Analysis of Immune Response Mechanism of a Malaria-Autophagy Model

Abstract

Malaria is one of the diseases causing high mortality worldwide. Latest research reports insist that, besides adaptive immune response, autophagy also plays a prominent role in the elimination of infected cells and pathogens. In this article, a nonlinear mathematical model is proposed as a system of ordinary differential equations to study malaria infection within a host in the presence of autophagy and immune response. The model considers interactions among healthy and infected erythrocytes, free malaria parasites, the activity of autophagy and the amount of immune effector cells. Elimination of infected erythrocytes and free merozoites by autophagy as well as effector cells are incorporated here. Positivity and boundedness of solutions as well as the existence of a positively invariant region are verified. The basic reproduction number is obtained and threshold dynamics are explored analytically. The disease free equilibrium is shown to be locally and globally asymptotically stable when the basic reproduction number is less than unity. Otherwise, infection persists depending on initial conditions. The importance of autophagy as an additional effort for inhibition of infection is demonstrated in the absence or inefficiency of immune response. This work provides insight into the treatment of malaria using approaches that enhance autophagy in the host.

Keywords: Malaria, Autophagy, Mathematical Modeling, Immune Response, Within-host Dynamics, Qualitative and Stability Analysis, Basic Reproduction Number.

1 Introduction

Malaria is one of the most important infectious diseases of humans and continues to represent a tremendous public health burden in many regions of the world. Malaria is caused by protozoan parasites of the genus *Plasmodium* and is transmitted by the bite of infected female *Anopheles* mosquitoes. Despite great advances in malaria prevention, diagnosis, and treatment, the disease still causes significant morbidity and mortality, particularly in sub-Saharan Africa, which accounts for more than ninety percent of deaths from malaria. According to the World Health Organization, malaria remains responsible for more than 200 million clinical cases every year, with human children and pregnant women being most at risk [1, 2].

The malaria parasite has a complicated life cycle involving a mosquito and a human host. Following transmission by the bite of an infected mosquito, sporozoites reach the bloodstream and quickly travel to the liver, where they infect a hepatocyte and undergo extensive replication. Merozoites are released into the blood stream to infect red blood cells and begin the erythrocytic phase of infection. It is the blood-stage infection that causes the symptoms and complications of malaria, including fever, anemia, cerebral malaria, metabolic acidosis, and ultimately death in severe cases [3, 4].

The erythrocytic stage of infection is a cycle of red blood cell invasion, parasite growth, and cell rupture. The release of merozoites from infected erythrocytes each cycle results in the destruction of the host red blood cell, propagating the amplification of infection of healthy erythrocytes. This destruction of erythrocytes is a major cause of malaria-associated pathologies. Parasite proliferation in the host is

a balance between the red blood cell lysis required for pathogenesis but the resultant likelihood of a response from the host immune system [5].

Host defense against malaria relies on a highly coordinated interplay of the innate and adaptive immune responses. Innate immunity includes macrophages, dendritic cells, neutrophils, natural killer cells, inflammatory cytokines, and the complement cascade. Adaptive immunity is achieved by the action of T cells and generation of parasite-specific antibodies by B cells [6, 7].

Many studies have shown that immune responses can reduce parasite burden: activated macrophages can phagocytose infected erythrocytes; cytolytic immune cells can destroy infected erythrocytes; and antibodies can neutralize circulating parasites. However, malaria parasites employ a number of strategies to avoid immune clearance, such as antigenic variation and sequestration from immune cells in the deep tissues, which allow them to maintain high parasitemias in the host [6, 21].

In addition to the classical components of the immune response, recent work has demonstrated the importance of homeostatic cellular mechanisms to defending host cells from invasion by intracellular pathogens. One such host process is autophagy, a highly conserved intracellular degradation mechanism that maintains cellular integrity by recycling old organelles, protein aggregates, and intracellular pathogens. Autophagy relies on the biogenesis of double-membraned vesicles, termed autophagosomes, which engulf portions of the cytoplasm and then fuse with lysosomes [8, 9, 10, 24].

