Existence-Uniqueness and Monotone Approximation for an Erythropoiesis Age-Structured Model

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Abstract: We develop a monotone approximation to the solution of an age-structured model which describes the regulation of erythropoiesis, the process by which red blood cells are developed. The convergence of this approximation to the unique solution of the model is also established.

1. Introduction

Hematopoiesis is the process in which stem cells residing primarily in the bone marrow, spleen, and liver proliferate and differentiate into the major types of blood cells [3]. The major categories of cellular elements that make up 40% of the total blood volume are erythrocytes (red blood cells), leukocytes (white blood cells), and thrombocytes (platelets) [9]. Erythrocytes, whose primary function is to deliver oxygen to the tissues, are the largest component (by volume) of the hematopoietic system [9]. Erythropoiesis is the process in which red blood cells are developed, and the control of erythropoiesis is governed by the hormone erythropoietin. Erythropoietin is an acidic glycoprotein and a poor antigen that stimulates red blood cell production [7]. It is produced primarily in the kidneys, with 90% of

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erythropoietin being secreted by renal tubular epithelial cells when blood is unable to deliver oxygen [9]. Thus, erythropoietin acts by controlling the rate of differentiation of bone marrow cells and is released in the bloodstream based on a negative feedback mechanism that detects partial pressures of oxygen in the blood. It has a relatively short half-life, creating a rapid response to the changing conditions in the body [3, 16].

With its many stages of development and due to the fact that cells in differing stages have different properties, erythropoiesis process lends itself naturally to age-structured modeling. In particular, we consider in this paper the following age-structured model which describes the regulation of erythropoiesis:

$$
\begin{aligned}
&\frac{\partial p(t,\mu)}{\partial t}+\frac{\partial p(t,\mu)}{\partial \mu}=\sigma(t,\mu)p(t,\mu), && 0<t<T, \quad 0<\mu<\mu_F,\\
&\frac{\partial m(t,\nu)}{\partial t}+\frac{\partial m(t,\nu)}{\partial \nu}=-\gamma(t,\nu,\varphi_m(t))m(t,\nu), && 0<t<T, \quad 0<\nu<\nu_F,\\
&\frac{dE(t)}{dt}+k_E(t)E(t)=f(t,\varphi_m(t)), && 0<t<T,\\
&p(t,0)=s_0(t)E(t), && 0<t<T,\\
&m(t,0)=p(t,\mu_F), && 0<t<T,\\
&p(0,\mu)=p_0(\mu), && 0\le\mu\le\mu_F,\\
&m(0,\nu)=m_0(\nu), && 0\le\nu\le\nu_F,\\
&E(0)=E_0,
\end{aligned}
\tag{1.1}
$$

where $\mu_F < \nu_F$ and $\varphi_m(t) = \int_0^{\nu_F} m(t,\nu)d\nu$. We remark that the above model is a generalization of the age-structured model which was developed and studied in [3, 4, 11, 12, 13].

The model (1.1) has two major classifications of cells: precursor cells $p(t,\mu)$ and mature cells $m(t,\nu)$. The precursor cells are structured by their maturity level μ, relative to their hemoglobin content. Hemoglobin is the principal constituent of mature erythrocytes; it binds with oxygen in the lungs and releases the oxygen in the tissues [9]. The function $\sigma(t,\mu)$ represents the net change in the birth and death rate of precursor cell. The mature red blood cells are structured by age ν; these are the red blood cells circulating in the blood stream. The total number of mature cells is given by $\varphi_m(t)$. In reality, the death rate of mature red blood cells depends not only on maturity of these cells, but also on the total number of such cells present in the bloodstream. In particular, this rate should increase when more red blood cells are present and decrease when less red blood cells are present. Hence, it is assumed that this rate is a function of time, maturity and total number of mature red blood cells given by $\gamma(t, \nu, \varphi_m(t))$ with γ being a nondecreasing function of φ_m (see Section 2).

The concentration of the hormone erythropoietin is given by $E(t)$. The decay rate of erythropoietin is represented by $k_E(t)$, and $f(t, \varphi_m(t))$ is the feedback function that controls the release of the hormone erythropoietin. The feedback regulator also depends on the total number of mature cells in the bloodstream. This function influences the release of erythropoietin, which increases the production of red blood cells when there are too few red blood cells in the body; while if there is not enough oxygen being carried to the tissues, the amount of erythropoietin released increases. If there are too few cells, the amount of erythropoietin released decreases and red blood cell maturation is slowed.

The number of stem cells recruited into the precursor population is proportional to the concentration of erythropoietin in the system; $s_0(t)$ is the time-dependent constant of proportionality. The number of precursor cells at the greatest maturity level is equal to the number of mature cells at the smallest age level. These assumptions are taken into account in the boundary conditions of the model. The largest maturity level is denoted by μ_F while the largest age level is represented by ν_F.

In this paper, we prove existence-uniqueness of solutions to this model. Our arguments here are in the spirit of those used in [1, 2] for the classical size-structured population model. Such arguments are based on a novel definition of upper and lower solutions, the establishment of a comparison principle, and the construction of a monotone approximation. In fact, it is the first time that this monotone approach is applied to an age-structured model which describes the regulation of erythropoiesis. Previous approaches used in [5] relied on the fact that σ, γ, and k_E were constants and $f(t, \varphi_m(t))$ was assumed to be of a particular form, a Hill function. The method of characteristics was then employed to find a solution to each of the partial differential equations. For the precursor cell equation, this was relatively straightforward and used standard arguments. But, for the mature cell equation, the solution's dependency on the initial conditions and boundary conditions was complicated by the fact that the mature cells' boundary is dependent upon the precursor cells, and thus the differential equation for the mature cells had to be examined in four separate time domains. Using this approach allowed the mature cell equation to be rewritten as a delay differential equation; this equation was coupled with the erythropoietin ordinary differential equation. Standard results showed a unique solution to the delay system existed in each time domain. The method of steps coupled with simple induction arguments yielded existence and uniqueness for all time. Although this approach proved a unique solution existed for the model, the assumptions were strong and cannot be applied to the general formulation of the model presented here.

