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Comparison of mathematical frameworks for modeling erythropoiesis in the context of malaria infection

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ABSTRACT

Malaria is an infectious disease present all around the globe and responsible for half a million deaths per year. A within-host model of this infection requires a framework capable of properly approximating not only the blood stage of the infection but also the erythropoietic process that is in charge of overcoming the malaria induced anemia. Within this context, we compare ordinary differential equations (ODEs) with and without age classes, delayed differential equations (DDEs), and discrete recursive equations (DREs) with age classes. Results show that ODEs without age classes are fair approximations that do not provide a crisp temporal representation of the processes involved, and inclusion of age classes only mitigates the problem to some degree. DDEs perform well with respect to generating the essentially fixed delay between cell production and cell removal due to age, but the inclusion of any other processes, such as sudden blood loss, becomes cumbersome. The framework that was found to perform best in representing the dynamics of red blood cells during malaria infection is a DRE with age classes. In this model structure, the amount of time a cell remains alive is easily controlled, and the addition of age dependent or independent processes is straightforward. All events that populations of cells face during their lifespan, like growth or adaptation in differentiation or maturation rate, are properly represented in this framework.

1. Introduction

Malaria is a worldwide infectious disease responsible for over half a million deaths per year [1] and for the perpetuation of genetic diseases like thalassemias, sickle-cell disease, and G6P dehydrogenase deficiency due to heterozygous advantage [2–4]. Malaria is caused by parasitic protozoans belonging to the genus *Plasmodium* and is transmitted by female *Anopheles* mosquitoes [5]. Upon entering the host, the protozoan takes temporary refuge in the liver where it multiplies and may remain dormant for several months, if not years. When the parasite leaves the liver, it starts infecting red blood cells (RBCs), where it replicates. This stage ultimately causes most symptoms of malaria. Under normal healthy conditions, RBCs exhibit an almost deterministic lifespan with relatively small variation. However, during the blood stage infection, the parasitemia level increases and the number of erythrocytes plummets, thereby causing an increasing demand on erythropoiesis to replace lost cells. Erythropoiesis is regulated by negative feedback through erythropoietin, such that a hypoxia-induced increase in the concentration of erythropoietin promotes survival, proliferation and differentiation of erythroid progenitor cells. During the erythropoietic process, the erythroid progenitor cells undergo a number of mitotic events while differentiating through the several stages. Each differentiation stage is characterized by a specific duration and a fixed number of mitotic events, until ultimately a polychromatic erythroblast has formed. Concomitant with the destruction of RBCs, malarial infection also causes dysregulation of the erythropoietic process, due to interference with regulating cytokines and the production of the malaria pigment, hemozoin. This dysregulation is characterized by a failure to up-regulate RBC production properly, thereby resulting in anemia [6–9].

The development of mathematical models characterizing the dynamics between hosts and malaria parasites requires an effective framework capable of addressing the dynamical regulation of RBC production, the parasite's life cycle characteristics, and interventions by the immune system [29]. Specifically, in order to capture the dynamics of erythropoiesis properly, a modeling framework needs to be able to address the adaptability of the cell differentiation process whose total duration, as well as the number of cell divisions between one stage and the next, responds to current needs. In principle, such features can be approximated with ordinary differential equations (ODEs) and mass action representations of the transitions between stages [30]. However, this framework does not properly capture the delays that cells encounter between entering and exiting a

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given stage of differentiation, because ODEs implicitly assume that removal from any of the differentiation stages is a probabilistic event. Delay differential equations (DDEs) are able to capture this delay, but the framework is rather inflexible, and any attempts to account for other processes of cell removal from a pool before the end of the time delay become cumbersome. Delays can also be generated in ODE models per approximation [10,11] or by an explicit representation of the age-structure of cell populations within each stage [12]. Nonetheless, the issue of properly capturing the aging process, that is, the movement of cells from one age class to the next, still persists, as in the case of population models without age-structures. By contrast, discrete, recursive, age-structured models using difference equations (DREs) produce the required delays with relative ease, and if a transition matrix formulation is used, one can readily ensure that all cells in a given age class move to the next class at the correct time. In this paper, we compare these four alternative approaches and highlight their advantages and disadvantages.

Both malaria blood stage infections and hematopoietic processes have been the subject of numerous modeling activities, using not only ODEs [13–16], but also DDEs [17–19], discrete equations [12] and PDEs [20–22]. However, to the best of our knowledge, the different approaches have not been compared in a systematic manner that highlights the advantages and disadvantages of each framework.

2. Methods

Malaria is obviously an exceedingly complex disease, and even a cursory discussion is beyond the scope of this article. Nonetheless, it is necessary to highlight some details of immediate relevance to modeling erythropoiesis.

