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A second-order high resolution finite difference scheme for a structured erythropoiesis model subject to malaria infection

Azmy S. Ackleh [a,*], Baoling Ma [b], Jeremy J. Thibodeaux [c]

[a] Department of Mathematics, University of Louisiana at Lafayette, Lafayette, LA 70504, USA
[b] College of Engineering and Science, Program of Mathematics and Statistics, Louisiana Tech University, Ruston, LA 71272, USA
[c] Department of Mathematical Sciences, Loyola University New Orleans, New Orleans, LA 70118, USA

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ABSTRACT

We develop a second-order high-resolution finite difference scheme to approximate the solution of a mathematical model describing the within-host dynamics of malaria infection. The model consists of two nonlinear partial differential equations coupled with three nonlinear ordinary differential equations. Convergence of the numerical method to the unique weak solution with bounded total variation is proved. Numerical simulations demonstrating the achievement of the designed accuracy are presented.

1. Introduction

Malaria infection has been a major health problem for hundreds of years. As a result, it has been a topic of intense study. In relatively recent years, the mathematical community has joined the group of researchers of this disease [16–18,20,22,27,32–35]. These works include several approaches to understanding the disease. Some are concerned with the spread of the disease throughout a human population [16,17,35]. Others focus on the dynamics of the disease within a particular host [18,20,22,27,32–34]. In [32], a new approach was taken. There, the dynamics of the red blood cell population were included with models that had been previously studied [5,8,12–14].

Numerical methods for studying size-structured models have included finite-element methods [12], monotone approximations [4], finite difference schemes [5–7,19,30], and integration along characteristics [2,9,10,14,21,23,25]. Higher order schemes for solving such models have also been developed (e.g. [2,9,11,21,23]). The paper [1] presents a good review of several numerical methods developed for solving size-structured population models. In that paper the methods are compared with regards to accuracy, efficiency, generality and mathematical methodology. In the area of finite difference schemes, earlier work on such problems utilized implicit first-order methods that proved valuable in both providing numerical approximations and a tool for obtaining existence-uniqueness results. Later, second-order schemes were introduced [7,9,21,23,30] as it became apparent that the first-order schemes required rather small step sizes and long computation times to provide accurate numerical results. Here we will develop a second-order finite difference scheme for the erythropoiesis model subject to malaria infection studied in [32,33]. Although a first-order finite difference scheme has been developed in [32], to our knowledge, the scheme we present here is the first high-order method developed for computing solutions of the erythropoiesis model subject to malaria infection presented in (2.1).

The paper is organized as follows: Section 2 will provide some biological background and introduce the model. Section 3 will introduce the finite difference scheme and the notation used throughout the paper. Section 4 provides estimates for the finite difference scheme and Section 5 concludes with showing that the finite difference scheme converges to the unique weak solution of the model. In Section 6 we demonstrate the order of the method with numerical results and apply the method to a linear problem with a smooth solution. We also show that the method outperforms a first-order method when solutions are discontinuous. Finally, we make some concluding remarks in Section 7.

2. The structured model

The host of the malaria parasite, $Y(t)$, is the mature red blood cell (density $m(t,\nu)$). So we begin our discussion with the process of red blood cell production (erythropoiesis). This process begins when the body detects low oxygen levels in the blood and responds by releasing erythropoietin, whose concentration we denote by $E(t)$, from the kidneys (modeled by $f(t, M(t))$). This hormone is the signal for stems cells in the bone marrow to join the

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* Corresponding author.
E-mail addresses: ackleh@louisiana.edu (A.S. Ackleh), baolingm@latech.edu (B. Ma), thibodea@loyno.edu (J.J. Thibodeaux).

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red blood cell precursor population, whose density we denote by $p(t,\mu)$. This recruitment of stem cells is assumed to be proportional to the erythropoietin concentration, with $\phi(t)$ being the function of proportionality. These cells are structured by their maturity level, μ, which is relative to their hemoglobin content. The rate of this process is dependent on the erythropoietin concentration. We denote this rate by $g(E(t))$. Once they reach full maturation, μ_F, they leave the bone marrow and enter the mature red blood cell population. We structure the mature red blood cell population with the variable v, which denotes age. Precursors undergo mitosis during the beginning of the maturation phase. They also have a natural death rate, which is dependent on the erythropoietin concentration. We denote the net result of this birth and death with $\sigma(\mu, E(t))$. Mature red blood cells have no nucleus, and thus do not divide. Their age-dependent death rate is denoted by $\gamma(t, v, M(t))$. The decay rate of erythropoietin is known to depend on the total precursor population [29] and is denoted by $a_E(P(t))$.