The paper is organized as follows. In Section 2 we give the definition of upper and lower solutions and establish a comparison principle. In Section 3 we develop a monotone sequence and prove its convergence to the unique solution of (1.1). Finally, in Section 4 we give some concluding remarks.

2. Comparison principle and uniqueness result

Throughout the discussion we assume that the parameters in (1.1) are measurable functions and satisfy the following assumptions: There exists a positive constant M such that

(A1) $|\sigma| \leq M,\ 0 \leq k_E, s_0 \leq M,\ 0 \leq p_0, m_0 \leq M.$

(A2) $0 \leq \gamma \leq M$ with $\gamma_\varphi \geq 0$.

(A3) $0 \leq f \leq M$ with $f_\varphi \leq 0$.

(A4) E_0 is a positive constant.

We begin by defining the mild solution of problem (1.1) as follows:

$$p(t,\mu) = p_0(\mu - t)\exp\left(\int_0^t \sigma(\tau, \mu - t + \tau)d\tau\right) \qquad \text{if } t \le \mu, \tag{2.1a}$$

$$p(t,\mu) = s_0(t-\mu)E(t-\mu)\exp\left(\int_{t-\mu}^t \sigma(\tau, \mu - t + \tau)d\tau\right) \qquad \text{if } t > \mu, \tag{2.1b}$$

$$m(t,\nu) = m_0(\nu - t)\exp\left(-\int_0^t \gamma(\tau, \nu - t + \tau, \varphi_m(\tau))d\tau\right) \qquad \text{if } t \le \nu, \tag{2.2a}$$

$$m(t,\nu) = p(t-\nu, \mu_F)\exp\left(-\int_{t-\nu}^t \gamma(\tau, \nu - t + \tau, \varphi_m(\tau))d\tau\right) \qquad \text{if } t > \nu, \tag{2.2b}$$

$$E(t) = \exp\left(-\int_0^t k_E(\tau)d\tau\right)\left(E_0 + \int_0^t f(\tau, \varphi_m(\tau))\exp\left(\int_0^\tau k_E(s)ds\right)d\tau\right). \tag{2.3}$$

We then introduce the following definition of a pair of coupled upper and lower solutions of problem (1.1).

Definition 2.1. *A pair of measurable functions $(\overline{p}(t,\mu), \overline{m}(t,\nu), \overline{E}(t))$ and $(\underline{p}(t,\mu), \underline{m}(t,\nu), \underline{E}(t))$ are called a nonnegative upper solution and a nonnegative lower solution of (1.1), respectively, if the following statements hold:*

(i) $0 \le \overline{p}, \underline{p} \le M,\ 0 \le \overline{m}, \underline{m} \le M,\ 0 \le \overline{E}, \underline{E} \le M.$

(ii) $$\overline{p}(t,\mu) \ge p_0(\mu - t)\exp\left(\int_0^t \sigma(\tau, \mu - t + \tau)d\tau\right) \qquad \text{if } t \le \mu, \tag{2.4a}$$

$$\overline{p}(t,\mu) \ge s_0(t-\mu)\overline{E}(t-\mu)\exp\left(\int_{t-\mu}^t \sigma(\tau, \mu - t + \tau)d\tau\right) \qquad \text{if } t > \mu. \tag{2.4b}$$

(iii) $\overline{m}(0,\nu) \ge m_0(\nu) \ge \underline{m}(0,\nu)$ *a.e. in* $(0,\nu_F)$. *For every* $t \in (0,T)$ *and every nonnegative* $\zeta \in C^1[0,T] \times [0,\nu_F]$,

$$\begin{aligned} &\int_0^{\nu_F} \overline{m}(t,\nu)\zeta(t,\nu)d\nu \\ &\quad \ge \int_0^{\nu_F} \overline{m}(0,\nu)\zeta(0,\nu)d\nu - \int_0^t \overline{m}(\tau,\nu_F)\zeta(\tau,\nu_F)d\tau + \int_0^t \overline{p}(\tau,\mu_F)\zeta(\tau,0)d\tau \\ &\quad + \int_0^t\int_0^{\nu_F} [\zeta_\tau(\tau,\nu) + \zeta_\nu(\tau,\nu)]\overline{m}(\tau,\nu)d\nu d\tau \\ &\quad - \int_0^t\int_0^{\nu_F} \gamma(\tau,\nu,\varphi_{\underline{m}}(\tau))\overline{m}(\tau,\nu)\zeta(\tau,\nu)d\nu d\tau. \end{aligned} \tag{2.5}$$

(iv) $$\overline{E}(t) \ge \exp\left(-\int_0^t k_E(\tau)d\tau\right)\left(E_0 + \int_0^t f(\tau, \varphi_{\underline{m}}(\tau))\exp\left(\int_0^\tau k_E(s)ds\right)d\tau\right). \tag{2.6}$$

$(\underline{p}, \underline{m}, \underline{E})$ *satisfies (2.4)-(2.6), respectively, with "* $\geq$ *" replaced by "* $\leq$ *" and* $\varphi_{\underline{m}}$ *by* $\varphi_{\overline{m}}$ *in (2.5), (2.6).*

Based on such a definition, we can establish the following comparison result.

