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Original Article

Predicting the duration of antimalarial treatment with heme degradation inhibitors of blood schizonticides using mathematical models

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Abstract

A mathematical model of the death rate of malaria parasite due to the antimalarial drugs is established in this paper to predict the treatment duration and the drug dosage. This model is based on probabilities, pharmacokinetics and pharmacodynamics (PK/PD), biology, medical sciences, theoretical physics and chemistry. The death rate of malaria parasite is derived from the flow rates of drug molecules to the malaria parasite by using the theory of blood convection and probabilities. Using the malaria model, numerical results are generated. In conclusion, the numerical estimate of treatment duration from our model ranges from 1 to 10 days, conforming to actual clinical data.

Keywords: malaria, death rate, probability

1. Introduction

For several thousand years, humans have suffered and been killed by various lethal diseases. Infectious diseases caused by pathogens such as bacteria, virus, protozoa (especially malaria) and fungi have caused much fatalities across the general population. In particular, the malarial disease is among the most lethal infectious diseases in human history (Li, Ruan & Xiao, 2011). Severity of the malarial disease is well documented in many countries, especially those in Africa and Asia (Centers for Disease Control and Prevention [CDC], 2016). Malaria is an infectious and contagious disease caused by the specific protozoa called *Plasmodium*. There are 5 species in the genus *Plasmodium* that can infect humans, namely *P.vivax, P. ovale, P. malariae, P. falciparum* and *P. knowlesi.* All these are transmitted by the female *Anopheles* mosquitoes (Li, Ruan, & Xiao, 2011). In order to treat the patients with malarial infection, physicians have tried to administer various antimalarial drugs and use clinical trials to collect data on the duration of treatment by drug. Furthermore, each patient's blood samples must be sent to a laboratory to evaluate the pathogen density, and the treatment has to be monitored continuously before calling off the intravenous or oral drug administration. Therefore, an effective mathematical model to predict the termination time of the treatment is the main focus of this study.

The pathophysiology of malaria in human body consists of two cycles: sexual and asexual cycles. After a female *Anopheles* mosquito bites and releases sporozoites in her saliva into human bloodstream, the sporozoites will travel via bloodstream and enter the liver. Once there, the germ will invade the hepatocytes or liver cells, replicate itself and leave the liver cells to infect healthy red blood cells (RBCs). This intracellular malaria parasite in infected red blood cells (iRBC) then develops into various stages: early to late trophozoite and early to late schizont, sequentially. During the late schizont stage, the intracellular parasites, which are called merozoite, will be released by ruptureof the iRBCcell membrane (Li, Ruan, & Xiao, 2011).They will spread throughout

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the bloodstream and infect new healthy RBCs. This process is known as the asexual cycle. While the parasites are in the iRBCs, they need to extract heme from hemoglobin in cytoplasm of the RBCs and convert it into hemozoin or malarial pigment. The process is vital to the parasites since heme is water-soluble and toxic to them, while water-insoluble hemozoin is not. Thus, one of the methods to get rid of the parasite is to inhibit this process. Our study will focus only on the anti-malarial drugs that target the hemozoin or heme degradation inhibition (ter Kuile *et al.*, 1993; Wilairatana & Looareesuwan, 1996).

There is a prior mathematical model pertaining to the population of the normal within-host malaria parasites, by Austin, White, and Anderson (1998). However their model does not take into account of the effects of drug treatment. In this paper, we will incorporate the drug treatment effects on the population of malaria parasites. The main idea is that blood flow will transfer the drug molecules tobind iRBCs, and therefore eliminate the iRBCs (Figure 1). Nevertheless, to translate this real situation into mathematical models, some assumptions and hypotheses are needed, along with fundamental physics, chemistry, microbiology and pharmacology. The following assumptions and hypotheses were made: (i) the collision or binding rate between drug molecule and iRBC depends on their relative velocity, (ii) probability of binding or capturing between drug molecule and iRBC depends on five factors, derived from theoretical physics and chemistry, (iii) the drug is effective in the sense that under right conditions one drug molecule can annihilate one iRBC, and (iv) the plasma level of the drug is constant (time-independent). Hence, the formulation of this mathematical model is based on various scientific disciplines. For instance, the relative velocity and convective rate, which are used to construct the flow rate of drug for eliminating malaria parasite, are based on physics. Also knowledge from chemistry and pharmacology are needed for plasma concentration of the drug. Moreover, the mathematical model of within-host malaria is derived from the pathology of malaria. Incorporating all these factors should support creating an accurate model of the death rate of malaria parasite.

