive and negative feedback control. Such a system is the process of erythropoiesis. In erythropoiesis, the production of the RBC should be small when the amount of EPO present is low. When the amount of EPO is high, the production RBC should be high. The reverse holds for the control of EPO by the oxygen in the tissue. The production of EPO should be high under hypoxia conditions (lack of oxygen). The amount of oxygen in the blood should be directly related to the number of RBC in the blood.

Thus our model for erythropoiesis is described by the following equations

$$\frac{dx}{dt} = \frac{\alpha y}{1+\beta y} - \mu_1 x \qquad (1)$$

$$\frac{dy}{dt} = \frac{k}{1+kz} - \mu_2 y \qquad (2)$$

and $$\frac{dz}{dt} = \gamma x - \mu_3 z \qquad (3)$$

where $x(t)$ is the amount of RBC; $y(t)$, the amount of EPO; $z(t)$, the amount of O_2; $\mu_i, i = 1,2,3$, the removal rate of each variable by either death or clearance by the kidney/liver. We have denoted the net input rate for the variables RBC, EPO and O_2 as α, k and γ, respectively.

There is a lag between the time the EPO acts on the pre-RBC and the time that the fully developed RBC emerges. Eqn. (1) should be replaced by

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

The system described by eqns. (1) to (3) have two steady state (0,0,0) and (x_s, y_s, z_s). We consider

the case of the non washout steady state given by $x_s = \frac{k\alpha}{\mu_1(k\beta+\mu_2)}$, $y_s = \frac{k\mu_3}{\mu_2(\mu_3+k\gamma x_s)}$, $z_s = \frac{\gamma x_s}{\mu_3}$. To proceed further, we perform an bifurcation analysis. We let $X = x - x_s$, $Y = y - y_s$, and $Z = z - z_s$ to linearization in the system (1)-(3).

In studying a time delay model, linearization of the system at its steady state will produce either a transcendental characteristic equation or an exponential polynomial equation. It is well known that the steady state is stable if all the eigenvalues of the exponential polynomial equation have negative real part, and is unstable if at least one root has a positive real part [13-14]. Thus a Hopf bifurcation occurs when the real part of a certain eigenvalue changes from negative to zero and to positive (i.e. the steady state changes from stability to instability). This is usually caused by the time delay.

The characteristic equation for the above system is

$$L(\lambda) \equiv \lambda^3 + a\lambda^2 + b\lambda + c + de^{-\lambda\tau} = 0 \quad (5)$$

where

$$a = \mu_1 + \mu_2 + \mu_3 \quad (6)$$

$$b = \mu_1\mu_2 + (\mu_1 + \mu_2)\mu_3 \quad (7)$$

$$c = \mu_1\mu_3\mu_2 \quad (8)$$

and $$d = -\gamma F(y_s)G(z_s) \quad (9)$$

We first look at eqn. (5) when $\tau = 0$. We find by the Routh-Hurwitz condition [13] that all roots of eqn. (5) for $\tau = 0$ will have negative real parts when $a > 0$, $c + d > 0$ and $ab > c + d$. The steady state (x_s, y_s, z_s) will be asymptotically stable.

For $\tau \neq 0$, we write the eigenvalues as $\lambda(\tau) = \alpha(\tau) + i\omega(\tau)$, where α and ω are functions of τ. Since the Hopf bifurcation condition are satisfyied for $\tau < \tau_0$, we will have $\lambda = i\omega(\tau_0)$. Using the Lemma given in Khan and Greenhalgh [14], we can establish that the critical delay time τ_0 does indeed exist.