Theorem 2.2. *Suppose that (A1)-(A4) hold. Let* $(\overline{p}, \overline{m}, \overline{E})$ *and* $(\underline{p}, \underline{m}, \underline{E})$ *be a nonnegative upper solution and a nonnegative lower solution of (1.1), respectively. Then* $\overline{p} \geq \underline{p}$ *a.e. in* $(0, T_0) \times (0, \mu_F)$, $\overline{m} \geq \underline{m}$ *a.e. in* $(0, T_0) \times (0, \nu_F)$, *and* $\overline{E} \geq \underline{E}$ *a.e. in* $(0, T_0)$, *where* $T_0 = \min\{T, \mu_F\}$.

Proof. Let $\widetilde{p} = \underline{p} - \overline{p}$, $\widetilde{m} = \underline{m} - \overline{m}$, and $\widetilde{E} = \underline{E} - \overline{E}$. In view of (2.4), $\widetilde{p}(t, \mu) \leq 0$ for $t \leq \mu$. In particular, $\widetilde{p}(t, \mu_F) \leq 0$. Furthermore, $\widetilde{m}$ satisfies

$$\widetilde{m}(0, \nu) = \underline{m}(0, \nu) - \overline{m}(0, \nu) \leq 0 \quad \text{a.e. in } (0, \nu_F) \tag{2.7}$$

and

$$\begin{aligned} &\int_0^{\nu_F} \widetilde{m}(t, \nu)\zeta(t, \nu)d\nu \\ &\quad \leq \int_0^{\nu_F} \widetilde{m}(0, \nu)\zeta(0, \nu)d\nu - \int_0^t \widetilde{m}(\tau, \nu_F)\zeta(\tau, \nu_F)d\tau + \int_0^t \widetilde{p}(\tau, \mu_F)\zeta(\tau, 0)d\tau \\ &\qquad + \int_0^t \int_0^{\nu_F} [\zeta_\tau(\tau, \nu) + \zeta_\nu(\tau, \nu)]\widetilde{m}(\tau, \nu)d\nu d\tau \\ &\qquad - \int_0^t \int_0^{\nu_F} \gamma(\tau, \nu, \varphi_{\overline{m}}(\tau))\widetilde{m}(\tau, \nu)\zeta(\tau, \nu)d\nu d\tau \\ &\qquad + \int_0^t \int_0^{\nu_F} \zeta(\tau, \nu)A_1(\tau, \nu) \int_0^{\nu_F} \widetilde{m}(\tau, \xi)d\xi d\nu d\tau, \end{aligned} \tag{2.8}$$

where $A_1(t, \nu) = \overline{m}(t, \nu)\gamma_\varphi(t, \nu, \theta_1(t))$ with $\theta_1(t)$ between $\varphi_{\overline{m}}(t)$ and $\varphi_{\underline{m}}(t)$.

Choose $\chi \in C_0^\infty(0, \nu_F)$ with $0 \leq \chi \leq 1$ and let $\zeta(\tau, \nu) = e^{M\tau}\chi(t - \tau + \nu)$. Since $\widetilde{m}(0, \nu) \leq 0$, $\widetilde{p}(\tau, \mu_F) \leq 0$, $\chi(t - \tau + \nu_F) = 0$, and $\chi_\tau + \chi_\nu = 0$, we find

$$\begin{aligned} &e^{Mt} \int_0^{\nu_F} \widetilde{m}(t, \nu)\chi(\nu)d\nu \\ &\quad \leq \int_0^t \int_0^{\nu_F} e^{M\tau}[M - \gamma(\tau, \nu, \varphi_{\overline{m}}(\tau))]\widetilde{m}(\tau, \nu)\chi(t - \tau + \nu)d\nu d\tau \\ &\qquad + \int_0^t \int_0^{\nu_F} e^{M\tau}\chi(t - \tau + \nu)A_1(\tau, \nu) \int_0^{\nu_F} \widetilde{m}(\tau, \xi)d\xi d\nu d\tau. \end{aligned} \tag{2.9}$$

Therefore, we have

$$\int_0^{\nu_F} \widetilde{m}(t, \nu)\chi(\nu)d\nu \leq c_1 \int_0^t \int_0^{\nu_F} \widetilde{m}(\tau, \nu)^+ d\nu d\tau, \tag{2.10}$$

where $c_1 = \sup_{[0,T_0]\times[0,\nu_F]} \left[M - \gamma(t,\nu,\varphi_{\overline{m}}(t)) + \int_0^{\nu_F} A_1(t,\nu)d\nu \right]$, and $\widetilde{m}(t,x)^+ = \max\{\widetilde{m}(t,x), 0\}$.

Since this inequality holds for every χ, we can choose a sequence $\{\chi_n\}$ on $(0,\nu_F)$ converging to

$$\chi = \begin{cases} 1 & \text{if } \widetilde{m}(t,\nu) > 0, \\ 0 & \text{otherwise.} \end{cases}$$

Consequently, we find

$$\int_0^{\nu_F} \widetilde{m}(t,\nu)^+ d\nu \le c_1 \int_0^t \int_0^{\nu_F} \widetilde{m}(\tau,\nu)^+ d\nu d\tau,$$

which by Gronwall's inequality leads to

$$\int_0^{\nu_F} \widetilde{m}(t,\nu)^+ d\nu = 0,$$

i.e., $\widetilde{m}(t,\nu) \le 0$. Then it follows from (2.6) that

$$\begin{aligned} \widetilde{E}(t) &\le \exp\left(-\int_0^t k_E(\tau)d\tau\right) \int_0^t [f(\tau,\varphi_{\underline{m}}(\tau)) - f(\tau,\varphi_{\overline{m}}(\tau))] \exp\left(\int_0^\tau k_E(s)ds\right) d\tau \\ &= \exp\left(-\int_0^t k_E(\tau)d\tau\right) \int_0^t B(\tau) \int_0^{\nu_F} \widetilde{m}(\tau,\nu)d\nu \exp\left(\int_0^\tau k_E(s)ds\right) d\tau \\ &\le 0, \end{aligned} \tag{2.11}$$

where $B(t) = -f_\varphi(\theta_2(t))$ with $\theta_2(t)$ between $\varphi_{\overline{m}}(t)$ and $\varphi_{\underline{m}}(t)$. The above inequality, combined with (2.4b) then yields that $\widetilde{p}(t,\mu) \le 0$ for $t > \mu$. This completes the proof.

