We adapt a simple model of predator-prey to the population involved in a crisis of malaria. The study is made only in the stream blood inside the human body except for the liver. Particularly we look at the dynamics of the malaria parasites “merozoites” and their interaction with the blood components, more specifically the red blood cells (RBC) and the immune response grouped under the white blood cells (WBC). The stability analysis of the system reveals an important practical direction to investigate as regards the ratio WBC over RBC since it is a fundamental parameter that characterizes stable regions. The model numerically presents a wide range of possible features of the disease. Even with its simplified form, the model not only recovers well-known results but in addition predicts possible hidden phenomenon and an interesting clinical feature a malaria crisis.
1 Introduction

The malaria is mainly a tropical disease. It was formerly more spread in the world but it has been eradicated in Europe [1, 2] and in a big part of central and south of America since 1950 [3]. The malaria principally touches, nowadays, the tropical and subtropical regions and the majority sub-Saharan Africa countries. Currently, 40% of the world-wide population, mostly living the poorest countries, are exposed to this blight. Moreover the disease touches equally tourists. About 3% of them return infected from an infected zone. Each year, malaria is responsible for more than 300 million cases of sharp diseases and for at least a million deaths. The economic growth of countries with strong malaria transmission has always been less than that of countries spared by the malaria. Malaria therefore hinders seriously the economic development. Today it is known that in Africa, malaria is, at the same time, an illness of poverty and a reason of poverty. Malaria can represent up to 40% of the expenses of public health, 30 – 50% of hospital admission and up to 50% of (ambulant) external consultations. For these reasons, some economists attribute the annual deficit growth to malaria which reaches up to 1.3% in certain countries. The financial weight of malaria is huge. Malaria costs, in Africa, more than 12 billion $US a year in loss of Gross Domestic Product. In the short term, some socio-economic consequences of the malaria are:

- The loss of working time (sick leave, days of hospitalization and recovery).
- The expenses in the treatment and prevention.
- The economic losses due to infantile mortality and morbidness.
- Anemia on the children and the adults, leading to exposure to blood transfusions diseases and viruses, such as HIV-AIDS, of Hepatitis C, etc.
- Negative influences on the child’s physical, cognitive and decreasing development, hence affecting his scholastic performances due to repetitive episodes of malaria.

Intensive studies have been done to understand and cure malaria so as to overcome the educational, economic and human damages caused by the disease. In particular, it was found that malaria is caused by a unicellular parasite called plasmodium [4]. The parasite is transmitted from one person to another by the bites of a female mosquito called anopheles that needs blood for its subsistence. The blood is then an important component for the transmission and the development of the plasmodium. Once inside the human body, the plasmodium migrates to the liver and after a certain period of multiplication and transformations, it gives rise to the viral agents called the merozoites. A great number of works investigated the dynamical expansion of the disease in a given region [5]. Attention was mostly focused on the interaction between mosquitoes and the human population. Very little investigation was done on the dynamic of populations inside the human organism [6, 7, 8]. In particular McQueen et al. [6] focused on the observation that three
of the four malaria-parasite species that infect humans are restricted to particular age classes of red blood cells (RBC). They have found that age structuring has profound effects on the course of infection [7]. Tumwiine et al. [8] considered an intra-host model for the dynamics of malaria, using an ordinary differential system of four equations to describe the dynamics of the blood stage malaria parasites and their interaction with host cells (RBC and immune effectors). They established the equilibrium points of the system and analyzed their stability using the theory of competitive systems, compound matrices and stability of periodic orbits. They found that in the presence of the immune response, the numerical analysis of the model shows that the endemic equilibrium is unstable. In what follows, we first describe our model in which only three equations are used instead of four or more equations and then we present the results of our investigation on the dynamic study of species that are merozoites, RBC, and white blood cells (WBC).