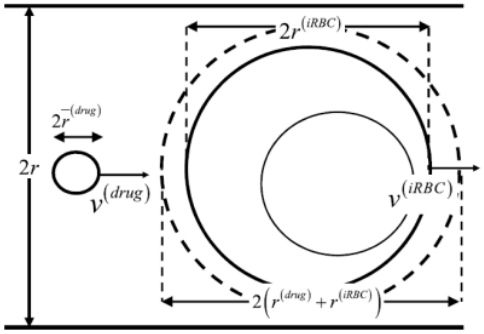

Figure 1. The transportation of the drug molecule to an intracellular parasite within infected red blood cell (iRBC) by convection with the bloodstream

First, the shape of drug molecules is assumed to be spherical instead of prolate spheroid, as shown in Figure 1, and we will estimate the average radius of the drug molecule as follows. Define $r_w^{(drug)}$ and $r_l^{(drug)}$ to be the half width and half length of the prolate spheroidal shape of a drug molecule. Next, we evaluate an average radius for this drug molecule (Pabst & Gregorová, 2007), as the geometric mean of $r_w^{(drug)}$ and $r_l^{(drug)}$. Thus, the average radius of drug molecule in (Brinkman, 1949; Pabst & Gregorová, 2007), called Stokes radius and denoted by $r^{(stoke)}$, can be derived from its prolate volume $V^{(prolate)}$ in terms of $r_w^{(drug)}$ and $r_l^{(drug)}$ as follows.

$$V^{(sphere)} = V^{(prolate)},$$

$$\frac{4}{3}\pi\left(r^{(stoke)}\right)^3 = \frac{4}{3}\pi r_l^{(drug)}\left(r_w^{(drug)}\right)^2,$$

$$r^{(stoke)} = \left(r_l^{(drug)}\left(r_w^{(drug)}\right)^2\right)^{1/3},$$

Similar to the case of a particle diffused in a fluid such as oil, we model the diffusion of drug molecules and iRBC in the bloodstream accordingly.Therefore, as illustrated in Figure 1, the average radius of a drug molecule, defined as $\bar{r}^{(drug)} = \left(r_l^{(drug)}\left(r_w^{(drug)}\right)^2\right)^{1/3}$, can be written in the similar form as $r^{(stoke)}$.

Before estimating the death rate of the malaria parasite due to the drug, it is important to note the pathogenesis of the malaria and how the antimalarial drug mechanisms work. The purpose of heme degradation in *Plasmodium sp.* is to eliminate heme by converting water-soluble and toxic heme into water-insoluble and nontoxic substances, called hemozoin or malarial pigmentthat can be excreted (de Villiers & Egan, 2009). This study focuses on chloroquine, mefloquine and halofantrine as the antimalarial drugs that use heme degradation inhibition by binding iron (Fe(II)) in Fe(II)-protoporphyrin IX (Fe(II)PPIX or heme). On the other hand, we also useartesunate of the artimisinin group of antimalarial drugs,which inhibits heme degradation without binding Fe(II)PPIX. The mechanism of artesunate has not yet been clearly understood, but there is strong evidence that either intraparasitic ferrous heme and free ferrous iron will convert artesunate into free radicals by cleaving the artesunate's peroxide bridge. Afterward, these intraparasitic free radicals would eliminate the parasite by destroying the lipid layer of the parasitic cell membrane, the vacuole sac, and other parasitic structures such as parasitic enzymes. As parasitic enzymes convert water-soluble toxic hemes (Fe(II)-protoporphyrin IX (Fe(II)PPIX)) into excretable hemozoins (heme crystals (Fe(III) PPIX)) in the vacuole sac are destroyed, the heme degradation are inhibited. When the vacuole sac ruptures, free radicals are released and therefore destroy the parasites (ter Kuile *et al.*, 1993; Wilairatana & Looareesuwan, 1996).

2. Materials and Methods

This section reviews the contents of each subsection that will be used to formulate the death rate model of the malaria parasites due to drug. First, we discuss the relative velocity of drug molecule and iRBC, based on theoretical physics, which we use to find the specific blood volume that contains the particulate drug mass to kill the parasite. Second, five probabilistic binding factors of drug molecule with iRBC

that we will use to determine the effective drug molecules will be discussed. The five probability factors are (i) position probability factor used to determine binding chance by position alignment between drug and iRBC, (ii) binding probability factor of the drug molecule and intracellular parasite, but not the iRBC's cytoplasm, (iii) capture probability factor which is the ability of drug to transport and does not deviate from target, (iv) orientation probability factor which is the probability of local collision between the drug and iron molecules in heme, (v) population probability factor is the ability of the drug molecule to attach only to iRBC, but not the normal RBC. Since the five probability factors are sequentially continuous and independent, they can be multiplied to give the total probability factor. In order to use the total probability factor to evaluate the effectiveness of the drug molecules, we need to compute the mass of the drug. To do so, we have to convert the specific blood volume derived from the relative velocity into drug mass by using the plasma drug concentration while taking into account parameters of chemistry, such as Avogadro's number and molecular mass as well. Consequently, we are able to calculate the total drug molecules within all capillaries and venules of the human host. Note that the death rate of malaria parasites due to the drug is the same as the death rate of the iRBC's, since we consider only the blood schizonticides. Finally, by decreasing the dynamic population of iRBCs in normal malaria model with our death rate caused by the drug, we then predict the duration of treatment by numerical simulations, as shown in Figure 2.