3 Problem Solution

3.1 Critical Delay

The critical delay time $\tau_0 > 0$ is the value for minimum all the values of τ for which $\alpha(\tau) = 0$. Letting τ_i be the value at which this occurs and set $\omega = \omega(\tau_i)$ to be the value of the imaginary part of the eigenvalue at this time, we

$$\tau_i^{(j)} = \frac{1}{\omega_i}\left[\arcsin\left(-\frac{\omega_i^3 - b\omega_i}{d}\right) + 2(j-1)\pi\right],$$

$$i = 1,2,3,\ j = 0,1,2,.. \quad (10)$$

and choose

$$\tau_0 = \tau_{i_0}^{(j_0)} = \min_{i=1,2,3,\ j\geq 1}\left\{\tau_i^{(j)}\right\} \quad (11)$$

3.2 Numerical Simulation

To determine the response of the production rate to EPO stimulation, we have carried out some experiments in the laboratory. We grew stem cells taken from normal humans. We then added small amounts of EPO to the growing stem cells and counted the number of erythrocytes being produced on the 7th, 10th, 12th, and 15th day. Since we used only two concentrations of the EPO (2μ/ml and 0.2 μ/ml) in our experimentation, we set α to be either 2μU/ml and 0.2 μU/ml in our computer simulations. We found that the production rate (expressed in percentage) of erythrocytes due to the EPO stimulation to be in the range 0.5-1.55% in normal humans. The details of these experiments will be published elsewhere.

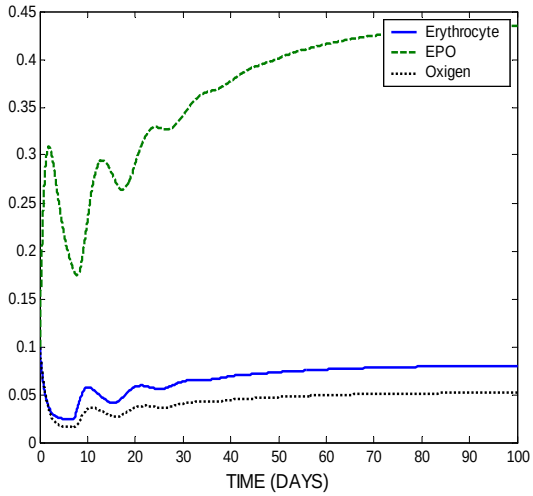
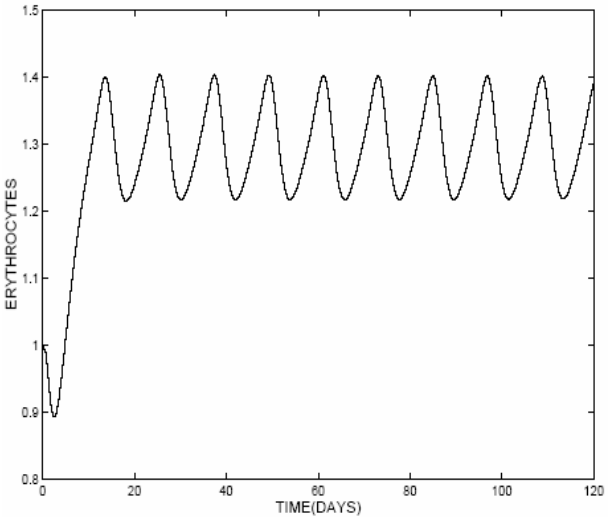


Figure 1. Time Behaviors of the Concentrations of RBC, EPO and O_2 Predicted by Eqns. (1) – (3)

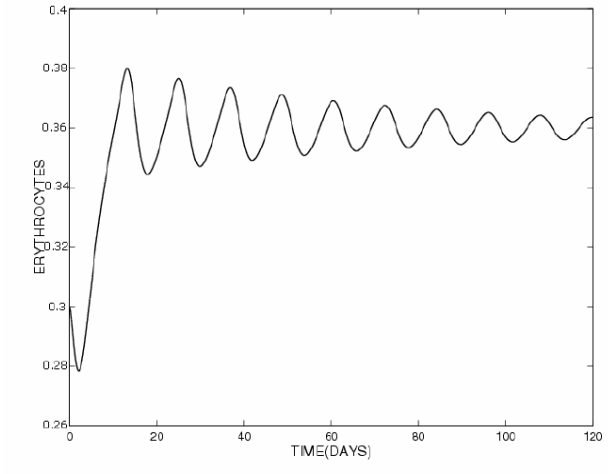
The time behaviors of the three variables seen in Figure 1 were obtain by solving eqns. (1) to (3) using the following values; $\alpha = 0.2$, $k = 5, \tau = 7$,

$x_0 = y_0 = z_0 = 0.1$, $\mu_1 = 0.945$, $\mu_2 = 0.472$, $\mu_3 = 0.158$, $y = 1.026$, $x_s = 0.0849$, $y_s = 0.0849$, $z_s = 0.0849$. As we see, the RBC's, EPO's and the O_2 exhibit a damped oscillation into the steady state.