Based on the definition (2.1)-(2.3), we can also establish the following uniqueness result.

Theorem 2.3. *Let $(p(t,\mu), m(t,\nu), E(t))$ be a nonnegative solution of problem (1.1) for $0 \le t \le T_0$. Then (p,m,E) is unique.*

Proof. Suppose that $(p_1(t,\mu), m_1(t,\nu), E_1(t))$ and $(p_2(t,\mu), m_2(t,\nu), E_2(t))$ are two nonnegative solutions of (1.1). Clearly, $p_1(t,\mu) = p_2(t,\mu)$ for $t \le \mu$. By (2.2a) we have

$$m_1(t,\nu) - m_2(t,\nu) = m_0(\nu - t)\exp(-\theta_3(t,\nu)) \int_0^t A_2(\tau,\nu) \int_0^{\nu_F} [m_1(\tau,\xi) - m_2(\tau,\xi)]d\xi d\tau,$$

where $\theta_3(t,\nu)$ is between $\int_0^t \gamma(\tau,\nu - t + \tau,\varphi_{m_1}(\tau))d\tau$ and $\int_0^t \gamma(\tau,\nu - t + \tau,\varphi_{m_2}(\tau))d\tau$ and $A_2(\tau,\nu) = \gamma_\varphi(\tau,\nu - t + \tau,\theta_4(\tau))$ with $\theta_4(\tau)$ between $\varphi_{m_1}(\tau)$ and $\varphi_{m_2}(\tau)$. Thus, for $t \le \nu$

$$|m_1(t,\nu) - m_2(t,\nu)| \le c_2 \int_0^t \int_0^{\nu_F} |m_1(\tau,\xi) - m_2(\tau,\xi)|d\xi d\tau. \tag{2.12}$$

On the other hand, since $p_1(t-\nu,\mu_F)=p_2(t-\nu,\mu_F)$, by (2.2b) we have

$$m_1(t,\nu)-m_2(t,\nu)=p_1(t-\nu,\mu_F)\exp(-\theta_5(t,\nu))\int_{t-\nu}^{t}A_3(\tau,\nu)\int_0^{\nu_F}[m_1(\tau,\xi)-m_2(\tau,\xi)]d\xi d\tau,$$

where $\theta_5(t,\nu)$ is between $\int_{t-\nu}^{t}\gamma(\tau,\nu-t+\tau,\varphi_{m_1}(\tau))d\tau$ and $\int_{t-\nu}^{t}\gamma(\tau,\nu-t+\tau,\varphi_{m_2}(\tau))d\tau$ and $A_3(\tau,\nu)=\gamma_\varphi(\tau,\nu-t+\tau,\theta_6(\tau))$ with $\theta_6(\tau)$ between $\varphi_{m_1}(\tau)$ and $\varphi_{m_2}(\tau)$. Thus, for $t>\nu$

$$\begin{aligned}|m_1(t,\nu)-m_2(t,\nu)|&\le c_3\int_{t-\nu}^{t}\int_0^{\nu_F}|m_1(\tau,\xi)-m_2(\tau,\xi)|d\xi d\tau\\&\le c_3\int_0^{t}\int_0^{\nu_F}|m_1(\tau,\xi)-m_2(\tau,\xi)|d\xi d\tau.\end{aligned}\tag{2.13}$$

A combination of (2.12) and (2.13) then yields that for any $(t,\nu)\in[0,T_0]\times[0,\nu_F]$

$$|m_1(t,\nu)-m_2(t,\nu)|\le c_4\int_0^{t}\int_0^{\nu_F}|m_1(\tau,\nu)-m_2(\tau,\nu)|d\nu d\tau.\tag{2.14}$$

Integration of (2.14) over $(0,\nu_F)$ gives

$$\int_0^{\nu_F}|m_1(t,\nu)-m_2(t,\nu)|d\nu\le c_4\nu_F\int_0^{t}\int_0^{\nu_F}|m_1(\tau,\nu)-m_2(\tau,\nu)|d\nu d\tau,$$

which by Gronwall's inequality implies

$$\int_0^{\nu_F}|m_1(t,\nu)-m_2(t,\nu)|d\nu=0.$$

Thus, by (2.14) we have $m_1(t,\nu)=m_2(t,\nu)$ for $(t,\nu)\in[0,T_0]\times[0,\nu_F]$. Consequently, taking note of (2.3), $E_1(t)=E_2(t)$ for $0\le t\le T_0$, which, together with (2.1b) then shows that $p_1(t,\mu)=p_2(t,\mu)$ for $\mu<t\le T_0$.