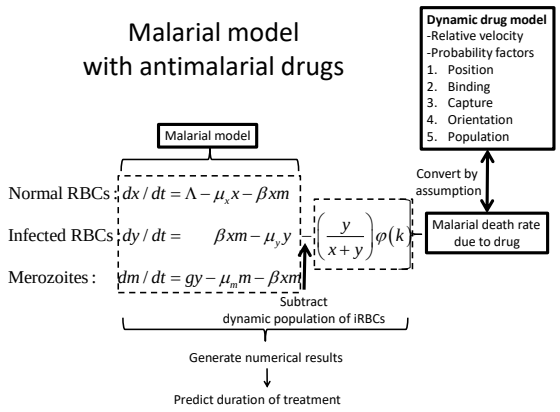

Figure 2. Flow chart for estimating the death rate of malaria parasites killed by a drug, using five probability factors and the relative velocity of drug molecule and parasite, to predict required duration of treatment.

2.1 Relative velocity of drug molecule and infected red blood cell

According to physical principles, since iRBC is larger than a drug molecule, the velocity of iRBC is slower than that of a drug molecule, i.e. $v^{(iRBC)} < v^{(drug)}$ (Agasanapura, Baltus, & Chellam, 2011), where $v^{(iRBC)}$ and $v^{(drug)}$ are the velocities of iRBC and drug molecule, respectively. Define $v^{(relative)} = v^{(drug)} - v^{(iRBC)}$ to be the relative velocity of drug and iRBC. After time t, the vasculature length traversed by the drug molecule is $tv^{(relative)}$. Now, $v^{(iRBC)}$ and $v^{(drug)}$ can be obtained using a local lag coefficient (denoted by G) (Agasanapura, Baltus, & Chellam, 2011), $v^{(iRBC)} = G^{(iRBC)}v^{(blood)}$ and $v^{(drug)} = G^{(drug)}v^{(blood)}$, where $G^{(drug)}$ and $G^{(iRBC)}$ are two local lag coefficients for drug and iRBC, respectively. Note that $G^{(drug)} > G^{(iRBC)}$. Hence, the relative velocity is

$$v^{(relative)} = v^{(drug)} - v^{(iRBC)} = \left(G^{(drug)} - G^{(iRBC)}\right)v^{(blood)}$$

2.2 Position probability factor

The collision of drug molecules and iRBCs can be modeled by modifying the probabilistic model of ship grounding in (Mazaheri, 2009), traveling straight through a waterway in a straight line. In this study, iRBCs are assumed to be stationary and act as obstacles or shoals, waiting for drug molecules to bind. The width of waterway corresponds to the diameter of vasculature. We generalize this approach from one dimension (1D) to 2D. By our assumptions, iRBC's are spherical as shown in Figure 1. Since the positions of drug molecule and iRBC have been already aligned, the position probability factor is defined as

$$p^{(position)} = \frac{\pi\left(r^{(iRBC)} + \bar{r}^{(drug)}\right)^2}{\pi r^2} = \left(\frac{r^{(iRBC)} + \bar{r}^{(drug)}}{r^{(vessel)}}\right)^2$$

where $r^{(vessel)}$ is the radius of a human blood vessel in its cross-section.

2.3 Binding probability factor

In 2007, Preetam Ghosh had his doctoral dissertation concerning Stochastic Models for In-silico Event-based Biological Network Simulation (Preetam, 2007). They used some probability theory to calculate the chance of binding between a protein molecule and DNA. This suggests that the probability of collision between protein molecule and DNA during time Δt is $p^{(binding)} = \frac{\delta V}{V}$. ,where δV is a collision volume. In this work, after an antimalarial drug molecule enters iRBC with position probability factor, it must also enter an intracellular parasite to bind heme and inhibit heme degradation. Consequently we define the total volume of iRBC and the volume of an intracellular parasite as $V^{(iRBC)}$ and $V^{(parasite)}$, respectively. Note that $V^{(parasite)}$ is the collision volume analogous to δV in (Preetam, 2007). Hence, for the antimalarial drug molecule to attach and eliminate the parasite, the binding probability factor is estimated as

$$p^{(binding)} = \frac{\delta V}{V} = \frac{V^{(parasite)}}{V^{(iRBC)}}.$$

Note that the binding probability factor and the parasite volume fraction in (Ye *et al.*, 2013), used in our numerical simulation, are the same.

2.4 Capture probability factor

Before determining the position and binding probability factors, the transportation of drug molecule can

deviate from the target iRBC. The larger the distance between drug molecule and iRBC is, the lower is the chance of binding. Hence, the capture probability in (Berg & Purcell, 1977) was estimated as

$$p^{(capture)} = \frac{r^{(iRBC)}}{r^{(iRBC)} + l},$$

and is used in the current model, with l the length of a human blood vessel.

2.5 Orientation probability factor

In chemistry, two substrates bind together only when correctly oriented to make the binding sites meet (Taroni, Jones, & Thornton, 2000). Thus, the orientation probability factor, defined as the probability that binding site of substrate attaches to an active site of enzyme, is the ratio of binding area to total surface area on the drug molecule

$$p^{(orientation)} = \frac{\pi z^2}{4} / \left\{ 2\pi \left(r_w^{(drug)} \right)^2 \left(1 + \frac{r_w^{(drug)}}{e r_l^{(drug)}} \sin^{-1} e \right) \right\}$$

The binding area ($\frac{\pi z^2}{4}$) is assumed circular with diameter z, and the total surface area of a drug molecule, which is a prolate spheroid, is $2\pi \left(r_w^{(drug)} \right)^2 \left(1 + \frac{r_w^{(drug)}}{e r_l^{(drug)}} \sin^{-1} e \right)$, where e is the eccentricity of the ellipse.