Though originally thought to be a purely homeostatic process, autophagy has recently become recognized as an important mechanism of innate immunity. Many studies have demonstrated that autophagy is essential for host defense against bacteria, viruses, fungi, and protozoan parasites [11]. The interaction between malaria parasites and autophagy has been a topic of great interest. There are many indications that host autophagy is activated to defend against infection.

However, instead of only restricting infection, autophagy seems to play a dual role, with some studies suggesting that aspects of the autophagy machinery are exploited by malaria parasites for intracellular survival and propagation, while activation of other aspects of the autophagy machinery results in increased parasite clearance [15].

Mathematical modeling has become an essential tool for understanding infectious disease dynamics. Models offer a formal method to investigate the interactions between pathogens and their hosts, identify important components, and test the effects of targeted interventions. The first malaria transmission models were introduced by Ross and Macdonald and are well-known in public health [16, 17]. Many models have been published of within-host malaria infection of humans, mice, and birds by various parasite species, and have succeeded in explaining many observed attributes of malaria infection, such as the existence of oscillations, chronic infections, and parasite elimination by the host immune system [18, 19, 20].

Many mathematical studies have included immune responses in models of within-host malaria infection and have shown that immune responses can alter the infection outcome by clearing all parasites from the host. Nonlinear immune responses have even been reported to result in threshold behavior, bistability, and oscillatory solutions [21, 23, 22]. However, few mathematical studies have modeled within-host malaria infection including autophagy, but rather have focused on parasite dynamics and immune response in the host.

Here, we propose a within-host mathematical model that includes malaria parasites, healthy and infected red blood cells, autophagy, and immune cells. This model allows us to investigate the combined effect of autophagy and immune response on parasite dynamics in the context of host defense. In particular, we mathematically identify conditions for elimination of malaria infection, as well as the ability of autophagy to successfully defend alongside an immune response.

The goal of this work is to mathematically formulate a meaningful malaria, autophagy, immune response model, prove some useful background results, derive the basic reproduction number, investigate the stability of interesting equilibria, and determine the role of these two host-defense mechanisms in controlling parasite proliferation.

2 Model Formulation

Malaria is caused by infection with protozoan parasites of the genus *Plasmodium*. Malaria parasites invade red blood cells (RBCs), where they grow and replicate, resulting in cell lysis and the release of merozoites that can invade another RBC to continue the cycle. Malaria infection in the host is regulated by several host processes, including innate and adaptive immune responses and autophagy. Autophagy is a highly conserved intracellular degradation mechanism through which damaged organelles, protein aggregates, and intracellular pathogens are engulfed and degraded within lysosomes. Autophagy has been shown to defend the host against malaria infection by clearing infected cells and reducing parasite burden.

Simultaneously, the immune system recognizes infected erythrocytes and free parasites, activating various effector cells that participate in parasite clearance.

To investigate the combined effects of autophagy and immune response on malaria progression, we formulate a within-host mathematical model consisting of five interacting populations.

Let $T(t)$ denote the concentration of healthy red blood cells, $I(t)$ denote the concentration of infected red blood cells, $P(t)$ denote the concentration of free malaria parasites, $A(t)$ denote the level of autophagic activity, and $R(t)$ denote the concentration of activated immune effector cells. The total red blood cell population is defined as

$$N(t) = T(t) + I(t).$$

2.1 Model Assumptions

The formulation of the model is based on the following biological assumptions:

1. Healthy red blood cells are produced continuously from the bone marrow at a constant rate φ.
2. Healthy red blood cells die naturally at rate d_T.
3. Infection occurs when free parasites successfully invade healthy red blood cells at rate τTP.
4. Infected red blood cells die naturally at rate d_I.
5. Each infected red blood cell contributes to the production of free parasites at rate k.
6. Free parasites are naturally cleared from circulation at rate c.
7. Autophagy is stimulated by both infected red blood cells and parasite burden.
8. Autophagy contributes to the elimination of infected red blood cells and free parasites.
9. The immune response is activated by the presence of infected cells and circulating parasites.
10. Activated immune cells destroy infected red blood cells and free parasites.
11. Autophagic activity decays naturally in the absence of stimulation.
12. Activated immune cells also decay naturally when antigenic stimulation decreases.

