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Mathematical model of susceptibility, resistance, and resilience in the within-host dynamics between a *Plasmodium* parasite and the immune system

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ABSTRACT

We developed a coupled age-structured partial differential equation model to capture the disease dynamics during blood-stage malaria. The addition of age structure for the parasite population, with respect to previous models, allows us to better characterize the interaction between the malaria parasite and red blood cells during infection. Here we prove that the system we propose is well-posed and there exist at least two global states. We further demonstrate that the numerical simulation of the system coincides with clinically observed outcomes of primary and secondary malaria infection. The well-posedness of this system guarantees that the behavior of the model remains smooth, bounded, and continuously dependent on initial conditions; calibration with clinical data will constrain domains of parameters and variables to physiological ranges.

1. Introduction

The goal of this article is to formulate a mathematical model to characterize the within-host dynamics present in the disease malaria, between different host cell types and pathogens of the *Plasmodium* species. *Plasmodium* is a large genus of parasitic protozoa (unicellular eukaryotic organisms), with complex genomes and sophisticated life cycles. The genome, behavior, and epidemiological characterization of *Plasmodium* are orders of magnitude more complex than that of viruses or bacteria. The clinical manifestation of infection by *Plasmodium*, the disease malaria, has a wide spectrum of symptoms, varying from asymptomatic to highly severe. Malaria affects birds, reptiles, and some mammals (mostly rodents and primates).

The *Plasmodium* life cycle is comprised of several stages. The infection process in humans starts with the injection of sporozoites by female Anopheline mosquitoes into the skin of the host. This is followed by the liver stage, in which the inoculated sporozoites grow and multiply asexually within hepatocytes for 1–2 weeks to produce merozoites. The newly produced merozoites emerge from the liver and enter the blood stream. The blood-stage infection starts immediately after the hepatic stage; merozoites invade red blood cells (RBCs) where they also reproduce asexually. In some instances, the parasites develop into the sexual stage form called gametocytes. Gametocyte-infected red blood cells (iRBCs) infect newly feeding Anopheline mosquitoes and through sexual reproduction followed by many more rounds of asexual multiplication are ultimately transformed into sporozoites, thus completing the infection cycle between an Anopheline mosquito and its host.

The parasite's blood-stage infection in both human and non-human primates generally has a regular cycle of 24–72 h depending on the species of the *Plasmodium* parasite [1,2]. The parasites invade healthy RBCs and replicate asexually, remodeling and ultimately destroying the RBCs in the process. The destruction of RBCs during blood-stage malaria infection sometimes results in severe anemia, which is one of the major complications of malaria and a leading cause of mortality. Human and non-human primate RBCs have a normal life span of 120–100 days, respectively, where afterwards RBCs are cleared rapidly [3]. Both the age structure of RBCs and iRBCs play an important role in the hematodynamics of the host during malaria infection. It has been shown previously that *Plasmodium vivax* infects RBCs of different age groups at different rates and the interaction between the life cycle of the malaria parasite and the immune system

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can lead to synchrony of the parasite [4,5]. Anemia caused by malaria infection is a complex process not only involving the malaria parasites and host RBCs, but also the innate and adaptive immune system of the host [6,7]. It has been previously postulated that there are at least three factors that contribute to severe anemia resulting from blood stage malarial infection: (i) The destruction of RBCs directly by the parasite, (ii) the destruction of RBCs by a non-parasitic factor, possibly the host immune system, and (iii) the disruption of the host's erythropoietic process [3,6,8]; erythropoiesis refers to the differentiation and maturation of hematopoietic stem cells (HSCs) through committed cell lineages culminating in the production of erythrocytes/RBCs.

Classic models of erythropoiesis rest on three variables representing the precursor/progenitor population of immature erythrocytes, the population of mature RBCs, and the concentration of erythropoietin (Epo), a signaling molecule critical to erythrocyte production. [9] represented these three variables with a system of ordinary differential equations (ODEs) with one delay accounting for the time for Epo dependent maturation of progenitors into erythrocytes (about 6 days) [9]. In [10] developed an "age-structured" partial differential equation (PDE) model for erythropoiesis [10]. Belair et al.'s model characterizes the proliferation and aging of the precursor and mature erythrocyte populations as nonlinear, first order PDEs and includes an ODE to represent Epo dynamics over time. Building on Belair's 1995 model, [11] investigated the addition of state-dependent delays to the model [11].

Due to the difficulty involved in measuring Epo accurately over an extended period of time, we formulated the rate at which mature RBCs enter circulation as only dependent upon the current number of RBCs and the number of RBCs at equilibrium. Such a formulation has previously been shown by Savil et al. to capture the erythropoiesis process using data derived from a murine model [12]. As the only formulation of an erythropoiesis model without an Epo component that has been validated by time course data, we believe that such a formulation would also be able to capture the fluctuation in the erythropoietic process due to loss of RBCs within our hematodynamic system.

Most recent and most relevant to our study, Thibodeaux et al. published two papers (2010, 2013) modifying [10] model in an attempt to simulate and analyze erythropoietic dynamics subject to malaria infection [13,14]. They conjoined an ODE-based model of malaria infection with an age-structured PDE model of erythropoiesis, and examined the dynamics of this new system to simulate the effects of hemozoin (Hz) on the suppression of erythropoiesis.

