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On the estimation of sequestered parasite population in falciparum malaria patients

Derdei Bichara*, Nathalie Cozic*, Abderrahman Iggidr*

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Abstract: The aim of this paper is to give an estimation of total parasitological burden of the patient and the rate of infection β in a malaria's intra-host model by using control theory tools.

Key-words: intra-host model, observers, estimation, Plasmodium falciparum, age-structured model

* Inria-Nancy Grand Est & University of Lorraine. LMAM(UMR CNRS 7122), Metz, France.

**RESEARCH CENTRE
NANCY – GRAND EST**

615 rue du Jardin Botanique
CS20101
54603 Villers-lès-Nancy Cedex

On the estimation of sequestered parasite population in falciparum malaria patients

Résumé : L'objectif de ce papier est de donner une estimation de la charge parasitaire totale d'un patient à partir de sa charge parasitaire périphérique. On donne aussi une méthode d'estimation du taux d'infection β dans un modèle intra-hôte du paludisme en utilisant les outils de la théorie du contrôle.

Mots-clés : modèles intra-hôte, observateurs, estimation, Plasmodium falciparum, modèles structurés en classes d'âge

1 Introduction

Malaria is a disease that causes at least one million deaths around the world each year, with ninety per cent among African children. The most deadly malaria is caused by the most virulent strain of parasite *Plasmodium*: The *Plasmodium falciparum*. The intra-host models describe the dynamic of interaction of parasite(virus, specie,...) into the host(human being, environment,...). These models have been used to understand the evolution of *Plasmodium Falciparum* into the host. An abundant literature has been dedicated to malaria's intra-host model [1, 5, 12, 13, 14] and the references therein. See [16] for a review. The most papers are, in the whole, related to the seminal Anderson, May and Gupta's model [1] which is the 3 dimensional system:

$$\begin{cases} \dot{x} = \Lambda - \mu_x x - \beta x m \\ \dot{y} = \beta x m - \mu_y y \\ \dot{m} = r \mu_y y - \mu_m m - \beta x m \end{cases} \quad (1)$$

where x is the concentration of uninfected erythrocytes in the blood, y is the concentrations of the infected erythrocytes, and m the concentration of free merozoites. Parameters μ_x , μ_y and μ_m are the death rates of the uninfected erythrocytes, infected parasites and free merozoites respectively. The parameter β is the contact rate between RBC and merozoites. Uninfected blood cells are recruited at a constant rate Λ from the bone marrow and have a natural life-expectancy of $1/\mu_x \times$ days. Death of an infected erythrocyte results in the release of an average number of r merozoites. Free merozoites die or successfully invade a healthy erythrocyte. For the epidemiology of malaria, we refer to [1, 19].

As we can see in (1), the dynamic of the infected erythrocytes is described by one differential equation. However, experimental analysis has shown that the dynamic of *Plasmodium falciparum* might change according to its "age". Hence, a model, where the dynamic of the healthy cells is coupled with an age-structured model for the infected cells and the dynamic of free merozoites, has been considered [12, 5]:

$$\begin{cases} \dot{x} = \Lambda - \mu_x x - \beta x m \\ \dot{y}_1 = \beta x m - \alpha_1 y_1 \\ \dot{y}_2 = \gamma_1 y_1 - \alpha_2 y_2 \\ \dots \\ \dot{y}_n = \gamma_{n-1} y_{n-1} - \alpha_n y_n \\ \dot{m} = r \gamma_n y_n - \mu_m m - \beta x m \end{cases} \quad (2)$$

In practice, to know a patient's stage of infection, the total parasite concentration $\sum_{i=1}^n y_i$ in the bloodstream is needed. The exact number of stage of infected cells that leads to the maturation of the infected cells is unknown. According to [4] there are five main stages: young ring, old ring, trophozoite, early schizont and finally late schizont.

However, only the peripheral infected RBC (young parasites), also called circulating, can be observed (can be seen on peripheral blood smears) and the other ones, hided in some organs like brain and heart, are called sequestered. There is no clinical method of measuring those sequestered infected cells.

Also, if the different parameters in (2) can be estimated by biological considerations, the parameter β which is the Red Blood cells (RBC)'s rate of infection is hardly known. In fact, in [16], the authors claimed that the parameter β cannot be estimated directly and that any estimation of β depends on \mathcal{R}_0 and growth rate.