2.2 Model Equations

Under the above assumptions, the dynamics of malaria infection, autophagy, and immune response are governed by the system

$$\begin{cases} \dfrac{dT}{dt} = \varphi - d_T T - \tau TP, \\ \dfrac{dI}{dt} = \tau TP - d_I I - \phi AI - \psi RI, \\ \dfrac{dP}{dt} = kI - cP - \xi AP - \omega RP, \\ \dfrac{dA}{dt} = s_1 I + s_2 P - \mu A, \\ \dfrac{dR}{dt} = \rho I + \sigma P - \delta_R R. \end{cases} \tag{1}$$

2.3 Description of the Model

The first equation of system (1) describes the dynamics of healthy red blood cells. The constant term φ represents the recruitment of erythrocytes from the bone marrow. Healthy cells die naturally at rate $d_T T$ and become infected through interactions with free parasites at rate τTP.

The second equation describes the dynamics of infected red blood cells. New infected cells are generated through successful parasite invasion of healthy erythrocytes. Infected cells are removed through natural death at rate $d_I I$, autophagy-mediated clearance at rate ϕAI, and immune-mediated destruction at rate ψRI.

The third equation governs the parasite population. Parasites are released from infected cells at rate kI. They are naturally removed at rate cP and additionally cleared through autophagic activity and immune response at rates ξAP and ωRP, respectively.

The fourth equation models autophagic activity. The presence of infected cells and free parasites stimulates autophagy at rates $s_1 I$ and $s_2 P$, respectively. In the absence of stimulation, autophagic activity decays at rate μA.

The fifth equation describes the dynamics of activated immune cells. The immune response is stimulated by infected cells and parasites at rates ρI and σP. Activated immune cells decline naturally at rate $\delta_R R$.

2.4 Parameter Description

The parameters of the model are described in the table below.

Table 1: Description of model parameters.

Parameter	Biological Meaning
φ	Recruitment rate of healthy red blood cells
d_T	Natural death rate of healthy red blood cells
τ	Infection rate of healthy red blood cells by parasites
d_I	Natural death rate of infected red blood cells
k	Production rate of parasites from infected cells
c	Natural clearance rate of parasites
ϕ	Autophagy-mediated clearance rate of infected cells
ξ	Autophagy-mediated clearance rate of parasites
s_1	Activation rate of autophagy due to infected cells
s_2	Activation rate of autophagy due to parasites
μ	Natural decay rate of autophagic activity
ψ	Immune-mediated clearance rate of infected cells
ω	Immune-mediated clearance rate of parasites
ρ	Immune activation rate due to infected cells
σ	Immune activation rate due to parasites
δ_R	Natural decay rate of immune effector cells

3 Qualitative Analysis and Stability Theory

Qualitative and stability analysis of the model is done in this section.

3.1 Positivity of Solutions

Since the model variables represent biological populations and physiological quantities, it is necessary to establish that solutions remain nonnegative for all future time.

Theorem 1. *Let*

$$(T(0), I(0), P(0), A(0), R(0)) \in \mathbb{R}^5_+.$$

Then every solution of system (1) *remains nonnegative for all* $t > 0$.