Malaria parasites in the blood, known as merozoites, only replicate within RBCs and, depending on the *Plasmodium* species, may show a preference for cells of a given age. Once inside the RBC, the parasite completes its life cycle in 24–72 h, depending on its species. At the end of the life cycle, the RBC membrane ruptures, and a new brood of merozoites is released into the blood stream. For each infected RBC, between 8 and 32 new merozoites [23] may be produced, again depending on the species. This ongoing process of RBC invasion and rupture leads to a decrease in the number of RBCs, to which the erythropoietic system responds. This system generates RBCs from multipotent hematopoietic stem cells in the bone marrow through several stages of differentiation and maturation. The process is controlled by hormones, like erythropoietin, that act by changing the rate of differentiation and level of proliferation. In essence, cells of each stage will, after a certain amount of time that is needed for differentiation and maturation, move into the next stage, while simultaneously undergoing a population expansion, so that more cells leave each stage than entered it. These same cells can also be subject to apoptosis. Thus, each stage may be characterized by two properties: the differentiation time and the amplification factor. In cells exclusively undergoing maturation, the amplification factor is 1. Since both of these properties depend on hormones, an appropriate modeling framework should allow for dynamical changes in these two properties, as they are encountered in malaria (for a review, see [24]). Once matured, RBCs have an essentially fixed life span of about 120 days in humans [25]; also, they do not grow or proliferate. However, a small percentage of seemingly healthy RBCs are removed throughout their lifetime in an apparently random manner. If an RBC is infected by *Plasmodium*, it bursts after one to three days, depending on the parasite species.

In order to investigate the best framework to model the malaria blood stage infection, the components were separated into two groups: cells with fixed lifespans (infected and non-infected RBCs) and cells with variable lifespans (erythropoietic progenitor and precursor cells).

2.1. Modeling the aging process of infected and non-infected RBCs

Three frameworks were compared for their ability to generate a fixed delay between cell production and removal: (A) delay differential equations (DDEs); (B) ordinary differential equations (ODEs) with age classes; and (C) discrete recursive equations (DREs) with age classes (Fig. 1). In order to render the comparison fair, the three systems were parameterized so that they exhibit external and internal equivalence as much as possible [26]. To be specific, a delay of 6 time units was chosen. This setting is explicitly enforced in the DDE by setting a delay of $\tau = 6$, and the number of age classes in the ODE and discrete systems is set, accordingly, to $n = 6$. Accordingly, the time-step of the discrete framework is defined as 1 unit. The influx of cells (F_{in}) into each of the three models is arbitrarily set to 2.

The DDE framework (Fig. 1A) is therefore modeled as

$$\frac{dX}{dt} = F_{in}(t) - F_{out}(t), \tag{1.1}$$

where the efflux of cells, F_{out}, is given by the number of cells that had entered the system τ time-units earlier:

$$\frac{dX}{dt} = F_{in}(t) - F_{in}(t-\tau). \tag{1.2}$$

With this formulation and with the initial condition $F_{in}(t) = 2$, for $-\tau \le t \le 0$, the steady-state is determined by the initial state of $X(0)$. We set this steady state to 12 to be consistent with all other frameworks.

The ODE framework with age-classes (Fig. 1B) is formulated as:

$$\frac{dx_1}{dt} = F_{in}(t) - k \cdot x_1 \tag{2.1}$$

$$\frac{dx_i}{dt} = k \cdot x_{i-1} - k \cdot x_i, \quad i = 2,\ 3,\ 4, \ldots, n \tag{2.2}$$

For fair comparisons with other frameworks, k must equal n/τ, which enforces that cells remain in the system on average for τ time units. The total number of cells present in the system at any time point t is given by

$$X(t) = \sum_i x_i(t). \tag{3}$$

With a $n = 6$, $\tau = 6$ and $F_{in}(0) = 2$, this framework has a steady-state $X = 12$.

The DRE framework with age classes (Fig. 1C) is formulated as:

$$\vec{X}_{t+1} = V \cdot \vec{X}_t + \begin{bmatrix} F_{in}(t) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \qquad V = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \end{bmatrix} \tag{4}$$

As in the case of the ODE with age-classes, the total number of cells present at a particular time point t equals the sum of the elements of $\vec{X}_t$:

$$X_t = \sum_i x_{i,t}. \tag{5}$$

The steady-state for $F_{in}(0) = 2$ is again $X_\infty = 12$.

To test the effect of a changing cell production in the models above, $F_{in}(t)$ was shifted from 2 to 5 for the time period $t \in]5,7]$ and returned to 2 for $t \in]7,20]$:

$$F_{in}(t) = \begin{cases} 2 & \text{for } t\ [0, 5] \\ 5 & \text{for } t\ (5, 7] \\ 2 & \text{for } t\ (7, 20] \end{cases} \tag{6}$$