The estimation of sequestered parasite population have been a challenge for biologist and modeler. Many authors [18, 8, 6] have studied this problem. In this paper, we propose a different

and simple method to estimate the total parasite concentration from the measured circulating parasites and we show how the parameter β can be estimated. To this end, we use some control theory's tools. More precisely, we built an observer, i.e: an auxiliary dynamical system whose states tend exponentially to the states of the original system (2). Moreover, this auxiliary system does not depend on the badly known parameter β . The notion of disturbance which allow us to decouple the β from the auxiliary system, is well known in control theory to avoid problems of modeling such as nonlinearities, noise in measurement and so forth [10, 11].

2 Design of the observer

We suppose that the parasitized erythrocytes population within the host is divided in 5 different stages: y_1, y_2, y_3, y_4, y_5 . The two first stages correspond to the concentration of free circulating parasitized erythrocytes and the three last stages correspond to the sequestered ones. Let x be the concentration of healthy cells, and m the concentration of merozoites. The healthy cells x are produced by a constant recruitment Λ from the thymus and they become infected by an effective contact with merozoite m . At the late stage of infected cells, they blow up and release r merozoites. The model that we consider is the following:

$$\begin{cases} \dot{x} = \Lambda - \mu_x x - \beta x m \\ \dot{y}_1 = \beta x m - (\gamma_1 + \mu_1) y_1 \\ \dot{y}_2 = \gamma_1 y_1 - (\gamma_2 + \mu_2) y_2 \\ \dots \\ \dot{y}_5 = \gamma_4 y_4 - (\gamma_5 + \mu_5) y_5 \\ \dot{m} = r \gamma_5 y_5 - \mu_m m - \beta x m \end{cases} \quad (3)$$

The different parameters of this model are defined as follows:

- Λ : Recruitment of the healthy red blood cells (RBC).
- β : Rate of infection of RBC by merozoites.
- μ_x : Natural death rate of healthy cells.
- μ_i : Natural death rate of i -th stage of infected cells.
- γ_i : transition rate from i -th stage to $(i + 1)$ -th stage of infected cells.
- r : Number of merozoites released by the late stage of infected cells.
- μ_m : natural death rate of merozoites.

As suggested in [4], we suppose that we can measure the circulating parasitaemia, i.e: $y_1 + y_2$ and we want to find out an estimation of the sequestered parasitaemia, $y_3 + y_4 + y_5$. Here, we shall use some classical notations from control theory. Let $z(t)$ be the state at time t of the system (3), i.e., $z = (x, y_1, \dots, y_5, m) \in \mathbb{R}^7$. The measurable output of system (3) will be denoted by \mathcal{Y} . Here, the measurable output corresponds to the concentration of the circulating parasitized erythrocytes, and hence we have $\mathcal{Y}(t) = y_1(t) + y_2(t)$. System (3) can then be written as:

$$\dot{z} = Az + \beta x m E + \Lambda e_1 \quad (4a)$$

$$\mathcal{Y} = Cz \quad (4b)$$

where $z \in \mathbb{R}^7$, $y \in \mathbb{R}$ are the state vector, the disturbance and measurement, respectively. The matrices A , C , and E are defined as follows:

$$A = \begin{pmatrix} -\mu_x & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\mu_1 - \gamma_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & \gamma_1 & -\mu_2 - \gamma_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma_2 & -\mu_3 - \gamma_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & \gamma_3 & -\mu_4 - \gamma_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & \gamma_4 & -\mu_5 - \gamma_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & r\gamma_5 & -\mu_m \end{pmatrix},$$

$$E = \begin{pmatrix} -1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ -1 \end{pmatrix}, \quad e_1 = \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \quad \text{and} \quad C = (0, 1, 1, 0, 0, 0, 0)$$

The equation (4a) describes the dynamics of the system while equation (4b) gives information about what is measured.