2 Model and analysis

There are four types of plasmodium that are pathogenic for humans: The plasmodium falciparum which is the most lethal and guilty form, the plasmodium vivax, the plasmodium malariae and the oval plasmodium. The falciparum and vivax are the most current ones. The whole cycle of the plasmodium which involves mosquitoes is not discussed in this work neither do we take into account the plasma part of the blood. We are mainly concerned with the evolution of merozoites inside the human body. We shall recall that blood is a living tissue that circulates through the heart, arteries, veins, and capillaries, carrying nourishments, electrolytes, hormones, vitamins, antibodies, heat, and oxygen to the body’s tissues. The mission of transporting the oxygen and dispatching it through the organism is indebted to RBC because of the hemogloblin, a complex iron-containing protein that carries oxygen. RBC will act as prey of merozoites while WBC grouping all immune factors which are responsible for protecting the body from invasion by foreign substances such as bacteria, fungi, and viruses, represent predators for merozoites. The following simplest predator-prey system is considered as the model:

\[
\begin{align*}
\dot{r} &= c_r(n_r - r) - d_r m r + \frac{c_r m k^l r}{1 + a m^k r} \\
\dot{w} &= c_w(n_w - w) + \frac{c_w m k^w}{1 + b m^k w} \\
\dot{m} &= (c_m r - d_m w) m 
\end{align*}
\]

The first equation of the system gives the temporal evolution of RBC per \( mm^3 \) of blood. \( n_r \) is the normal amount of RBC for a person in good health. We consider mean values because some blood parameters including \( n_r \) vary with age, sex, and the living region (the altitude for example) of the person. \( c_r \) and \( d_r \) are the proliferation and death coefficients of RBC, respectively. Note that the latter coefficient also includes the weak coefficient of over-manufacturing RBC due to invasion. The second equation of the above system denotes the dynamic of WBC per \( cm^3 \) of blood; \( n_w \) being the normal amount of WBC. Most of them are produced in the bone marrow from the same
kind of stem cells that produce RBC. Although they outnumber RBC by two to one, it is found that in the blood stream, there are about 600 RBC for every WBC. This might be due to the fact that on one hand they occur elsewhere in the body as well, most notably in the spleen, liver, and lymph glands; on the other hand, the blood might have and remain approximately constant with a given concentration of constituents. Obviously, the \( n_w \) parameter varies as that of RBC previously mentioned. The WBC proliferation coefficient \( c_w \) will be taken in this work as one per cent of \( n_r \), the normal amount of RBC. \( c_{wm} \) is the coefficient of over-manufacturing WBC due to the invasion. It will be considered very small but not negligible. Typically, we choose it from \([0.8 - 2\%]\) of \( c_w \). These numerical values of \( c_w \) and \( c_{wm} \) are chosen to fit and to be in agreement with the well-known common results. Without lost of the general point of view, we set for simplicity \( k \) and \( n \) equal to 1 and also, \( c_{rm}, a \) and \( b \) equal to zero. The last equation of the system describes the merozoites population as basically predators for RBC but preys from the WBC point of view. The creation and death coefficients, \( c_m \) and \( d_m \) respectively, varies not only with the type of plasmodium but also with the host characteristics. In some cases, the crisis of malaria can be provoked by more than one type of plasmodium at the same time and for this reason, the previously mentioned coefficients might be time-dependent. However, without loss of generality, we consider them as constant.

The stability analysis of the system of equations in (1) gives two cases. The first case corresponds to a healthy person with no plasmodium inside the body. We derived \( m_0 = 0 \), \( r_0 = n_r \) and \( w_0 = n_w \). We found this solution stable for the following condition

\[
\frac{c_m}{d_m} < \frac{n_w}{n_r} \tag{2}
\]

The second case corresponds to a person living with the parasite in the blood. This leads to the following relations

\[
w_0 = \frac{c_m}{d_m} r_0 = \alpha_m r_0 \\
r_0 = \frac{\alpha_m c_r c_{wm} n_r + c_w d_r n_w}{\alpha_m (c_r c_{wm} + c_w d_r)} \\
m_0 = c_r \left( \frac{n_r}{r_0} - 1 \right)/d_r \tag{3}
\]

In this case, \( m_0 \) can be either positive or negative. However it is nonsense negative values for the steady state and this case must not be considered as solution. \( m_0 \) is positive because the number of RBC \( r_0 \) starts to decrease since there is an invasion and then will remain less than the normal amount \( n_r \) for a person in good health.

The stability of this stationary solution is determined by the roots of the polynomial

\[
\lambda^3 + c_2 \lambda^2 + c_1 \lambda + c_0 = 0 \tag{4}
\]

with the coefficients expressed as follows

\[
c_2 = -(a + b + c); c_1 = ab + ac + bc + c_m r_0 m_0 (c_{wm} - d_r); \\
c_0 = -abc + c_m r_0 m_0 (ad_r - bc_{wm})
\]
where \( a = - (c_r + d_r m_0) \), \( b = c_{wm} m_0 - c_w \), and \( c_m r_0 - d_m w_0 \).