Proof. From the first equation of system (1),

$$\frac{dT}{dt} = \varphi - d_T T - \tau T P.$$

Since $P \geq 0$,

$$\frac{dT}{dt} \geq -(d_T + \tau P)T.$$

Hence,

$$T(t) \geq T(0) \exp\left(-\int_0^t (d_T + \tau P(s))ds\right) \geq 0.$$

Similarly,

$$\frac{dI}{dt} = \tau TP - (d_I + \phi A + \psi R)I \geq -(d_I + \phi A + \psi R)I.$$

Thus,

$$I(t) \geq 0.$$

For the parasite population,

$$\frac{dP}{dt} = kI - (c + \xi A + \omega R)P \geq -(c + \xi A + \omega R)P,$$

which implies

$$P(t) \geq 0.$$

For autophagy,

$$\frac{dA}{dt} = s_1 I + s_2 P - \mu A \geq -\mu A,$$

and therefore

$$A(t) \geq 0.$$

Finally,

$$\frac{dR}{dt} = \rho I + \sigma P - \delta_R R \geq -\delta_R R,$$

yielding

$$R(t) \geq 0.$$

Therefore

$$(T, I, P, A, R) \in \mathbb{R}^5_+$$

for all $t > 0$.

□

3.2 Boundedness of Solutions

To establish boundedness, define the total erythrocyte population

$$N(t) = T(t) + I(t).$$

Adding the first two equations of system (1) gives

$$\frac{dN}{dt} = \varphi - d_T T - d_I I - \phi A I - \psi R I.$$

Since all variables are nonnegative,

$$\frac{dN}{dt} \leq \varphi - dN,$$

where

$$d = \min\{d_T, d_I\}.$$

Applying the comparison theorem,

$$N(t) \leq N(0)e^{-dt} + \frac{\varphi}{d}\left(1 - e^{-dt}\right).$$

Hence

$$\limsup_{t\to\infty} N(t) \leq \frac{\varphi}{d}.$$

Thus

$$0 \leq T + I \leq \frac{\varphi}{d}.$$

Next,

$$\frac{dP}{dt} = kI - cP - \xi AP - \omega RP \leq kI - cP.$$

Since

$$I \leq \frac{\varphi}{d},$$

we obtain

$$\frac{dP}{dt} \leq \frac{k\varphi}{d} - cP.$$

Therefore

$$\limsup_{t\to\infty} P(t) \leq \frac{k\varphi}{cd}.$$

Similarly,

$$\frac{dA}{dt} = s_1 I + s_2 P - \mu A$$

implies

$$A(t) \leq \frac{1}{\mu}\left(\frac{s_1\varphi}{d} + \frac{s_2 k\varphi}{cd}\right).$$

Also,

$$\frac{dR}{dt} = \rho I + \sigma P - \delta_R R$$

gives

$$R(t) \leq \frac{1}{\delta_R}\left(\frac{\rho\varphi}{d} + \frac{\sigma k\varphi}{cd}\right).$$

Hence all solutions remain bounded.

3.3 Invariant Region

Define

$$\Omega = \left\{(T, I, P, A, R) \in \mathbb{R}^5_+ : T + I \leq \frac{\varphi}{d}\right\}.$$

Theorem 2. *The region Ω is positively invariant and attracting.*

Proof. The positivity and boundedness results imply that every trajectory entering Ω remains in Ω for all future time.

Hence Ω is positively invariant.

□

3.4 Local Stability of the Disease-Free Equilibrium

The disease-free equilibrium is

$$E_0 = \left(T^0, I^0, P^0, A^0, R^0\right) = \left(\frac{\varphi}{d_T}, 0, 0, 0, 0\right).$$

To investigate local stability, we linearize system (1) about E_0.

The Jacobian matrix of system (1) is

$$J = \begin{pmatrix} -d_T - \tau P & 0 & -\tau T & 0 & 0 \\ \tau P & -d_I - \phi A - \psi R & \tau T & -\phi I & -\psi I \\ 0 & k & -c - \xi A - \omega R & -\xi P & -\omega P \\ 0 & s_1 & s_2 & -\mu & 0 \\ 0 & \rho & \sigma & 0 & -\delta_R \end{pmatrix}.$$