The problem we are interested in is: how to use the dynamical model (4a) together with the information provided by the measurements (4b) in order to get estimates of the state variables that can not be measured? A solution to this problem can be provided by what is called in Control Theory an "observer". An observer is an auxiliary dynamical system which uses the information $\mathcal{Y}(t)$ provided by the system and which produces an estimate $\hat{z}(t)$ of the state $z(t)$ such that the estimation error $\hat{z}(t) - z(t)$ tends exponentially fast to zero as time t goes to infinity. An observer for system (4a-4b) can be given, for instance, by:

$$\begin{cases} \dot{\hat{w}} = f(\hat{w}, \mathcal{Y}) \\ \hat{z}(t) = g(\hat{w}(t)) \end{cases} \quad (5)$$

One has to find the functions f and g in such a way that the solutions $\hat{z}(t)$ of (5) and the solutions $z(t)$ of (4a) satisfy for all initial conditions $(\hat{z}(0), z(0))$:

$$\|\hat{z}(t) - z(t)\| \leq \exp(-\lambda t) \|\hat{z}(0) - z(0)\| \text{ for some positive real number } \lambda.$$

However, the construction of the observer requires the knowledge of all the parameters of the model. This is not the case for our system since the parameter β is unknown. Therefore we are going to consider the term $\beta x m$ appearing in the system (4a) as an unknown input and we shall use the notation: $d(t) = \beta x(t) m(t)$. With this, system (4a) can be considered as a linear system with unknown input $d(t)$ and can be written:

$$\begin{cases} \dot{z} = Az + \Lambda e_1 + d(t) E \\ \mathcal{Y} = Cz \end{cases} \quad (6)$$

Using some ideas from [11], we shall construct an estimator (observer) for system (6).

We define the matrix \bar{A} by

$$\bar{A} = (I_d - EC)A$$

where I_d denotes the identity matrix. For our system, we have

$$\bar{A} = \begin{pmatrix} -\mu_x & -\mu_1 & -\mu_2 - \gamma_2 & 0 & 0 & 0 & 0 \\ 0 & -\gamma_1 & \mu_2 + \gamma_2 & 0 & 0 & 0 & 0 \\ 0 & \gamma_1 & -\mu_2 - \gamma_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma_2 & -\mu_3 - \gamma_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & \gamma_3 & -\mu_4 - \gamma_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & \gamma_4 & -\mu_5 - \gamma_5 & 0 \\ 0 & -\mu_1 & -\mu_2 - \gamma_2 & 0 & 0 & r\gamma_5 & -\mu_m \end{pmatrix}.$$

It can be shown that the pair (\bar{A}, C) is detectable (see appendix) and hence there exists a column matrix $L = (l_1, l_2, \dots, l_7)^t \in \mathbb{R}^7$ such that the matrix $\bar{A} - LC$ is Hurwitz, i.e., all its eigenvalues are with negative real part. We can now give our main result.

Now we have all the ingredients to derive a method to dynamically estimate the state $z(t)$ of our system.

Theorem 2.1 *An exponential observer for system (6) is given by*

$$\begin{cases} \dot{w} = (\bar{A} - LC)w + \{(L + (\bar{A} - LC)E)\mathcal{Y} + \Lambda e_1 \\ \hat{z} = w + E\mathcal{Y} \end{cases} \quad (7)$$

This observer is inspired from [11]. One can remark that the computation of the estimates $\hat{z}(t)$ does not depend on the parameter β .

proof We prove that the estimation error $e(t) = \hat{z}(t) - z(t)$ converges exponentially towards zero. Indeed, we have

$$\begin{aligned} \dot{e} &= \dot{\hat{z}} - \dot{z} \\ &= \dot{w} + E\dot{\mathcal{Y}} - \bar{A}z - E\dot{\mathcal{Y}} - \Lambda e_1 \\ &= (\bar{A} - LC)w + \{(L + (\bar{A} - LC)E)\mathcal{Y} + \Lambda e_1 + E\dot{\mathcal{Y}} - \bar{A}z - E\dot{\mathcal{Y}} - \Lambda e_1 \\ &= (\bar{A} - LC)w + \{(L + (\bar{A} - LC)E)\mathcal{Y} - \bar{A}z \\ &= (\bar{A} - LC)(\hat{z} - E\mathcal{Y}) + \{(L + (\bar{A} - LC)E)\mathcal{Y} - \bar{A}z \\ &= (\bar{A} - LC)\hat{z} - (\bar{A} - LC)E\mathcal{Y} + L\mathcal{Y} + (\bar{A} - LC)E\mathcal{Y} - \bar{A}z \\ &= (\bar{A} - LC)\hat{z} + LCz - \bar{A}z \\ &= (\bar{A} - LC)(\hat{z} - z) \\ &= (\bar{A} - LC)e \end{aligned}$$

This shows that $\|e(t)\| \rightarrow 0$ with exponential convergence rate since all the eigenvalues of the matrix $\bar{A} - LC$ are with negative real part.