3. Monotone sequences and existence of solutions

We begin with the introduction of a pair of nonnegative lower and upper solutions of problem (1.1). Let $\underline{p}^0(t,\mu)=0$, $\underline{m}^0(t,\nu)=0$, and $\underline{E}^0(t)=0$. We then introduce that for $0\le t\le T_0$ $(\equiv\mu_F)$,

$$\overline{p}^0(t,\mu)=p_0(\mu-t)\exp\left(\int_0^{t}\sigma(\tau,\mu-t+\tau)d\tau\right)\qquad\text{if } t\le\mu,\tag{3.1a}$$

$$\overline{p}^0(t,\mu)=s_0(t-\mu)\overline{E}^0(t-\mu)\exp\left(\int_{t-\mu}^{t}\sigma(\tau,\mu-t+\tau)d\tau\right)\qquad\text{if } t>\mu,\tag{3.1b}$$

$$\overline{m}^0(t,\nu) \equiv \max\{\sup_{[0,\nu_F]} m_0(\nu), \sup_{[0,T_0]} \overline{p}^0(t,\mu_F)\}, \tag{3.2}$$

$$\overline{E}^0(t) = \exp\left(-\int_0^t k_E(\tau)d\tau\right)\left(E_0 + \int_0^t f(\tau,0)\exp\left(\int_0^\tau k_E(s)ds\right)d\tau\right). \tag{3.3}$$

The above representations are uncoupled, since $\overline{m}^0(t,\nu)$ is constructed from $\overline{p}^0(t,\mu_F)$ in (3.1a) and $\overline{p}^0(t,\mu)$ in (3.1b) is obtained from $\overline{E}^0(t)$. It can be easily shown that $(\underline{p}^0, \underline{m}^0, \underline{E}^0)$ and $(\overline{p}^0, \overline{m}^0, \overline{E}^0)$ are a pair of coupled lower and upper solutions of (1.1) for $0 \le t \le T_0$.

We then define two sequences $\{\underline{p}^k, \underline{m}^k, \underline{E}^k\}_{k=0}^\infty$ and $\{\overline{p}^k, \overline{m}^k, \overline{E}^k\}_{k=0}^\infty$ as follows: For $k = 1, 2, \cdots$

$$\begin{aligned}
&\frac{\partial \underline{p}^k(t,\mu)}{\partial t} + \frac{\partial \underline{p}^k(t,\mu)}{\partial \mu} = \sigma(t,\mu)\underline{p}^k(t,\mu), && 0<t<T, \quad 0<\mu<\mu_F,\\
&\frac{\partial \underline{m}^k(t,\nu)}{\partial t} + \frac{\partial \underline{m}^k(t,\nu)}{\partial \nu} = -\gamma(t,\nu,\varphi_{\overline{m}^{k-1}}(t))\underline{m}^k(t,\nu), && 0<t<T, \quad 0<\nu<\nu_F,\\
&\frac{d\underline{E}^k(t)}{dt} + k_E(t)\underline{E}^k(t) = f(t,\varphi_{\overline{m}^k}(t)), && 0<t<T,\\
&\underline{p}^k(t,0) = s_0(t)\underline{E}^k(t), && 0<t<T,\\
&\underline{m}^k(t,0) = \underline{p}^k(t,\mu_F), && 0<t<T,\\
&\underline{p}^k(0,\mu) = p_0(\mu), && 0\le\mu\le\mu_F,\\
&\underline{m}^k(0,\nu) = m_0(\nu), && 0\le\nu\le\nu_F,\\
&\underline{E}^k(0) = E_0
\end{aligned} \tag{3.4}$$

and

$$\begin{aligned}
&\frac{\partial \overline{p}^k(t,\mu)}{\partial t} + \frac{\partial \overline{p}^k(t,\mu)}{\partial \mu} = \sigma(t,\mu)\overline{p}^k(t,\mu), && 0<t<T, \quad 0<\mu<\mu_F,\\
&\frac{\partial \overline{m}^k(t,\nu)}{\partial t} + \frac{\partial \overline{m}^k(t,\nu)}{\partial \nu} = -\gamma(t,\nu,\varphi_{\underline{m}^{k-1}}(t))\overline{m}^k(t,\nu), && 0<t<T, \quad 0<\nu<\nu_F,\\
&\frac{d\overline{E}^k(t)}{dt} + k_E(t)\overline{E}^k(t) = f(t,\varphi_{\underline{m}^k}(t)), && 0<t<T,\\
&\overline{p}^k(t,0) = s_0(t)\overline{E}^k(t), && 0<t<T,\\
&\overline{m}^k(t,0) = \overline{p}^k(t,\mu_F), && 0<t<T,\\
&\overline{p}^k(0,\mu) = p_0(\mu), && 0\le\mu\le\mu_F,\\
&\overline{m}^k(0,\nu) = m_0(\nu), && 0\le\nu\le\nu_F,\\
&\overline{E}^k(0) = E_0.
\end{aligned} \tag{3.5}$$

Using the method of characteristics [6, 14], solutions to the above problems can be found explicitly as follows:

$$\underline{p}^k(t,\mu) = p_0(\mu - t)\exp\left(\int_0^t \sigma(\tau,\mu - t + \tau)d\tau\right) \qquad \text{if } t \le \mu, \quad (3.6a)$$

$$\underline{p}^k(t,\mu) = s_0(t-\mu)\underline{E}^k(t-\mu)\exp\left(\int_{t-\mu}^t \sigma(\tau,\mu - t + \tau)d\tau\right) \qquad \text{if } t > \mu, \quad (3.6b)$$

$$\underline{m}^k(t,\nu) = m_0(\nu - t)\exp\left(-\int_0^t \gamma(\tau,\nu - t + \tau,\varphi_{\overline{m}^{k-1}}(\tau))d\tau\right) \qquad \text{if } t \le \nu, \quad (3.7a)$$

$$\underline{m}^k(t,\nu) = \underline{p}^k(t-\nu,\mu_F)\exp\left(-\int_{t-\nu}^t \gamma(\tau,\nu - t + \tau,\varphi_{\overline{m}^{k-1}}(\tau))d\tau\right) \qquad \text{if } t > \nu, \quad (3.7b)$$

$$\underline{E}^k(t) = \exp\left(-\int_0^t k_E(\tau)d\tau\right)\left(E_0 + \int_0^t f(\tau,\varphi_{\overline{m}^k}(\tau))\exp\left(\int_0^\tau k_E(s)ds\right)d\tau\right). \quad (3.8)$$

A representation similar to (3.6)-(3.8) can be obtained for the solution $(\overline{p}^k,\overline{m}^k,\overline{E}^k)$ by interchanging $\underline{p}^k$ with $\overline{p}^k$, $\underline{m}^k$ with $\overline{m}^k$, $\underline{E}^k$ with $\overline{E}^k$, and $\varphi_{\overline{m}}$ with $\varphi_{\underline{m}}$ on the right side. Note that the monotone iterations $(\underline{p}^k,\underline{m}^k,\underline{E}^k)$ and $(\overline{p}^k,\overline{m}^k,\overline{E}^k)$ can be easily computed to produce a numerical approximation to the unique solution.