2.6 Population probability factor

Since both normal RBCs and iRBCs can be met by a drug molecule, the population probability factor

$$p^{(population)} = \frac{y(t)}{x(t) + y(t)},$$

is used to correct the probability so it is for the iRBCs only, where $x(t)$ and $y(t)$ are the populations of normal RBCs and iRBCs at time t, respectively.

2.7 Total probability

We have five independent probability factors for the binding chance between a drug molecule and iRBC. These are for position, binding, capture, orientation and population effects. The total probability factor is then

$$p^{(total)} = p^{(position)} \times p^{(binding)} \times p^{(capture)} \times p^{(orientation)} \times p^{(population)}.$$

2.8 Mathematical model of malaria

Our study uses the mathematical model of malaria in (Austin, White, & Anderson, 1998). This model has three dynamic populations: infected red blood cells (iRBCs), population of normal or uninfected red blood cells, and extracellular parasites or merozoites, denoted by $y = y(t)$, $x = x(t)$ and $m = m(t)$, respectively. The model is given by

$$dx/dt = \Lambda - \mu_x x - \beta x m,$$
$$dy/dt = \beta x m - \mu_y y,$$
$$dm/dt = g y - \mu_m m - \beta x m,$$

where μ_x, μ_y and μ_m are the natural death rates of uninfected RBCs, infected RBCs and merozoites, Λ is the production rate of normal RBCs, β is the infectivity of merozoites, and g is the number of merozoites released per infected RBCs (the parameter values are shown in Table 1).

Table 1. Parameters of chloroquine, mefloquine, halofantrine and artesunate.

Drug	r_l(nm)	r_w(nm)	M	α	k (ng/ml)	References
Chloroquine	0.7856	0.35525	319.8721	0.45	120	(Karbwang *et al.*, 1992; White, 1992)
Mefloquine	0.6333	0.33765	378.3122	0.02	500-638	(White, 1992)
Halofantrine	0.86655	0.427	500.4237	0.02	1000	(Veenendaal *et al.*, 1991; White, 1992)
Artesunate	0.7619	0.37065	384.4208	0.38	110-310	(Ashton *et al.*, 1998; Morris *et al.*, 2011)

2.9 Dynamic drug model

Our model to estimate the death rate of malaria parasite in this paper takes into account of both capillaries and venules. The death rate can be modeled in the following steps: (i) evaluate the number of drug molecules attaching to parasites per unit time (ii) use the assumption that the drug is effective in the sense that under the right conditions one drug molecule can annihilate one iRBC's cell. First we compute the amount of drug from the knowledge of the plasma drug concentration, in a specific blood volume. This specific blood volume is similar to the collision volume, which is explained in the binding probability factor of the previous section. The blood volume must be considered in all the vessels, the count of which is denoted by $N^{(vessel)}$.. Thus, if the cross-sectional area of a vessel is $\pi \left(r^{(vessel)} \right)^2$ and the length that blood volume sweeps over time t is $v^{(relative)} t$, then the total blood volume is $\pi \left(r^{(vessel)} \right)^2 N^{(vessel)} v^{(relative)} t$. Therefore, drug mass in this particular volume at time t can be calculated by multiplying with the plasma drug concentration at time t, denoted by $C(t)$. We can convert this drug mass into the number of drug molecules by dividing by the molecular mass of the drug M, and multiplying with Avogadro's number A. Since parasite elimination occurs in all vessels, the total number of drug molecules at time t, denoted by $N^{(drug)}$, is $N^{(drug)} = \pi \left(r^{(vessel)} \right)^2 C(t) A v^{(relative)} t / M$. Now we take into account the probabilistic chance of binding for effective elimination of the parasites as follows: (a) Obtain the interval

of time that drug molecules can follow parasites from the proportion of time in vessels, called transit time and denoted by τ, and the circulatory time, denoted by ρ. (b) Obtain the drug molecules that are not bound to any target by using the free fraction of drug, denoted by α. (c) multiply with the total probability factor as before. (d) divide by the total blood volume of patient, denoted by $V^{(blood)}$. Finally, convert $N^{(drug)}$ into the rate by dividing by t.

The death rate of the malaria parasites in this paper can be estimated as shown in Figure 3 with the parameters in Table 2. Note that the death rate is considered both in capillaries and in venules.