Once the malaria parasite enters the blood stream of a host, it seeks to infect a healthy red blood cell (infection rate k_s). These infected red blood cells, $X(t)$, travel throughout the blood stream while the parasite replicates within them. After some time, the cell bursts and releases a number, $r(t)$, of new parasites into the blood stream which then seek to continue the process. We denote the bursting rate of infected red blood cells by $s(t)$. Although some individuals may develop immunity to certain species of malaria after surviving infection, we assume that this is the first infection and so no immunity exists. Still, both infected red blood cells and free parasites will experience natural death rates, which we denote by α_x and α_y, respectively. While malaria parasites do not infect precursor cells, it was found in [15] that infected red blood cells release a toxin that suppresses precursor production. The rate of this reduction is modeled by function $H(X)$. Taking these processes into account leads to the following model:

$$
\begin{aligned}
&\frac{\partial p(t,\mu)}{\partial t} + g(E(t))\frac{\partial p(t,\mu)}{\partial \mu} = \sigma(t,\mu,E(t))p(t,\mu) - H(X(t))p(t,\mu),\\
&\qquad 0<t<T,\ 0<\mu<\mu_F,\\
&\frac{\partial m(t,v)}{\partial t} + \frac{\partial m(t,v)}{\partial v} = -\gamma(t,v,M(t))m(t,v) - k_sY(t)m(t,v),\\
&\qquad 0<t<T,\ 0<v<v_F,\\
&\frac{dE(t)}{dt} = f(t,M(t)) - a_E(P(t))E(t), \quad 0<t<T,\\
&\frac{dY(t)}{dt} = r(t)s(t)X(t) - k_sY(t)M(t) - \alpha_yY(t), \quad 0<t<T,\\
&\frac{dX(t)}{dt} = k_sY(t)M(t) - s(t)X(t) - \alpha_xX(t), \quad 0<t<T,\\
&g(E(t))p(t,0) = \phi(t)E(t), \quad 0<t<T,\\
&m(t,0) = g(E(t))p(t,\mu_F), \quad 0<t<T,\\
&p(0,\mu) = p^0(\mu), \quad 0\leqslant \mu \leqslant \mu_F,\\
&m(0,v) = m^0(v), \quad 0\leqslant v \leqslant v_F,\\
&E(0) = E^0, \quad Y(0) = Y^0, \quad X(0) = X^0.
\end{aligned} \tag{2.1}
$$

Here $P(t) = \int_0^{\mu_F} p(t,\mu)d\mu$ and $M(t) = \int_0^{v_F} m(t,v)dv$ are the total populations of precursor and mature red blood cells, respectively.

3. A second-order high resolution finite difference scheme

Let c be a sufficiently large positive constant. Throughout the discussion we impose the following regularity conditions on our model parameters in (2.1):