Clearly, $\underline{p}^0 \le \underline{p}^1$, $\underline{m}^0 \le \underline{m}^1$, and $\underline{E}^0 \le \underline{E}^1$. Meanwhile, $\overline{p}^1 = \overline{p}^0$ for $t \le \mu$, which implies $\overline{m}^1 \le \overline{m}^0$. Since $\varphi_{\underline{m}^0} \le \varphi_{\underline{m}^1}$, $\overline{E}^1 \le \overline{E}^0$, which implies $\overline{p}^1 \le \overline{p}^0$ for $t > \mu$. Moreover, since $-\gamma(t,\nu,\varphi_{\overline{m}^0}(t)) \le -\gamma(t,\nu,\varphi_{\overline{m}^1}(t))$, $\underline{m}^1(t,\nu)$ satisfies the following: for every $t \in (0,T_0)$ and every nonnegative $\zeta \in C^1[0,T_0]\times[0,\nu_F]$,

$$\begin{aligned}
&\int_0^{\nu_F} \underline{m}^1(t,\nu)\zeta(t,\nu)d\nu \\
&\quad \le \int_0^{\nu_F} m_0(\nu)\zeta(0,\nu)d\nu - \int_0^t \underline{m}^1(\tau,\nu_F)\zeta(\tau,\nu_F)d\tau + \int_0^t \underline{p}^1(\tau,\mu_F)\zeta(\tau,0)d\tau \\
&\quad + \int_0^t\int_0^{\nu_F} [\zeta_\tau(\tau,\nu) + \zeta_\nu(\tau,\nu)]\underline{m}^1(\tau,\nu)d\nu d\tau \\
&\quad - \int_0^t\int_0^{\nu_F} \gamma(\tau,\nu,\varphi_{\overline{m}^1}(\tau))\overline{m}(\tau,\nu)\zeta(\tau,\nu)d\nu d\tau.
\end{aligned} \quad (3.9)$$

On the other hand, since $-\gamma(t,\nu,\varphi_{\underline{m}^0}(t)) \ge -\gamma(t,\nu,\varphi_{\underline{m}^1}(t))$, $\overline{m}^1(t,\nu)$ satisfies (3.9) with " $\le$ " replaced by " $\ge$ ", $\underline{p}^1$ by $\overline{p}^1$, and $\varphi_{\overline{m}^1}$ by $\varphi_{\underline{m}^1}$. Thus from (3.6), (3.8), (3.9) for $(\underline{p}^1,\underline{m}^1,\underline{E}^1)$ and those for $(\overline{p}^1,\overline{m}^1,\overline{E}^1)$, it easily follows that $(\underline{p}^1,\underline{m}^1,\underline{E}^1)$ and $(\overline{p}^1,\overline{m}^1,\overline{E}^1)$ are a lower solution and an upper solution, respectively, and hence $\underline{p}^1 \le \overline{p}^1$, $\underline{m}^1 \le \overline{m}^1$, $\underline{E}^1 \le \overline{E}^1$.

Assume that for some $k > 1$, $(\underline{p}^k,\underline{m}^k,\underline{E}^k)$ and $(\overline{p}^k,\overline{m}^k,\overline{E}^k)$ are a lower solution and an upper solution of problem (1.1), respectively. By similar reasoning, we can show that

$\underline{p}^k \le \underline{p}^{k+1} \le \overline{p}^{k+1} \le \overline{p}^k$, $\underline{m}^k \le \underline{m}^{k+1} \le \overline{m}^{k+1} \le \overline{m}^k$, $\underline{E}^k \le \underline{E}^{k+1} \le \overline{E}^{k+1} \le \overline{E}^k$ and that $(\underline{p}^{k+1}, \underline{m}^{k+1}, \underline{E}^{k+1})$ and $(\overline{p}^{k+1}, \overline{m}^{k+1}, \overline{E}^{k+1})$ are also a lower solution and an upper solution of (1.1), respectively. Thus by induction, we obtain two monotone sequences that satisfy

$$\begin{aligned}
&\underline{p}^0 \le \underline{p}^1 \le \cdots \le \underline{p}^k \le \overline{p}^k \le \cdots \le \overline{p}^1 \le \overline{p}^0 && \text{a.e. in } [0,T_0]\times[0,\mu_F],\\
&\underline{m}^0 \le \underline{m}^1 \le \cdots \le \underline{m}^k \le \overline{m}^k \le \cdots \le \overline{m}^1 \le \overline{m}^0 && \text{a.e. in } [0,T_0]\times[0,\nu_F],\\
&\underline{E}^0 \le \underline{E}^1 \le \cdots \le \underline{E}^k \le \overline{E}^k \le \cdots \le \overline{E}^1 \le \overline{E}^0 && \text{a.e. in } [0,T_0]
\end{aligned}$$

for each $k = 0, 1, 2, \cdots$. Hence, it follows from the monotonicity of the sequences $\{\underline{p}^k, \underline{m}^k, \underline{E}^k\}$ and $\{\overline{p}^k, \overline{m}^k, \overline{E}^k\}$ that there exist functions $(\underline{p}, \underline{m}, \underline{E})$ and $(\overline{p}, \overline{m}, \overline{E})$ such that $\underline{p}^k \to \underline{p}$ and $\overline{p}^k \to \overline{p}$ pointwise in $(0,T_0)\times(0,\mu_F)$, $\underline{m}^k \to \underline{m}$ and $\overline{m}^k \to \overline{m}$ pointwise in $(0,T_0)\times(0,\nu_F)$, $\underline{E}^k \to \underline{E}$ and $\overline{E}^k \to \overline{E}$ pointwise in $(0,T_0)$. Clearly $\underline{p} \le \overline{p}$, $\underline{m} \le \overline{m}$, and $\underline{E} \le \overline{E}$ a.e.