Remark 2.1 *The estimation method proposed in Theorem 2.1 is valid for arbitrary number n of age-classes.*

For our model with $n = 5$, we have

$$\bar{A} - LC = \begin{pmatrix} -\mu_x & -\mu_1 - l_1 & -\mu_2 - \gamma_2 - l_1 & 0 & 0 & 0 & 0 \\ 0 & -\gamma_1 - l_2 & \mu_2 + \gamma_2 - l_2 & 0 & 0 & 0 & 0 \\ 0 & \gamma_1 - l_3 & -\mu_2 - \gamma_2 - l_3 & 0 & 0 & 0 & 0 \\ 0 & -l_4 & \gamma_2 - l_4 & -\mu_3 - \gamma_3 & 0 & 0 & 0 \\ 0 & -l_5 & -l_5 & \gamma_3 & -\mu_4 - \gamma_4 & 0 & 0 \\ 0 & -l_6 & -l_6 & 0 & \gamma_4 & -\mu_5 - \gamma_5 & 0 \\ 0 & -\mu_1 - l_7 & -\mu_2 - \gamma_2 - l_7 & 0 & 0 & r \cdot \gamma_5 & -\mu_m \end{pmatrix}$$

The eigenvalues of $\bar{A} - LC$ are : $-\mu_x$, $-(\gamma_1 + \gamma_2 + \mu_2)$, $-(\mu_3 + \gamma_3)$, $-(\mu_4 + \gamma_4)$, $-(\mu_5 + \gamma_5)$, $-\mu_m$, and $-(l_2 + l_3)$. Therefore the matrix $\bar{A} - LC$ is stable provided that $l_2 + l_3 > 0$. Since the eigenvalues of $\bar{A} - LC$ do not depend on l_1 nor on l_i for $i = 4, \dots, 7$, we simply choose $l_1 = l_4 = l_5 = l_6 = l_7 = 0$.

Therefore the dynamical estimator (7) for $n = 5$ is given by

$$\begin{cases} \dot{w}_1 = -\mu_x w_1 - \mu_1 w_2 - (\mu_2 + \gamma_2) w_3 \\ \dot{w}_2 = -(\gamma_1 + l_2) w_2 + (\mu_2 + \gamma_2 - l_2) w_3 \\ \dot{w}_3 = (\gamma_1 - l_3) w_2 - (\mu_2 + \gamma_2 + l_3) w_3 \\ \dot{w}_4 = \gamma_2 w_3 - (\mu_3 + \gamma_3) w_4 \\ \dot{w}_5 = \gamma_3 w_4 - (\mu_4 + \gamma_4) w_5 \\ \dot{w}_6 = \gamma_4 w_5 - (\mu_5 + \gamma_5) w_6 \\ \dot{w}_7 = -\mu_1 w_2 - (\mu_2 + \gamma_2) w_3 + r \gamma_5 w_6 - \mu_m w_7 \\ \hat{z}_1 = w_1 - \mathcal{Y} \\ \hat{z}_2 = w_2 + \mathcal{Y} \\ \hat{z}_3 = w_3 \\ \hat{z}_4 = w_4 \\ \hat{z}_5 = w_5 \\ \hat{z}_6 = w_6 \\ \hat{z}_7 = w_7 - \mathcal{Y} \end{cases} \quad (8)$$

Thanks to this observer, one can compute easily $w(t)$ and then $\hat{z}(t)$ which tends exponentially fast to $z(t)$. Therefore one can get an estimate of the total parasitological burden $\sum_{i=1}^5 y_i(t)$.