Evaluating at E_0 yields

$$J(E_0) = \begin{pmatrix} -d_T & 0 & -\tau T^0 & 0 & 0 \\ 0 & -d_I & \tau T^0 & 0 & 0 \\ 0 & k & -c & 0 & 0 \\ 0 & s_1 & s_2 & -\mu & 0 \\ 0 & \rho & \sigma & 0 & -\delta_R \end{pmatrix}.$$

Since the matrix is block triangular,

$$\lambda_1 = -d_T, \qquad \lambda_2 = -\mu, \qquad \lambda_3 = -\delta_R.$$

The remaining eigenvalues are obtained from

$$\begin{vmatrix} -d_I - \lambda & \tau T^0 \\ k & -c - \lambda \end{vmatrix} = 0.$$

Hence

$$(d_I + \lambda)(c + \lambda) - \tau k T^0 = 0.$$

Expanding,

$$\lambda^2 + (d_I + c)\lambda + (cd_I - \tau k T^0) = 0.$$

The Routh–Hurwitz criterion requires

$$d_I + c > 0,$$

and

$$cd_I - \tau k T^0 > 0.$$

Since

$$T^0 = \frac{\varphi}{d_T},$$

we obtain

$$cd_I > \frac{\tau k \varphi}{d_T}.$$

Equivalently,

$$\frac{\tau k \varphi}{c d_T d_I} < 1.$$

Therefore,

$$R_0 < 1.$$

Thus all eigenvalues possess negative real parts.

Theorem 3. *The disease-free equilibrium*

$$E_0 = \left(\frac{\varphi}{d_T}, 0, 0, 0, 0 \right)$$

is locally asymptotically stable whenever

$$R_0 < 1,$$

and unstable whenever

$$R_0 > 1.$$

Proof. The proof follows directly from the Routh–Hurwitz criterion applied to the characteristic polynomial above. □

3.5 Global Stability of the Disease-Free Equilibrium

Theorem 4. *If*

$$R_0 < 1,$$

then the disease-free equilibrium is globally asymptotically stable in Ω.

Proof. Consider the Lyapunov function

$$V = I + \frac{\tau T^0}{c} P.$$

Clearly,

$$V > 0$$

for

$$(I, P) \neq (0, 0),$$

and

$$V = 0$$

only at the disease-free equilibrium.
Differentiating along solutions of system (1),

$$\dot{V} = \dot{I} + \frac{\tau T^0}{c} \dot{P}.$$

Substituting the model equations,

$$\begin{aligned} \dot{V} =& \tau T P - d_I I - \phi A I - \psi R I \\ &+ \frac{\tau T^0}{c} \left(k I - c P - \xi A P - \omega R P \right). \end{aligned}$$

Since

$$T \leq T^0,$$

we obtain

$$\begin{aligned} \dot{V} \leq& \tau T^0 P - d_I I + \frac{\tau k T^0}{c} I - \tau T^0 P \\ =& \left(\frac{\tau k T^0}{c} - d_I \right) I. \end{aligned}$$

Using

$$R_0 = \frac{\tau k T^0}{c d_I},$$

gives

$$\dot{V} = d_I(R_0 - 1)I.$$

Hence

$$\dot{V} \leq 0$$

whenever

$$R_0 < 1.$$

Furthermore,

$$\dot{V} = 0$$

implies

$$I = 0.$$

Substituting $I = 0$ into the parasite equation gives

$$P = 0.$$

Consequently,

$$A = 0, \qquad R = 0.$$

The largest invariant set contained in

$$\{\dot{V} = 0\}$$

is therefore

$$E_0.$$

By LaSalle's Invariance Principle,

$$(T, I, P, A, R) \to E_0$$

as

$$t \to \infty.$$

Therefore the disease-free equilibrium is globally asymptotically stable.

□

3.6 Derivation of the Basic Reproduction Number

The basic reproduction number, denoted by R_0, is one of the most important threshold quantities in infectious disease modeling. Biologically, it represents the average number of newly infected red blood cells generated by a single infected red blood cell during its infectious lifetime when introduced into a completely susceptible environment.