Upon establishing the monotonicity of our sequences, we can prove the following convergence result.

Theorem 3.1. *Suppose that (A1)-(A4) hold. Then the sequences* $\{\underline{p}^k, \underline{m}^k, \underline{E}^k\}_{k=0}^\infty$ *and* $\{\overline{p}^k, \overline{m}^k, \overline{E}^k\}_{k=0}^\infty$ *converge uniformly to the unique solution* (p, m, E) *of problem (1.1).*

Proof. Since the monotone sequences are bounded by $(\underline{p}^0, \underline{m}^0, \underline{E}^0)$ and $(\overline{p}^0, \overline{m}^0, \overline{E}^0)$, from the pointwise convergence of the sequence, the solution representation for $(\underline{p}^k, \underline{m}^k, \underline{E}^k)$ given in (3.6)-(3.8) and that for $(\overline{p}^k, \overline{m}^k, \overline{E}^k)$, we find that $\{\underline{p}^k, \underline{m}^k, \underline{E}^k\}_{k=0}^\infty$ and $\{\overline{p}^k, \overline{m}^k, \overline{E}^k\}_{k=0}^\infty$ converge to $(\underline{p}, \underline{m}, \underline{E})$ and $(\overline{p}, \overline{m}, \overline{E})$ uniformly and monotonically, respectively. Here, $(\underline{p}, \underline{m}, \underline{E})$ satisfies

$$\underline{p}(t,\mu) = p_0(\mu - t)\exp\left(\int_0^t \sigma(\tau, \mu - t + \tau)d\tau\right) \qquad \text{if } t \le \mu, \tag{3.10a}$$

$$\underline{p}(t,\mu) = s_0(t-\mu)\underline{E}(t-\mu)\exp\left(\int_{t-\mu}^t \sigma(\tau, \mu - t + \tau)d\tau\right) \qquad \text{if } t > \mu, \tag{3.10b}$$

$$\underline{m}(t,\nu) = m_0(\nu - t)\exp\left(-\int_0^t \gamma(\tau, \nu - t + \tau, \varphi_{\overline{m}}(\tau))d\tau\right) \qquad \text{if } t \le \nu, \tag{3.11a}$$

$$\underline{m}(t,\nu) = \underline{p}(t-\nu, \mu_F)\exp\left(-\int_{t-\nu}^t \gamma(\tau, \nu - t + \tau, \varphi_{\overline{m}}(\tau))d\tau\right) \qquad \text{if } t > \nu, \tag{3.11b}$$

$$\underline{E}(t) = \exp\left(-\int_0^t k_E(\tau)d\tau\right)\left(E_0 + \int_0^t f(\tau, \varphi_{\overline{m}}(\tau))\exp\left(\int_0^\tau k_E(s)ds\right)d\tau\right), \tag{3.12}$$

and $(\overline{p}, \overline{m}, \overline{E})$ satisfies (3.10)-(3.12) with $\varphi_{\overline{m}}$ replaced by $\varphi_{\underline{m}}$.

We now show that $(\underline{p}, \underline{m}, \underline{E}) = (\overline{p}, \overline{m}, \overline{E})$. In view of (3.10)-(3.12), it suffices to show that $\underline{m} = \overline{m}$. To this end, let $\widetilde{m} = \overline{m} - \underline{m}$. Since $\overline{m} \geq \underline{m}$, $\widetilde{m}(t, \nu) \geq 0$ and $\widetilde{m}(0, \nu) = 0$. Taking note of (2.8) and the fact that $\underline{p}(t, \mu_F) = \overline{p}(t, \mu_F)$, by choosing $\zeta(t, \nu) = e^{Mt}$ we have that

$$\begin{aligned}\int_0^{\nu_F} \widetilde{m}(t, \nu) d\nu &\leq \int_0^{\nu_F} [M - \gamma(\tau, \nu, \varphi_{\underline{m}}(\tau))] \widetilde{m}(\tau, \nu) d\nu + \int_0^t \int_0^{\nu_F} A_1(\tau, \nu) \int_0^{\nu_F} \widetilde{m}(\tau, \xi) d\xi d\nu \\ &\leq c_0 \int_0^t \int_0^{\nu_F} \widetilde{m}(\tau, \nu) d\nu d\tau,\end{aligned}$$

where $c_0 = \sup\limits_{[0,T_0]\times[0,\nu_F]} \left[M - \gamma(t, \nu, \varphi_{\underline{m}}(t)) + \int_0^{\nu_F} A_1(t, \nu) d\nu \right]$. Thus, it follows from Gronwall's inequality that $\widetilde{m}(t, \nu) = 0$, i.e., $\underline{m} = \overline{m}$. Defining the common limit by (p, m, E), we find that (p, m, E) satisfies (2.1)-(2.3). Hence, the proof is completed.

Since $T_0 \equiv \mu_F$, viewing $(p(T_0, \mu), m(T_0, \nu), E(T_0))$ as a new initial condition, we can easily extend the above-mentioned arguments to the interval $0 \leq t \leq T$ for any $T > 0$. Thus we have the following global existence result.

Theorem 3.2. *The solution* (p, m, E) *of problem (1.1) exists for* $0 \leq t < \infty$.