3 Estimation of the rate of infection β

Let us consider the dynamic of y_1 , we have $\dot{y}_1 = \beta x m - (\gamma_1 + \mu_1) y_1$. By the variation of constants method, we can write:

$$y_1(t) = y_1(t_0) e^{-(\gamma_1 + \mu_1)(t-t_0)} + \beta \int_{t_0}^t x(s) m(s) e^{(\gamma_1 + \mu_1)(s-t)} ds$$

By replacing $x(t)$, $y_1(t)$ and $m(t)$ by their estimates states $\hat{x}(t)$, \hat{y}_1 and $\hat{m}(t)$, we have:

$$\hat{y}_1(t) = \hat{y}_1(t_0) e^{-(\gamma_1 + \mu_1)(t-t_0)} + \tilde{\beta} \int_{t_0}^t \hat{x}(s) \hat{m}(s) e^{(\gamma_1 + \mu_1)(s-t)} ds$$

Then

$$\hat{y}_1(t)e^{(\gamma_1+\mu_1)t} - \hat{y}_1(t_0)e^{(\gamma_1+\mu_1)t_0} = \tilde{\beta} \int_{t_0}^t \hat{x}(s)\hat{m}(s)e^{(\gamma_1+\mu_1)s} ds \quad (9)$$

If we discretize the segment $[t_0, t_{final}]$ in segments $[t_{i+1}, t_i]$, we will obtain:

$$\hat{y}_1(t_{i+1})e^{(\gamma_1+\mu_1)t_{i+1}} - \hat{y}_1(t_i)e^{(\gamma_1+\mu_1)t_i} = \tilde{\beta} \int_{t_i}^{t_{i+1}} \hat{x}(s)\hat{m}(s)e^{(\gamma_1+\mu_1)s} ds \quad (10)$$

For each i , let $U_i = \hat{y}_1(t_{i+1})e^{(\gamma_1+\mu_1)t_{i+1}} - \hat{y}_1(t_i)e^{(\gamma_1+\mu_1)t_i}$ and $V_i = \int_{t_i}^{t_{i+1}} \hat{x}(s)\hat{m}(s)e^{(\gamma_1+\mu_1)s} ds$. By numerical integration, we can compute, for each i , U_i and V_i . Thus, (10) can be written as:

$$U = \tilde{\beta}V$$

where U and V are vectors of appropriate dimension with U_i and V_i as components of U and V respectively.

Hence, by a linear regression, we can obtain $\tilde{\beta}$ which is a β 's estimation.

4 Application 1

In this section we show how our method to estimate the total parasitaemia from the peripheral infected cells that are measured can apply. By parasitaemia, we refer to the density of parasites in the blood. The measured parasitaemia are from data collected when malaria was used as therapy from neurosyphilis by the US Public Health Service at the National Institutes of Health laboratories in Columbia, South Carolina and Milledgeville, Georgia [2]. Patients were inoculated through mosquito bite or infected blood [2, 3]. Those data have been successfully used by many authors [2, 3, 7, 17] for different purposes concerning the parasite *Plasmodium falciparum*.

To apply our total parasitaemia estimation method, we choose data of four patients. These patients have been studied in [3] for the following reasons.

These reasons are the fact that these patients do not have any of the following features:

- (i) treatment with drugs reported to affect gametocytes (chloroquine, pyrimethamine, primaquine) or unknown drugs;
- (ii) super-inoculation with any malaria parasite in the course of the infection;
- (iii) parasitological status on the day before onset of curative treatment positive or uncertain;
- (iv) gametocyte counts never exceeding 100 μl (otherwise a reliable estimation of parameters would have been impossible);
- (iv) inoculation of a rarely used strain.

Those particular patients are relevant to our study because those patients did not have taken treatment with drugs reported to affect gametocytes [3] and then correspond with the choice of a low mortality rates of PRBC we have chosen here and in [4]. It remains to pick the different value of parameters. Among parameters in (3), some of them known or at least widely accepted. First, the infection rate β is unknown or hardly known, so our method here allows us to study the system without explicit using of β . With many classes, the most difficult task is how to choose the transition rates [4, 6] with the condition the sum of them (life-span of PRBCs) is 2 days. So, in this paper we use the transition and death rates from [4] for patients without fever,

i.e: at 37°C. Then we have:

i	Transition γ_i	Death rate μ_i
1	1.96	0
2	3.78	1.86
3	2.85	0
4	1.76	0.1
5	3.26	0

With these parameters, we will obtain $\sum_{i=1}^5 \frac{1}{\gamma_i + \alpha_i} = 1.9101065$ days, which is close to 2 days.