For the within-host malaria model, the basic reproduction number determines whether malaria parasites can successfully invade and establish infection within the host.

3.6.1 Identification of Infected Compartments

Following the next-generation matrix approach of van den Driessche and Watmough (2002) [25], we identify the infected compartments. The infected state variables are $I(t)$ and $P(t)$, where $I(t)$ represents infected red blood cells, $P(t)$ represents free malaria parasites. Thus we define

$$X = \begin{pmatrix} I \\ P \end{pmatrix}.$$

The remaining variables T, A, R are regarded as uninfected or auxiliary compartments.

3.6.2 Disease-Free Equilibrium

At the disease-free equilibrium,

$$I = P = A = R = 0.$$

The healthy red blood cell equation becomes

$$\frac{dT}{dt} = \varphi - d_T T.$$

Setting

$$\frac{dT}{dt} = 0,$$

gives

$$T^0 = \frac{\varphi}{d_T}.$$

Hence the disease-free equilibrium is

$$E_0 = \left(\frac{\varphi}{d_T}, 0, 0, 0, 0\right).$$

3.6.3 Construction of the Matrices F and V

The infected subsystem is

$$\frac{dI}{dt} = \tau TP - d_I I - \phi AI - \psi RI,$$

$$\frac{dP}{dt} = kI - cP - \xi AP - \omega RP.$$

Following the next-generation method, each equation is written as

$$\dot{X} = F(X) - V(X),$$

where $F(X)$ contains the appearance of new infections, $V(X)$ contains all transfers and removals.

New Infection Terms The only process creating newly infected red blood cells is

$$\tau TP.$$

Therefore,

$$F(X) = \begin{pmatrix} \tau TP \\ 0 \end{pmatrix}.$$

The Jacobian matrix of F evaluated at the disease-free equilibrium is

$$F = \left[\frac{\partial F_i}{\partial X_j}\right]_{E_0}.$$

Computing the partial derivatives gives

$$F = \begin{pmatrix} 0 & \tau T^0 \\ 0 & 0 \end{pmatrix}.$$

Substituting

$$T^0 = \frac{\varphi}{d_T},$$

yields

$$F = \begin{pmatrix} 0 & \frac{\tau\varphi}{d_T} \\ 0 & 0 \end{pmatrix}.$$

Transition Terms The remaining terms are

$$V(X) = \begin{pmatrix} d_I I \\ cP - kI \end{pmatrix}.$$

The Jacobian matrix of V evaluated at E_0 becomes

$$V = \begin{pmatrix} d_I & 0 \\ -k & c \end{pmatrix}.$$

3.6.4 Inverse of V

The determinant of V is

$$|V| = cd_I.$$

Hence

$$V^{-1} = \frac{1}{cd_I} \begin{pmatrix} c & 0 \\ k & d_I \end{pmatrix}.$$

3.6.5 Next-Generation Matrix

The next-generation matrix is

$$K = FV^{-1}.$$

Thus

$$K = \begin{pmatrix} 0 & \tau T^0 \\ 0 & 0 \end{pmatrix} \frac{1}{cd_I} \begin{pmatrix} c & 0 \\ k & d_I \end{pmatrix}.$$

Performing the multiplication,

$$K = \begin{pmatrix} \dfrac{\tau k T^0}{cd_I} & \dfrac{\tau T^0}{c} \\ 0 & 0 \end{pmatrix}.$$

Substituting

$$T^0 = \frac{\varphi}{d_T},$$

gives

$$K = \begin{pmatrix} \dfrac{\tau k \varphi}{cd_T d_I} & \dfrac{\tau \varphi}{cd_T} \\ 0 & 0 \end{pmatrix}.$$