- (H1) The function $H(X)$ is continuously differentiable and $0 \leqslant H(X) \leqslant c$ for $X \in [0,\infty)$.
- (H2) $g(E)$ is continuously differentiable and $0 < g(E) \leqslant c$ for $E \in [0,\infty)$.
- (H3) $\sigma(t,\mu,E)$ is continuous with respect to t, continuously differentiable with respect to E, and for any $(t,\mu,E) \in [0,T]\times[0,\mu_F]\times[0,\infty)$, $|\sigma(t,\mu,E)| \leqslant c$. Furthermore, $\sigma(t,\mu,E)$ has bounded total variation in μ uniformly in $(t,E)\in[0,T]\times[0,\infty)$.
- (H4) $\gamma(t,v,M)$ is continuous with respect to t, continuously differentiable with respect to M, and for any $(t,v,M)\in[0,T]\times[0,v_F]\times[0,\infty)$, $0\leqslant\gamma(t,v,M)\leqslant c$. Furthermore, $\gamma(t,v,M)$ has bounded total variation in v uniformly in $(t,E)\in[0,T]\times[0,\infty)$.
- (H5) The function $f(t,M)$ is continuous with respect to t, continuously differentiable with respect to M, and $0\leqslant f(t,M)\leqslant c$ for $(t,M)\in[0,T]\times[0,\infty)$.
- (H6) The function $a_E(P)$ is continuously differentiable and $0\leqslant a_E(P)\leqslant c$ for $P\in[0,\infty)$.
- (H7) The function $s(t)$ is continuous and $0\leqslant s(t)\leqslant c$ for $t\in[0,T]$.
- (H8) The function $r(t)$ is continuous and $0\leqslant r(t)\leqslant c$ for $t\in[0,T]$.
- (H9) The function $\phi(t)$ is continuously differentiable and $0\leqslant\phi(t)\leqslant c$ for $t\in[0,T]$.
- (H10) $E^0, Y^0, X^0, k_s, \alpha_x, \alpha_y$ are nonnegative constants.
- (H11) $p^0(\mu)$, $m^0(v)$ are nonnegative with $\|p^0\|_{BV(0,\mu_F)}$, $\|m^0\|_{BV(0,v_F)} \leqslant c$.

Note that in assumptions (H3) and (H4) we assume only bounded total variation smoothness in μ and v in order to allow discontinuities which arise in applications [5]. Now we give the definition of a weak solution to problem (2.1) as follows: A 5-tuple $(p,m,E,Y,X)\in(BV((0,T)\times(0,\mu_F)), BV((0,T)\times(0,v_F)), C[0,T], C[0,T], C[0,T])$ is called a weak solution to the problem (2.1) if it satisfies:

$$
\begin{aligned}
\int_0^{\mu_F} p(t,\mu)\zeta(t,\mu)d\mu = {} & \int_0^{\mu_F} p^0(\mu)\zeta(0,\mu)d\mu\\
& - \int_0^t g(E(\tau))p(t,\mu_F^-)\zeta(\tau,\mu_F)d\tau\\
& + \int_0^t \phi(\tau)E(\tau)\zeta(\tau,0)d\tau\\
& + \int_0^t\int_0^{\mu_F}[\zeta_\tau(\tau,\mu)+g(E(\tau))\zeta_\mu(\tau,\mu)]p(\tau,\mu)d\mu d\tau\\
& + \int_0^t\int_0^{\mu_F}[\sigma(\tau,\mu,E(\tau))-H(X(\tau))]p(\tau,\mu)\zeta(\tau,\mu)d\mu d\tau,\\
\int_0^{v_F} m(t,v)\varsigma(t,v)dv = {} & \int_0^{v_F} m^0(v)\varsigma(0,v)dv - \int_0^t m(\tau,v_F^-)\varsigma(\tau,v_F)d\tau\\
& + \int_0^t g(E(\tau))p(\tau,\mu_F^-)\varsigma(\tau,0)d\tau\\
& + \int_0^t\int_0^{v_F}[\varsigma_\tau(\tau,v)+\varsigma_v(\tau,v)]m(\tau,v)]dvd\tau\\
& - \int_0^t\int_0^{v_F}[\gamma(\tau,v,M(\tau))+k_sY(\tau)]m(\tau,v)\varsigma(\tau,v)dvd\tau,\\
E(t) = {} & E^0 + \int_0^t [f(\tau,M(s)) - a_E(P(\tau))E(\tau)]d\tau,\\
Y(t) = {} & Y^0 + \int_0^t [rs(\tau)X(\tau) - k_sY(\tau)M(\tau) - \alpha_yY(\tau)]d\tau,\\
X(t) = {} & X^0 + \int_0^t [k_sM(\tau)Y(\tau) - s(\tau)X(\tau) - \alpha_xX(\tau)]d\tau
\end{aligned} \tag{3.1}
$$

for each $t\in(0,T)$, every test function $\zeta\in C^1([0,T]\times[0,\mu_F])$ and every test function $\varsigma\in C^1([0,T]\times[0,v_F])$. Here, $p(t,\mu_F^-) = \lim_{\mu\to\mu_F^-}p(t,\mu)$ and $m(t,v_F^-) = \lim_{v\to v_F^-}m(t,v)$.