In this paper, the unit of concentration is micro-liter (μl) and the unit of time is day. The life span of healthy erythrocytes is 120 days [1, 7], so $\mu_x = \frac{1}{120}$ day⁻¹.

For the constant recruitment, we proceed as in [15], where the authors fixed the constant rate of erythrocytes' production at $\frac{5 \times 10^6}{120}$ cells $\mu l^{-1} day^{-1}$. This quantity is obtained from the parasite-free equilibrium state: $0 = \Lambda - \mu_x x_0$ where x_0 is the fixed concentration of RBC in adult males (absence of parasites!?) which is around 5×10^6 RBCs per μl .

Merozoite's life-span ($\frac{1}{\mu_m}$) is, according to [1], about 20 minutes, so $\mu_m = 72$ day⁻¹.

The number of merozoites released in the blood is between 8-32. So, we take here $r = 16$.

With these values, the choice l_2 and/or l_3 positive make the the matrix $\bar{A} - LC$ asymptotically stable. More precisely, with these values, the eigenvalues of the matrix $\bar{A} - LC$:

$$\text{Sp}(\bar{A} - LC) = \{-l_2 - l_3; -\mu_x; -\mu_m; -\mu_5 - \gamma_5; -\mu_4 - \gamma_4; -\mu_3 - \gamma_3; -\gamma_1 - \mu_2 - \gamma_2; \}$$

For the simulations we take $l_2 = l_3 = 5$. Here are different figures obtained through calculations:

Following the section 2 and by implementing the equation (9) on Maple, we obtain the following estimated values of β for different patients :

# <i>Patient</i>	$\beta (\times 10^{-6})$
S1204	0.44905
S1050	0.72557
G221	2.29484
G54	1.18315

5 Application 2

The exact number of classes in the circulating or sequestered phases of parasites is not completely known. We divide the the dynamics of parasite into two main classes, viz circulating parasites and sequestered parasites. Gravenor et al. [6] had considered that decomposition as well, but they consider only the dynamics of the infected cells. The figure 3 illustrate this decomposition. Hence,