From the Routh-Hurwitz analysis, it is obvious that there exists stable as well as unstable domains depending on the choice of parameters. As previously mentioned, \( c_m \) and \( d_m \) could depend on the host genetic profile. It is well known that people with sickle cell trait who possess one gene for normal hemoglobin and one gene for sickle hemoglobin have different resistance on malaria than people with only normal hemoglobins and those with only sickled hemoglobins [9-14]. Moreover, due to constant mutations of the malaria parasite, their parameters are involved to possible changes. We fix \( c_r = 50/24 h^{-1} \), \( d_r = 1/70 h^{-1} \) and \( c_m = 30/70 h^{-1} \). From relation (2), we consider the following expression \( d_m = \mu c_m n_r/n_w \) where \( \mu \) is a constant. Figures 1 and 2 show in the black zones the admitted values of \( n_r \) and \( n_w \) for stable solutions found in Eq.(3) for \( \mu = 3 \) and \( \mu = 4 \), respectively. For these values of \( \mu > 1 \), it is important to realize that both possible steady solutions of the model are stable. The blank spaces marked “A” represent the domains in which only one of the three real parts of eigenvalues in Eq.(4) is negative while the blank spaces marked with “B” do not admit solution in Eq.(3) with \( d_m \) fixed as above.

In general, during the crisis, the blasting of the ripe schizonts ends the first schizogonic erythrocyte cycle by liberating in the blood, with the waste of the plasmodial metabolism (pigments and cell rubbish), a new generation of plasmodiums, erythrocyte merozoites (a ripe schizont liberates after blasting 8 to 35 merozoites). The blasting of schizonts ripe corresponds to bouts of fever which might be the maximum of merozoites density since they are synchronized. Every cycle lasts between 48 and 96 hours according to the type of plasmodium. Then regular successions of similar cycles follow. Hence the 96 first hours are crucial for the crisis since we are investigating without the use of medicine. In addition to the different possible cases commonly known, i.e. the complete reestablishment of the patient for the best case, anemia, or also the death in the worse case [15, 16] which can be due to severe anemia, we found that the coexistence of the malaria parasite in the blood with a normal life (values of RBC and WBC being in a reasonable range) is also possible. Figure 3 presents a case of coexistence with few amounts of merozoites. The values of \( n_r \) and \( n_w \) are chosen around the frontier of the “A” region and the stability zone but \( \mu \) is no more greater than unity. Using this value of \( \mu < 1 \), one should realize that the condition of stability of the first steady state solution is no longer verified. The observed oscillations attenuate with time around the equilibrium point.

### 3 Conclusion

From a very simplified model of three equations, instead of four or more, we recovered commonly known phenomena in a malaria crisis, as well as a possible hidden phenomenon, and an interesting clinical feature to investigate from Eq.(2). One of the important results that our model exhibits is the coexistence of the viral agents together with other blood components in an equilibrium
This could be an explanation of some sudden crisis usually observed in residents of endemic regions who moved to a non-endemic region. With the global warming, it would be possible that such phenomenon increases the range of endemic areas in the world. Also, effects of their permanent presence in the body are still not totally known and these could be a source of many different health problems [17, 18]. The second important result of the present work is the clinical investigation that arises from Eq. (2). It would be important to find out the relation between the re-establishment of affected persons or longtime unaffected persons and the ratio \( n_w/n_r \). Our forthcoming studies will be on clinical investigation of the dynamics of \( c_m/d_m \) ratio and that of \( w/r \) since they are more accessible than \( n_w/n_r \) ratio, linked to the healthy patients’ state.

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References


Figure 1: Stable regions of steady state solutions from model equation for \( \mu = 3 \). The “A” mark denotes the region of only one real negative part from Eq.(4) while the “B” mark shows the portion where the two possible steady solutions cannot be found.

Figure 2: Same as Fig.1 but for \( \mu = 4 \).
Figure 3: Persistence life of merozoites in equilibrium with RBC and WBC. $\mu = 0.575$, $n_r = 5$ and $n_w = 8$. 