In order to capture the complex interactions between different age groups of iRBCs, RBCs and various immune cells during blood stage malaria [15], we propose a coupled age-structured PDE model of both iRBCs and host RBCs. Our model borrows from the erythropoiesis PDE model [13,14] and expands upon it by adding the parasite age structure system and the effect of immune cells on both RBCs and iRBCs.

This paper is organized as follows: Section 2 contains the detailed derivation and description of our hematodynamic model. Section 3 proves the well posedness of the system and the existence of at least two global behaviors of biological interest. Section 4 provides numerical simulation results of our model. Section 5 offers some conclusions, and presents future directions.

2. Model formulation

Let $u(a, t)$ be a function which approximates the concentration of RBCs of age a at time point t. RBCs of age $> a_{max}$ are rapidly cleared from the circulation, thus we assume that $u(a, t) = 0$ when $a > a_{max}$. Additionally, Let $v(\alpha, t)$ be a function that approximates the concentration of iRBCs of age α at time t. iRBCs of age α_{max} burst to produce merozoites, which in turn infect other RBCs, thus we assume that $v(\alpha, t) = 0$ when $\alpha > \alpha_{max}$. Assuming that the loss of RBCs during blood stage malarial infection is only due to parasite invasion, innate immune cells, adaptive immune cells, random loss of RBCs during aging and the rapid clearance of RBCs with age $> a_{max}$, and the destruction of RBCs by innate and adaptive immune cells follows the law of mass action, then the difference between the concentrations of RBCs across all ages between two time points, t_1 and t_2 is

$$\begin{aligned}\int_{a_0}^{a_{max}} u(a,t_2)\,da &= \int_{a_0}^{a_{max}} u(a,t_1)\,da \\ &\quad + \int_{t_1}^{t_2} u(a_0,t)\,dt - \int_{t_1}^{t_2} u(a_{max},t)\,dt \\ &\quad - \gamma \int_{a_0}^{a_{max}}\int_{t_1}^{t_2} v(\alpha_{max},t) r(a) p(u(a,t))\,dt\,da \\ &\quad - \sum_{i=1}^{T}\int_{a_0}^{a_{max}}\int_{t_1}^{t_2} w_i(t)\theta_i u(a,t)\,dt\,da \\ &\quad - \sum_{i=1}^{Q}\int_{a_0}^{a_{max}}\int_{t_1}^{t_2} s_i(t)\psi_i u(a,t)\,dt\,da \\ &\quad - \int_{a_0}^{a_{max}}\int_{t_1}^{t_2} h(a)u(a,t)\,dt\,da\,, \end{aligned} \tag{1}$$

where

$$p(u(a,t)) = \frac{u(a,t)}{\int_{a_0}^{a_{max}} u(a,t)} \tag{2}$$

is a probability density function such that $\int_{a_0}^{a_{max}} p(u(a,t))da = 1$.

The left hand side (LHS) term of (1) and the first three terms of the right hand side (RHS) of (1),

$$\begin{aligned}\int_{a_0}^{a_{max}} u(a,t_2)\,da &= \int_{a_0}^{a_{max}} u(a,t_1)\,da + \int_{t_1}^{t_2} u(a_0,t)\,dt \\ &\quad - \int_{t_1}^{t_2} u(a_{max},t)\,dt, \end{aligned} \tag{3}$$

account for the change of the concentration of RBCs from t_1 to t_2 due to the production of new RBCs and the rapid clearance of RBCs with age $> a_{max}$.

The term

$$-\gamma \int_{a_0}^{a_{max}}\int_{t_1}^{t_2} v(\alpha_{max},t) r(a) p(u(a,t))\,dt\,da\,, \tag{4}$$

accounts for the loss of RBCs due to infection from bursting iRBCs. $v(\alpha_{max}, t)$ is the concentration of bursting iRBCs at time t. $r(a)$ is the success rate of merozoites infecting RBCs of age a. γ is the expected number of merozoites each bursting iRBC produces. $p(u(a, t))$ is the expected percentage of merozoites infecting RBCs of specific age a at time t. The concentration of new iRBCs produced at time t is

$$\gamma \int_{a_0}^{a_{max}} v(\alpha_{max},t) r(a) p(u(a,t))\,da. \tag{5}$$

The term

$$-\sum_{i=1}^{T}\int_{a_0}^{a_{max}}\int_{t_1}^{t_2} w_i(t)\theta_i u(a,t)\,dt\,da, \tag{6}$$

accounts for the loss of RBCs due to T different kinds of innate immune cells. $w_i(t)$ is the concentration of the ith kind of innate immune cells at time t. θ_i represents the ith kind of innate immune cell's effectiveness at destroying RBCs. The term

$$\sum_{i=1}^{Q}\int_{a_0}^{a_{max}}\int_{t_1}^{t_2} s_i(t)\psi_i u(a,t)\,dt\,da, \tag{7}$$

accounts for the loss of RBCs due to Q different kinds of adaptive immune cells. $s_i(t)$ is the concentration of the ith