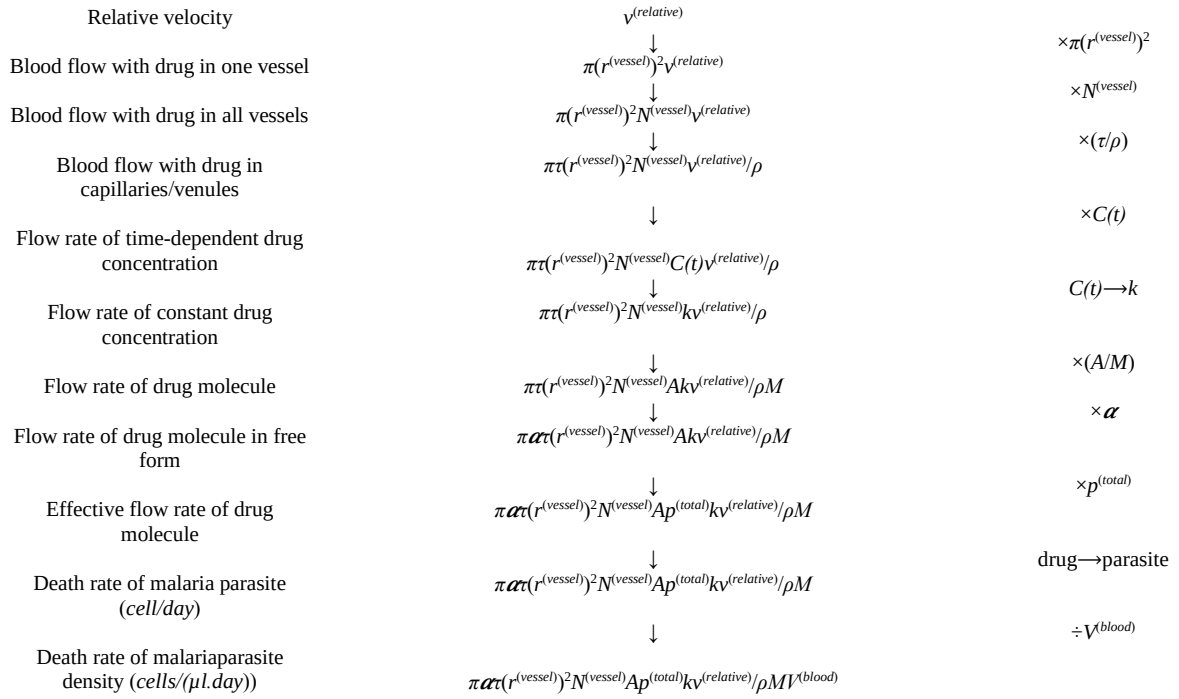

Figure 3. This diagram shows estimating the decay rate of malaria parasite density.

Table 2. Parameters for numerical simulations in case of malarial infection.

Symbol	Value	Variable	References
$G^{(drug)}$	1	lag coefficient of drug in capillary and venule	(Agasanapura, Baltus, & Chellam, 2011)
$G^{(iRBC)}$	0.6,0.9	lag coefficient of iRBC in capillary and venule, respectively.	(Agasanapura, Baltus, & Chellam, 2011)
$x(0)$	5×10^6	initial normal density of normal RBCs ($cells/\mu l$)	(Li, Ruan, & Xiao, 2011)
Λ	4.15×10^4	production rate of RBCs ($cells/\mu l/day$)	(Li, Ruan, & Xiao, 2011)
$r^{(RBC)}$	3.9	radius of RBC (μm)	(Ye *et al.*, 2013)
$r^{(iRBC)}$	3.9	radius of iRBC (μm)	(Ye *et al.*, 2013)
$V^{(iRBC)}$	86-116	volume of iRBC (μm^3)	(Ye *et al.*, 2013)
$\delta^{(iRBC)}$	0.03-0.8	parasite volume fraction	(Ye *et al.*, 2013)
g	12	product rate of merozoites ($/day$)	(Li, Ruan, & Xiao, 2011)
β	2×10^{-9}	infective rate ($\mu l/cell.day$)	(Li, Ruan, & Xiao, 2011)
μ_x	8.3×10^{-3}	decay rate of RBCs ($/day$)	(Li, Ruan, & Xiao, 2011)
μ_y	1	decay rate of iRBCs ($/day$)	(Li, Ruan, & Xiao, 2011)
μ_m	48	decay rate of merozoites ($/day$)	(Li, Ruan, & Xiao, 2011)
$m(0)$	10^4	initial density of merozoites ($cells/\mu l$)	(Austin, White, & Anderson, 1998; Li, Ruan, & Xiao, 2011)
ρ	60	blood circulatory time (s)	(Dilsizian, & Pohost, 2010)
$r^{(capillary)}$	3	radius of capillary (μm)	(Khurana, 2006)
$r^{(venule)}$	10	radius of venule (μm)	(Khurana, 2006)
τ	1	transit time (s) of capillary and venule	(Khurana, 2006)
l	200,50-500	Length (μm) of capillary and venule, respectively.	(Radivoj, & Krstic, 1997)
$v^{(blood)}$	0.3,4	blood velocity (mm/s) in capillary and venule, respectively.	(Khurana, 2006; Vosse van de, & van Dongen, 1998)
N	10^9,10^7	number of capillaries and venule, respectively.	(Pollak, 2005)
$V^{(blood)}$	5	whole blood volume (liters)	(Higgins *et al.*, 2009)
$X(t_0)$	10^5	parasite density in blood att_0	(Ali *et al.*, 2008; White, 2011)
A	6.02×10^{23}	Avogadro's number	(Staver, & Lumpe, 1993)
ε	40-50	Ratio of drug efflux in case of resistant parasite to susceptible parasite	(Schlesinger, & Herwaldt, 1988)

Hence, the death rate of the malaria parasites will be estimated as:

$$\Psi(t) = \frac{\pi\alpha N^{(vessel)}\tau\left(r^{(vessel)}\right)^2 C(t)Ap^{(total)}v^{(relative)}}{\rho MV^{(blood)}}.$$