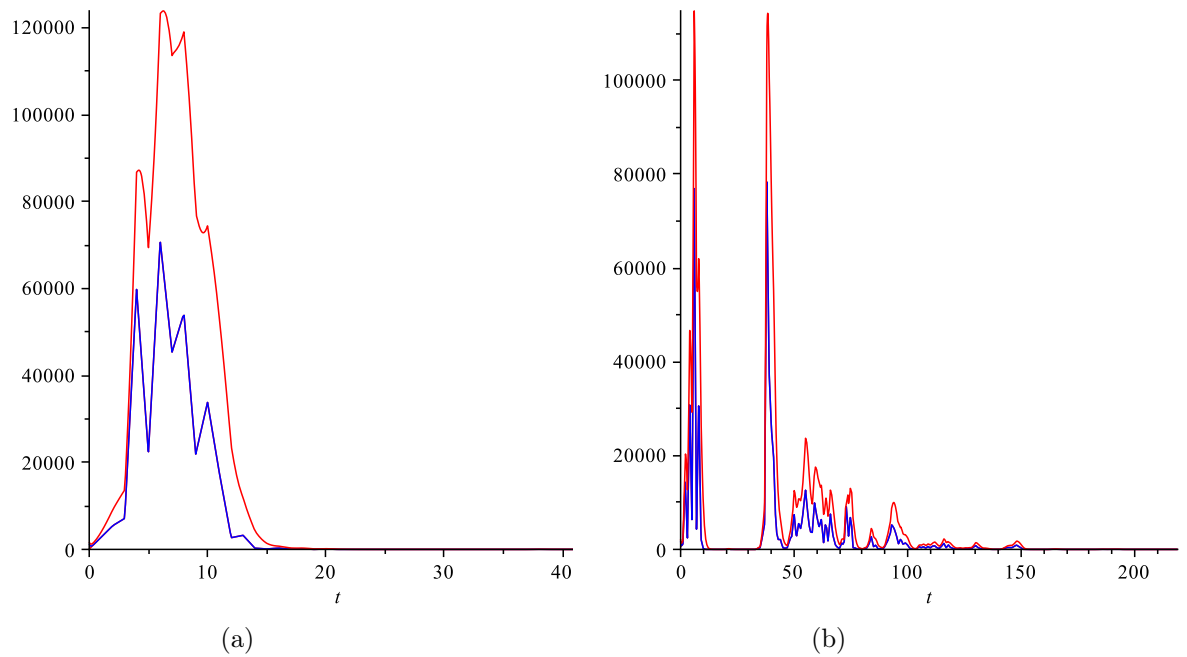


Figure 1: (a), Patient G54: Measures of total parasitaemia (red) and the measure of parasitaemia (data) and estimated peripheral parasitaemia (blue and red). (b) Patient S1204. The unit of time day represented by the x -axis while the y -axis represent parasitaemia per micro-liter.

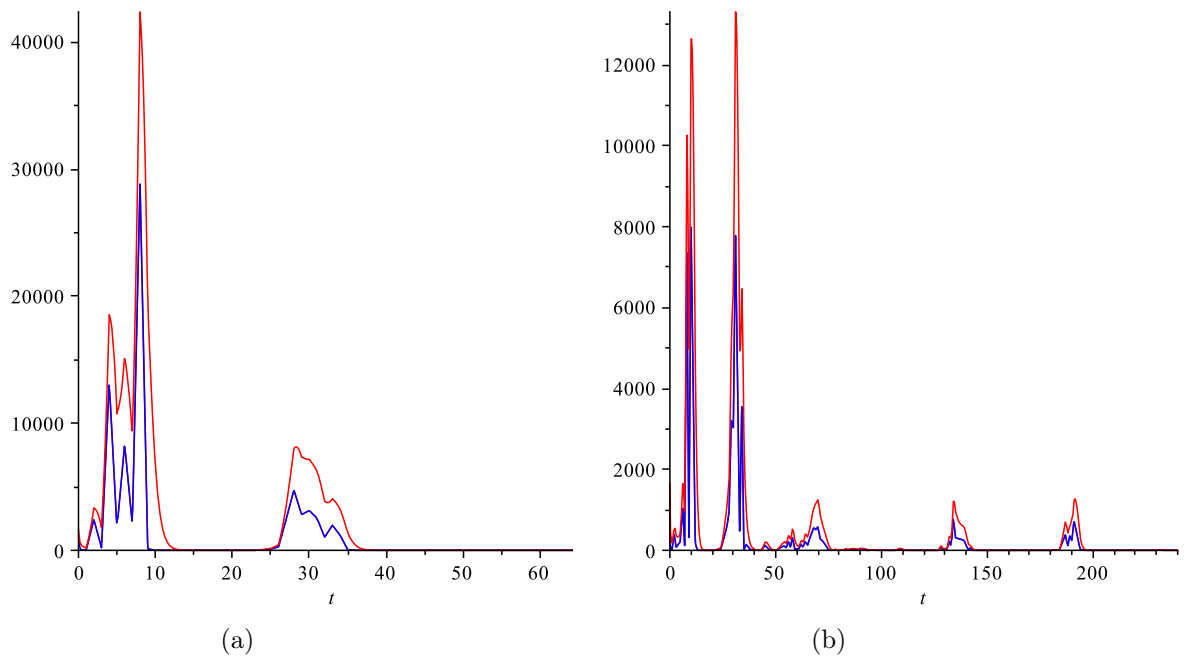


Figure 2: (a) Patient S1050: Measures of total parasitaemia (red) and the measure of parasitaemia (data) and estimated peripheral parasitaemia (blue and red). (b) Patient G221

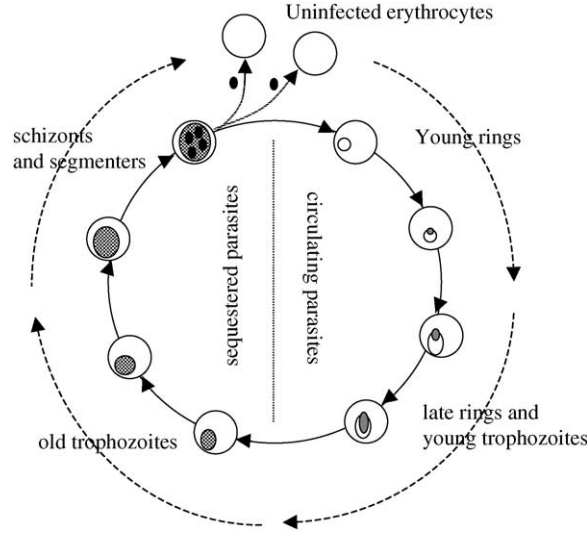


Figure 3: Decomposition of *Plasmodium falciparum* cycle into two classes.