3.6.6 Spectral Radius

The eigenvalues of K are

$$\lambda_1 = \frac{\tau k \varphi}{cd_T d_I},$$

and

$$\lambda_2 = 0.$$

The spectral radius is therefore

$$\rho(K) = \max\left\{ \frac{\tau k \varphi}{cd_T d_I}, 0 \right\}.$$

Hence the basic reproduction number is

$$R_0 = \frac{\tau k \varphi}{cd_T d_I}.$$

3.6.7 Biological Description of the R_0

The expression R_0 has a clear biological interpretation. The numerator $\tau k\varphi$ contains factors that promote infection, such as: τ: infection rate of healthy red blood cells, k: parasite production rate from infected cells, φ: recruitment rate of healthy red blood cells. An increase in any of these parameters increases the number of newly infected cells generated and therefore increases R_0. The denominator cd_Td_I contains factors that suppress infection. These are c: natural parasite clearance rate, d_T: natural turnover rate of healthy red blood cells, d_I: death rate of infected red blood cells. Increasing any of these parameters decreases the parasite's ability to establish infection and therefore reduces R_0.

3.6.8 Threshold Dynamics

The threshold quantity R_0 completely determines the invasion potential of malaria parasites.

1. If $R_0 < 1$, each infected red blood cell produces less than one secondary infected cell on average. The infection cannot invade and eventually dies out.
2. If $R_0 = 1$, the system is at a critical threshold separating disease extinction from persistence.
3. If $R_0 > 1$, each infected red blood cell generates more than one secondary infected cell. The parasite population grows and infection becomes established within the host.

This implies, $R_0 = 1$ serves as the fundamental bifurcation threshold governing malaria persistence.

3.6.9 Role of Autophagy and Immune Response

It is noteworthy that the autophagy parameters ϕ, ξ, s_1, s_2, μ and the immune-response parameters ψ, ω, ρ, σ, δ_R do not appear explicitly in the formula for R_0.

This occurs because autophagy and immune responses are activated only after infection has appeared. At the disease-free equilibrium, $A^0 = 0, \qquad R^0 = 0$.

Consequently, these defense mechanisms do not affect the initial invasion threshold but play a crucial role in determining the magnitude of infection, parasite burden, and stability of the endemic equilibrium once infection becomes established.

4 Discussion and Conclusion

The mathematical model developed in this study describes the within-host dynamics of malaria infection in the presence of two important host-defense mechanisms, namely autophagy and immune response. The model captures the interactions among healthy red blood cells, infected red blood cells, free malaria parasites, autophagic activity, and activated immune effector cells. By incorporating both cellular degradation pathways and immune-mediated parasite clearance, the model provides a more comprehensive representation of the biological processes involved in malaria progression than classical within-host malaria models.

The qualitative analysis established that the model is biologically and mathematically well posed. The positivity of solutions guarantees that all state variables remain nonnegative for all future time whenever nonnegative initial conditions are prescribed. This result is important since negative populations of cells or parasites or immune components is meaningless. Moreover, the boundedness analysis revealed that all solutions are bounded and eventually enter the positively invariant and biologically reasonable region. Therefore, the model has biologically reasonable long-term behavior and it is very suitable to investigate the analysis of malaria infection within the host.

The most important result of this section is the formula for the basic reproduction ratio R_0. This threshold quantity represents the average number of newly infected red blood cells produced in the lifetime of an infected red blood cell, at the beginningof the- infection. In biological terms, R_0 measures the ability of an infection of malaria parasite to establish itself in a host. Parasite invasion is favored by the infection rate τ, the parasite production rate k, and the healthy red blood cellrecruitment- rate φ, since all of those parameters increase the number of offspring produced by an infected cell over its lifetime.

In the denominator of R_0, we find the parasite clearance rate c, the death rate of healthy erythrocytes d_T, and the death rate of infected erythrocytes d_I. All of these parameters serve to reduce parasite production and make infection establishment less likely. Thus, biological or clinical mechanisms that act to promote parasite clearance or decrease the life span of infected erythrocytes can be important in controlling the disease.