Moreover, since antimalarial drug molecules can follow infected red blood cells in both capillaries and venules, the total death rate of the malaria parasites is:

$$\Psi^{(total)}(t) = \Psi^{(capillary)}(t) + \Psi^{(venule)}(t).$$

Note that by one of our assumptions, the anti-malarial drug with intravenous administration maintains a constant plasma drug concentration. Consequently, the flow rate of drug molecules depends only on the constant drug concentration *k*. Therefore, the flow rate of drug molecules $\Psi(k)$, which is time-independent, is used instead of $\Psi(t)$. Before generating numerical results, dynamic variables *x* and *y* in the population probability factor are extracted from $\Psi^{(total)}(k)$. If we define

$$\varphi(k) = \Psi^{(total)}(k) / p^{(population)} = \left(\frac{x+y}{y}\right)\Psi^{(total)}(k),$$

then, the death rate of malaria parasite is $\Psi^{(total)}(k) = \left(\frac{y}{x+y}\right)\varphi(k)$. This shows us that there is no the death rate of malaria parasite when there is no parasitaemia, i.e. $\Psi^{(total)}(k) \to 0$ as $y \to 0$. This matches the real situation.

Finally, the mathematical model of within-host malaria parasite after antimalarial drug administration becomes

$$dx/dt = \Lambda - \mu_x x - \beta xm,$$
$$dy/dt = \beta xm - \mu_y y - \left(\frac{y}{x+y}\right)\varphi(k),$$
$$dm/dt = gy - \mu_m m - \beta xm.$$

3. Results and Discussion

This section discusses numerical results for the antimalarial drugs: artesunate, chloroquine, mefloquine and halofantrine, in the cases of monotherapy, drug resistance and combination therapy. These numerical calculations used the parameters given in Tables 1 and 2. The first subsection on monotherapy shows numerical results for artesunate, chloroquine, mefloquine and halofantrine. Furthermore, we are using clinical data from White (2011) to compare with our numerical results, shown in Figure 4. The second subsection on drug resistance has numerical results for the four drugs coupled with resistance, shown in Figure 5. The third subsection on combination therapy has numerical results for chloroquine, mefloquine and halofantrine with resistance to them and in artemisinin-based combination therapy or ACT, shown in Figure 5.

3.1 Monotherapy

Since most parameters of *Plasmodium sp.*, such as physical structure (length, width, etc.) and biological data (growth, death, infective and merozoite-releasing rate) are quite similar, this study will treat all *Plasmodium sp.* as one case. To match our numerical results with the real situation, we use parasite clearance curves from White (2011), shown in Figure 4(a) and 4(b), which represent the real world. Figure 4(a) shows two parasite clearance curves of *P. falciparum* with the same treatment, showing time profiles of parasite density. Figure 4(b) shows normalized parasite clearance curves of *P. falciparum*, i.e. parasitaemia versus time, in patients with artesunate therapy in Western Cambodia and Western Thailand.

Figure 4(c), 4(d), 4(e) and 4(f) are numerical results for artesunate, chloroquine, mefloquine and halfantrine, respectively. These four figures show parasite density versus time post-admission (i.e., days of treatment). After numerical simulation, the duration of treatment and the clearance time of parasitesfor chloroquine, mefloquine, halofantrine and artesunate are quite similar. First, although each drug has its therapeutic plasma drug concentration, the treatment durations in our results are within the range from 1 to 10 days, as shown in Figure 4(c)-4(f), which are realisticby comparison with Figure 4(a) and 4(b). Second, the responses to the four drugs are linear and similar to the real information in Figure 4(a). Observe that although the average plasma drug concentrations in Figure 4(c)-4(f) are widely different, the duration of treatment from the simulations is within the range from 1 to 10 days. The reason is that most physicians intend to finish the treatment of malarial infection within one week, to prevent transition into severe or complicated malaria. Observe that clearance of parasite time formefloquine and halofantrine, shown in Figure 4(d) and 4(e), is longer than for chloroquine shown in Figure 4(f), despite the fact that mefloquine and halofantrine are more recent drugs than chloroquine. In fact, there is evidence of chloroquine resistance in *Plasmodium*. Thus, this study also includes numerical results for the case of drug resistance, in the next subsection.

3.2 Drug resistance

There are many ways that the malaria parasites can develop drug resistance. There is strong evidence that the malaria parasite cells can increase drug efflux (Sinha, Medhi, & Sehgal, 2014). However, resistance of *Plasmodium sp.* develops only for some specific drugs. For instance, chloroquine-resistant *P. vivax* exists only in a few countries, such as Papua New Guinea, Indonesia, Burma (Myanmar), India, and Central and South America (CDC, 2016). At present, there is no evidence of chloroquine resistance in *P. ovale*, *P. Malariae* and *P. knowlesi* (CDC, 2016). Furthermore, *P. falciparum* also may resists other non-quinoline groups, such as mefloquine and halofantrine (de Villiers & Egan, 2009). This study uses the drug efflux mechanism in the simulations. Thus, an additional assumption that all *Plasmodium species* resist the drugs in this study, except for artemisinin, is needed. We consider the case of drug resistance by assigning the ratio of drug effluxes from resistant and susceptible parasites, denoted by ε (see this value in Table 2). This parameter ε is applied by