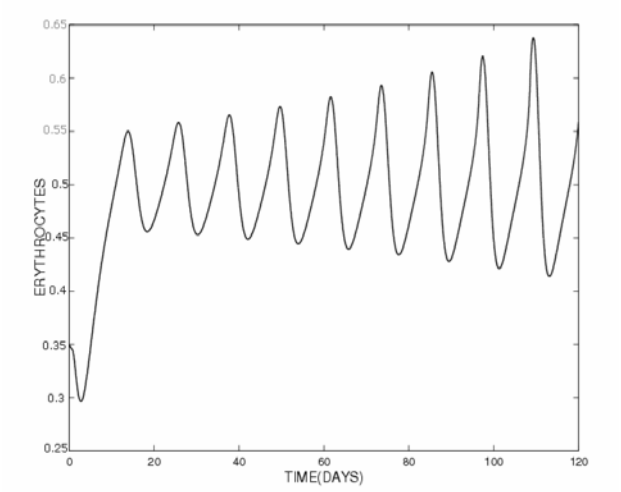
We now change the values of some of the parameters to $\alpha = 0.25$, $k = 3.033$, $\mu_1 = 1.1945$, $\mu_2 = 1.1945$, $\mu_3 = 0.115$ and $\gamma = 0.8667$. These values have no significance and were chosen so that by changing the delay time, we get the simulated responses which show the different behaviors. Using the values given, the critical delay time is 3.624 days. Setting $\tau = 3.624$ days, we obtain a sustained oscillation (See Figure 2a). Changing $\tau = 2.95$ days which is less than the critical delay time, we obtain an damped oscillation (See Figure 2b) The diverging oscillation seen in Figure 2c, occurs when $\tau = 4.125$ days. In other words, we are seeing the change in behaviors as the time delay τ increases for $\tau > \tau_0$, to $\tau = \tau_0$, and then to $\tau < \tau_0$.