4. Concluding Remarks

Benzene is a chemical found in both cigarette smoke and gasoline emissions [15, 17]; exposure to benzene results in a variety of blood and bone marrow disorders in both humans and laboratory animals [8, 10]. Modeling erythropoiesis was originally of interest because the toxicity of benzene in the bone marrow is of most importance. As was previously noted, the bone marrow is one of the primary sites where stem cells begin to proliferate and differentiate into red blood cells. Thus, exposure to benzene would contribute to the precursor cell death rate term, which is incorporated into the term $\sigma(t, \mu)$. This idea could certainly be used to investigate other chemicals or toxic agents that affect red blood cell production.

Existence and uniqueness results were previously established for the special case where both k_E and γ are constants, σ is piece-wise constant function depending only on μ, and f is the Hill function. Here we generalize the model to include a time-dependent erythropoietin decay rate k_E, a time-dependent net change rate of the precursor cells σ, a death rate for mature cells γ that is dependent on time, age, and total number of mature cells present in the system, and a general function f which represents the feedback that controls the release of the hormone erythropoietin. These generalities are a significant increase at the level of complexity of the model. As mentioned earlier, due to this complexity the previous arguments used to obtain existence-uniqueness results cannot apply to the general model presented here. Hence, we developed a totally different technique to obtain such results. Besides providing existence-uniqueness of solutions, this technique provides a monotone approximation which can be easily used to compute a numerical approximation of our model. This is an important feature since solutions to (1.1) cannot be explicitly obtained in general, and so a numerical method is needed. We also note that by incorporating the total number of mature cells as an input into the death rate term, the stresses put on the body by not having the proper number of total cells are taken into account.

Our future research efforts will focus on generalizing our results to the case where the function σ, which represents the net change in the birth and death rate of precursor cells, depends on $E(t)$. In reality, the birth rate depends on the concentration of erythropoietin E as well; since erythropoietin controls the rate of maturity of precursor cells, if more erythropoietin is present the cells mature more rapidly, while the maturity slows if less erythropoietin is available. Also, we intend to investigate the model when the term $\dfrac{\partial p(t,\mu)}{\partial \mu}$ has a coefficient other than one. This coefficient describes dynamically the velocity of maturation of any individual cell. If the velocity term was a function of $E(t)$, rather than one as it is in the current model, it would allow the dependency of the precursor cells' maturation on the presence of the hormone erythropoietin to be taken in account, just as with the birth rate.

References

[1] A.S. Ackleh and K. Deng, A Monotone Approximation for a Nonlinear Nonautonomous Size-Structured Population Model, *Appl. Math. Comput.*, **108** (2000), 103-113.

[2] A.S. Ackleh and K. Deng, Existence-Uniqueness of Solutions for a Nonlinear Nonautonomous Size-Structured Population Model: An Upper-Lower Solution Approach, *Canadian Appl. Math. Quart.*, **8** (2000), 1-15.

[3] J. Bélair, M.C. Mackey, and J.M. Mahaffy, Age-Structured and Two-Delay Models for Erythropoiesis, *Math. Biosci.*, **128** (1995), 317-346.

[4] J. Bélair and J.M. Mahaffy, Variable Maturation Velocity and Parameter Sensitivity in a Model for Hematopoiesis, *IMA J. Math. Appl. Med. Biol.*, to appear.

[5] C. E. Cole, *Benzene and Its Effect on Erythropoiesis: Models, Optimal Controls, and Analyses*, Ph.D. Thesis, North Carolina State University, 2001.

[6] R. Courant and D. Hilbert, *Methods of Mathematical Physics*, Vol. **II** Wiley, New York, 1962.

[7] D.W. Golde, M.J. Cline, D. Metcalf, and C.F. Fox, *Hematopoietic Cell Differentiation*, Academic Press, New York, 1978.

[8] G. Kalf, Recent Advances in the Metabolism and Toxicity of Benzene, *CRC Crit. Rev. Toxicol.,* **18** (1987), 141-159.

[9] J. Keener and J. Sneyd, *Mathematical Physiology*, Springer, New York, 1998.

[10] L. MacEachern, R. Snyder, and D. Laskin. Alterations in the Morphology and Functional Activity of Bone Marrow Phagocytes Following Benzene Treatment in Mice, *Toxicol. Appl. Pharmacol.,* **117** (1992), 147-154.

[11] J.M. Mahaffy, Age-structured Modeling of Hematopoiesis, Technical Report, Centre recherches mathmatiques, Universit de Montral, CRM-2609.

[12] J.M. Mahaffy, J.C. Bélair, and M.C. Mackey, Hematopoietic Model with Moving Boundary Condition and State Dependent Delay: Application in Erythropoiesis, *J. Theor. Biol.*, **190** (1998), 135-146.

[13] J.M. Mahaffy, S.W. Polk, and R.K.W. Roeder, An Age-Structured Model for Erythropoiesis Following a Phlebotomy, Technical Report, Centre Recherches Mathmatiques, Universit de Montral, CRM-2598.

[14] J.V. Sickle, Analysis of a Distributed-Parameter Population Model Based on Physiological Age, *J. Theor. Biol.,* **64** (1977), 571-586.

[15] L. Wallace, Marjor Sources of Exposure to Benzene and Other Volatile Organic Chemicals, *Risk Anal.*, **10** (1990), 59-64.

[16] W.J. Williams, E. Beutler, A.J. Erslev, and M.A. Lichtman, *Hematology*, **4th Ed.** McGraw-Hill, New York, 1990.

[17] A. Yardley-Jones, D. Anderson, and D.V. Parke., The Toxicity of Benzene and Its Metabolism and Molecular Pathology in Human Risk Assessment, *Br. J. Ind. Med.,* **48** (1991), 437-444.