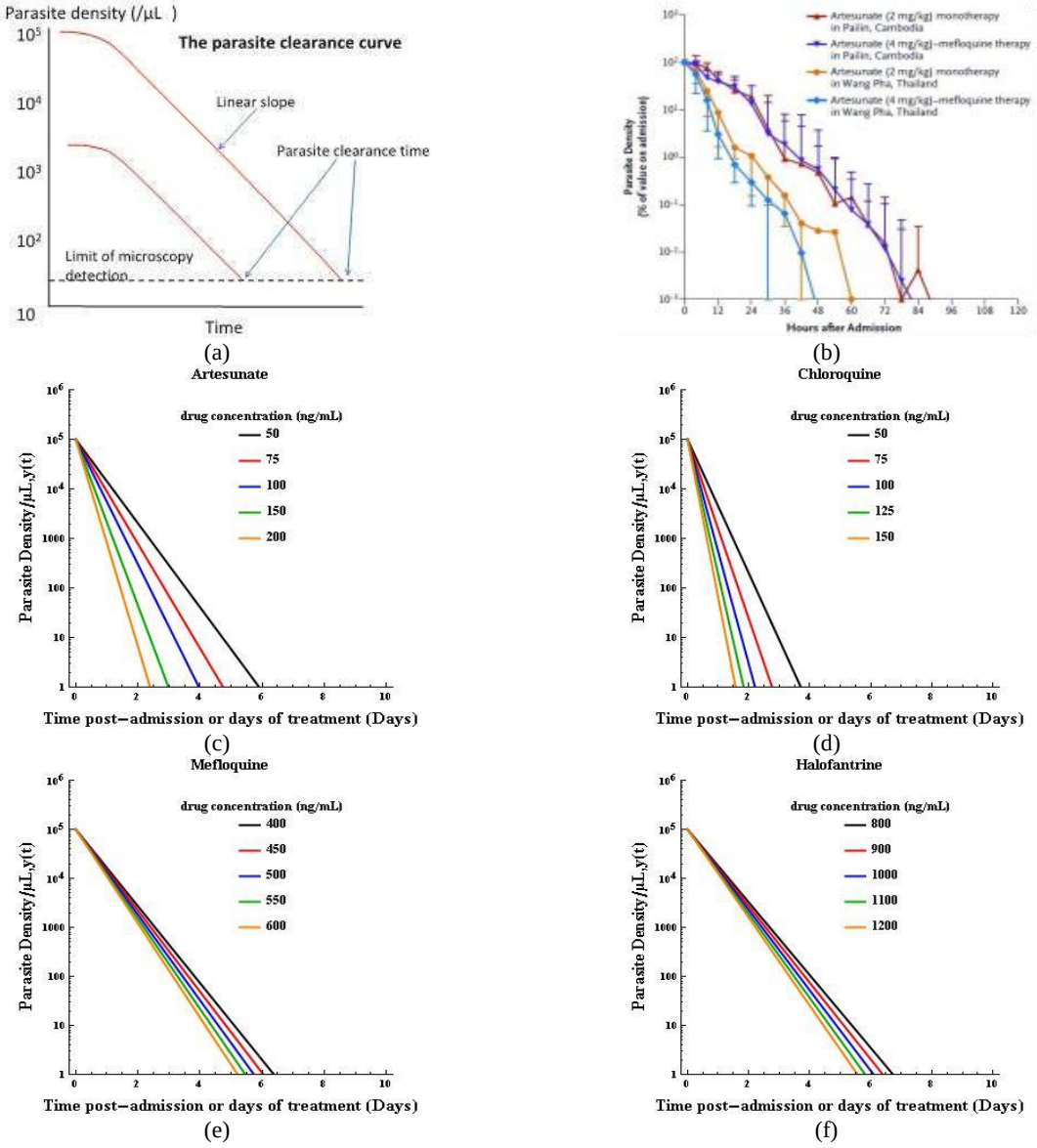

Figure 4. Comparison between real patient data(White, 2011) , shown in Figure 4(a) and 4(b) , and our numerical results for artesunate, chloroquine, mefloquine and halofantrine, shown in Figure 4(c), 4(d), 4(e) and 4(f), respectively.

dividing with the death rate of malaria parasites, so that the death rate with drug resistance becomes $\left(\frac{y}{x+y}\right)\frac{\varphi(k)}{\varepsilon}$. Note that after incorporating in the death rate the drug resistance ε, the treatment durations in Figure 5(a) , 5(c) and 5(e) are prolonged beyond those in normal cases. This shows us that the model for resistance conforms with reality. Clearly drug resistance can affect the duration of treatment.

3.3 Combination therapy

This study also considers the combination therapies where chloroquine, mefloquine and halofantrine are co-applied with artesunate, called artemisinin-based combination therapies or ACT. Before generating numerical results, the death rate of the malaria parasites due to the combination therapy is estimated by partial summation of the death rates in each drug combination. The death rate of malaria parasites in the case of ACT is $\left(\frac{y}{x+y}\right)\left(\frac{\varphi^{(drug)}(k)}{\varepsilon}+\varphi^{(artesunate)}(k)\right)$, where $\varphi^{(drug)}(k)$ is the death rate from use of chloroquine, mefloquine or halofantrine, and $\varphi^{(artesunate)}(k)$ is the death rate from artesunate. In simulations, the duration of treatment for clearance of the parasite in Figure 5(b) , 5(d) and 5(f) is shortened from that in Figure 5(a), 5(c) and 5(e) for chloroquine, mefloquine or halofantrine, respectively.