(2a). τ = 3.624 days



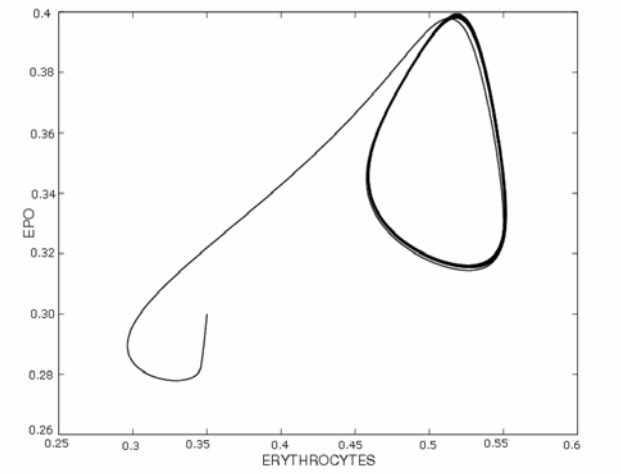
(2b). τ = 2.95 days



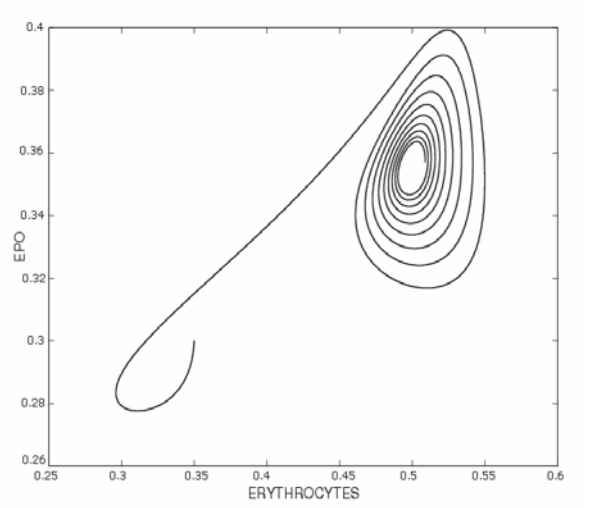
(2c). τ = 4.125 days

Figure 2. Time evolution of the erythrocytes number(x 10^{11}) for three values of the delay time τ.

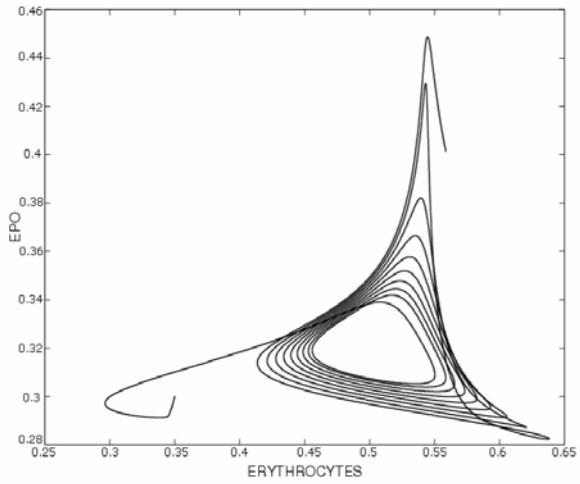
To better see the changes which arise when the tile delay is changed, we have plotted in Figure 3, the behaviors in the 2D RBC-EPO phase space. As is seen, the trajectory in Figure 3a, which is for $\tau = \tau_0$, begins from the left side of the frame and enters into a close orbit about the steady state. According to the Hopf bifurcation theory, the orbit is a limit cycle, meaning that the trajectory will always enter into the closed orbit no matter where the trajectory starts. Figure 3b shows the trajectory when the delay time is 2.95 days which is less than the critical delay time. As we see, the trajectory



(3a). τ = 3.624 days



(3b). τ = 2.95 days



(3c). τ = 4.125 days

Figure 3. Trajectory of the solution in the 2D Erythrocyte-EPO phase space for the three values of the delay time.

spirals into the steady state. Figure 3c shows the rajectory when the delay time is 4.125 days. Since the delay time is larger than the critical delay time, the trajectory is seen to spiral away from the steady state.

4 Conclusion

The reason for picking the delay time to be the bifurcation parameter is that several diseases such as the periodic hematological diseases are believed to be due to abnormalities in the feedback mechanisms which regulate the blood-cell number [2-7, 15-18]. In the absence of knowing how this is done in the bone marrow, we have introduce a time delay into the feedback loop in order to simulate the action of the unknown process taking placing in the bone marrow. Using the numerical values of the parameters listed in section 3, the critical time delay and the steady state (x_s, y_s, z_s) are calculated to be 3.624 days and for the system to undergo a Hopf bifurcation at the critical delay time.

In Figure 2, we see the time evolutions of the RBC in a typical human being for three time delays; 3.624 days (2a), 2.95 days (2b) and 4.125 days (2c). These time delays correspond to $\tau > \tau_0$, $\tau = \tau_0$ and $\tau < \tau_0$. Fig. (2a), the oscillation is a sustained one while in the bottom left frame, Fig. (2b), we see that the amount of RBC in the human is a damped oscillation. The sustained oscillations seen in Figure 1a, looks very much like the sustain oscillations in the circulating erythrocytes of a rabbit suffering from autoimmune haemolytic anema [19]. The oscillation in the figure is also similar to those seen in cases of cyclic thrombocytopenia which resulted from thrombopoietin deficiency [17, 18]. Of course, the mathematical models yielding the oscillations for the last two medical problems would be different. In (2c) frame, we see the amplitude of the oscillation growing in the stage of the oscillation.

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