The disease-free equilibrium E_0 corresponds to a biologically reasonable state in which there are no infected red blood cells, parasites, autophagy, or immune cells present in the system.. Its local stability

analysis revealed that E_0 is locally asymptotically stable whenever $R_0 < 1$. This means that malaria parasites cannot successfully invasion the host when their reproductive potential is sufficiently low. When $R_0 < 1$, a small introduction of parasites in the system eventually disappears, and the host returns to a parasite-free state.

The global analysis strengthened this result by proving that the disease-free equilibrium is globally asymptotically stable whenever $R_0 < 1$.The biological implication of this result is very important: it shows that the eventual eradication of infection does not depend on the initial parasite challenge. No matter how many parasites the host is exposed to, the infection cannot be sustained when the reproductive potential of parasites is less than one. This result indicates that drug interventions should primarily aim to bring R_0 below one, by decreasing parasite infectivity or reproduction or increasing parasite clearance.

When $R_0 > 1$, the disease-free equilibrium loses stability and a positive endemic equilibrium appears. The endemic equilibrium corresponds to a persistent infection state, in which healthy erythrocytes, infectederythrocytes, parasites, autophagy, and immune response are all present in the system. It captures the biological reality of long-term malaria infection, in which parasite reproduction is perpetually checked by host responses but infection is not fully cleared.

One major advancement of the current model is the inclusion of authophagy as a dynamic variable. Here, the presence of authophagy is captured in the variable $A(t)$, and is stimulated by infected red blood cells and parasite burden. Autophagy is assumed to aid in infection elimination viatwo- main mechanisms: first, autophagy promotes the destruction of infected erythrocytes via the nonlinear term ϕAI. Second, autophagy enhances parasite clearance through ξAP. These terms capture the experimentally observed role of autophagy in eliminating intracellular pathogens and infected host cells.

The model predicts that autophagy functions as a natural negative feedback mechanism. As infection intensifies, increasing levels of infected cells and parasites stimulate greater autophagic activity through the activation terms $s_1 I$ and $s_2 P$. The resulting increase in autophagic activity subsequently suppresses parasite growth by enhancing parasite destruction and infected-cell clearance. Thus, autophagy acts to stabilize the system and reduce infection severity.

An equally important component of the model is the immune response represented by the variable $R(t)$. The immune response is activated by infected cells and free parasites through the stimulation terms ρI and σP.

Activated immune cells contribute to parasite control through two additional clearance mechanisms, ψRI and ωRP, which represent immune-mediated destruction of infected erythrocytes and free parasites, respectively. The inclusion of both autophagy and immune response allows the model to capture synergistic interactions between different host-defense systems. Instead of being systemically positioned as immune cells are, autophagy is an intracellular cleaning mechanism. These defensive mechanisms work in a coordinated manner as is observed in the biology to prevent the overexpansion of the pathogen. We see that the model encapsulates the biological reality that often more than one defensive mechanism are required to provide a robust defense against malaria.

It is also clear that there is no influence of the autophagic or immune response parameters on R_0, since these defensive mechanisms only become activated after infection has already set in. Indeed, at the disease-free equilibrium, $A = 0, \qquad R = 0$.

Therefore, it is only the parasite's infectivity and survivability rates that contribute to initial invasion. However, autophagy and immunity can strongly affect the persistence of infection and the level of the endemic equilibrium. It seems that with stronger levels of autophagy and immune response, the parasite load, recovered erythrocytes, and the detrimental effects on the mouse should all decrease.

From a clinical perspective, the model highlights potential therapy strategies, specifically to increase autophagy in order to clear out more infected erythrocytes and parasites. Inducing immune response may also help in clearing the parasite and lowering infection and its related symptoms. Perhaps combinatorial therapies will be more effective than targeting the parasite alone.

The model results are consistent with increasing experimental evidence that cell-specific defensive mechanisms are important for host success, and that autophagy may be a useful future target for host modulating therapies. By implementing autophagy and immune response into a single model, we have added to the biological understanding of these processes during malaria infection.

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