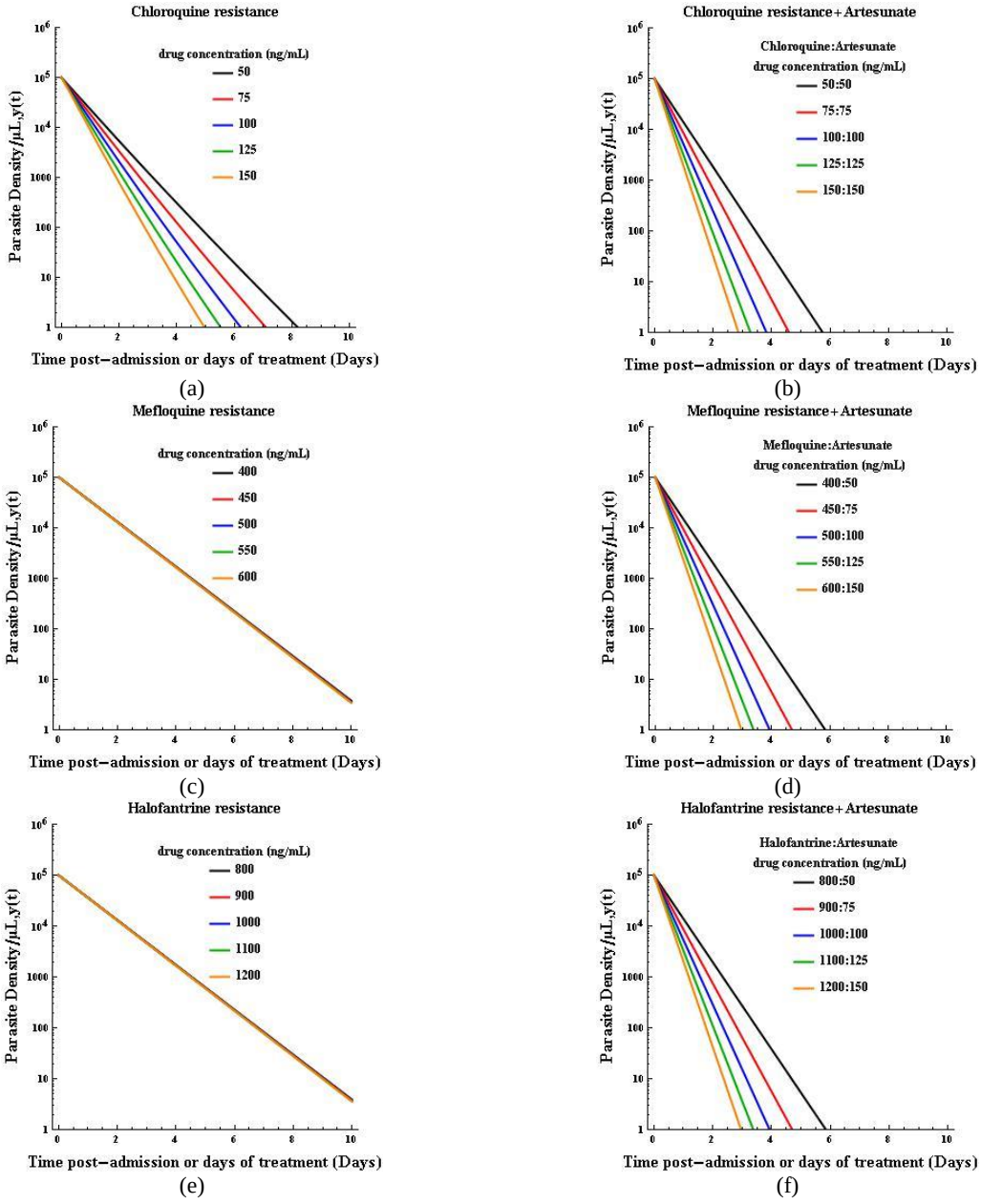

Figure 5. Numerical results forchloroquine, mefloquine and halofantrine with developed drug resistance, and for artesunate-based combination therapy (ACT).

4. Conclusions

The numerical simulations with our model illustrate that the duration of treatment, or the period needed to eliminate the infected red blood cells, is 1-10 days, which matches clinical data. Thus, the assumptions in this study, which incorporate the pathophysiology of malaria within the host in five probability factors derived from physics and chemistry for estimating effectiveness of drugs, pharmacokinetics and pharmacodynamics for effects of plasma drug concentration and the population of malaria parasites, are compatible with the real world situation. Furthermore, this approach is quite simple and effective in predicting the duration of treatment from only initial parasite density in the patient's blood, without requiring continuous monitoring of the patient's blood, since the other parameters for dynamic changes are already available.Finally, we hope that our model could be used to estimate the antimalarial drug dosage to treat patients.

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