two variables y_1 et y_2 describe the circulating parasites which are measured and sequestered parasites respectively. We obtain then the model:

$$\begin{cases} \dot{x} = \Lambda - \mu_x x - \beta x m \\ \dot{y}_1 = \beta x m - (\mu_1 + \gamma_1) y_1 \\ \dot{y}_2 = \gamma_1 y_1 - (\mu_2 + \gamma_2) y_2 \\ \dot{m} = r \gamma_2 y_2 - \mu_m m - \beta x m \end{cases} \quad (11)$$

In the control control framework, the system (11) could be written as:

$$\dot{x} = Ax + Ed + \Lambda e_1 \quad (12a)$$

$$y = Cx \quad (12b)$$

where:

$$A = \begin{pmatrix} -\mu_x & 0 & 0 & 0 \\ 0 & -\alpha_1 & 0 & 0 \\ 0 & \gamma_1 & -\alpha_2 & 0 \\ 0 & 0 & r\gamma_2 & -\mu_m \end{pmatrix}, E = \begin{pmatrix} -1 \\ 1 \\ 0 \\ -1 \end{pmatrix} \quad \text{and} \quad C = (0, 1, 0, 0).$$

The same observer (7) is valid. For the choice of parameter is a bit easier in this case. If we consider patients are not taking drugs, the mortality of parasite is very low [4]. Hence, we can consider, $\lambda_1 = 1.03$, $\lambda_2 = 0.74$ and $\mu_1 = 0.42$, $\mu_2 = 0.08$. Their unit remain days. We choose these parameter on the basis of the precedent application. The same constraint $\sum_{i=1}^2 \frac{1}{\lambda_i} = 1.9101065$ days is satisfied. The other parameters are standards and are the same as the above application. With the choice $L = (0, 5, 0, 0)^T$, we have successively:

$$\bar{A} = \begin{pmatrix} -\mu_x & -\gamma_1 - \mu_1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & \gamma_1 & -\gamma_2 - \mu_2 & 0 \\ 0 & -\gamma_1 - \mu_1 & r\gamma_2 & -\mu_m \end{pmatrix} \quad \bar{A} - LC = \begin{pmatrix} -\mu_x & -\gamma_1 - \mu_1 & 0 & 0 \\ 0 & -5 & 0 & 0 \\ 0 & \gamma_1 & -\gamma_2 - \mu_2 & 0 \\ 0 & -\gamma_1 - \mu_1 & r\gamma_2 & -\mu_m \end{pmatrix}$$

And

$$(\bar{A} - LC)E = \begin{pmatrix} -\mu_x & -\gamma_1 - \mu_1 & 0 & 0 \\ 0 & -5 & 0 & 0 \\ 0 & \gamma_1 & -\gamma_2 - \mu_2 & 0 \\ 0 & -\gamma_1 - \mu_1 & r\gamma_2 & -\mu_m \end{pmatrix} \begin{pmatrix} -1 \\ 1 \\ 0 \\ -1 \end{pmatrix} = \begin{pmatrix} \mu_x - \gamma_1 - \mu_1 \\ -5 \\ \gamma_1 \\ -\gamma_1 - \mu_1 + \mu_m \end{pmatrix}$$

and

$$L + (\bar{A} - LC)E = \begin{pmatrix} \mu_x - \gamma_1 - \mu_1 \\ 0 \\ \gamma_1 \\ -\gamma_1 - \mu_1 + \mu_m \end{pmatrix}$$

Hence, for this model, the observer is given by:

$$\dot{z} = \begin{pmatrix} -\mu_x & -\gamma_1 - \mu_1 & 0 & 0 \\ 0 & -5 & 0 & 0 \\ 0 & \gamma_1 & -\gamma_2 - \mu_2 & 0 \\ 0 & -\gamma_1 - \mu_1 & r\gamma_2 & -\mu_m \end{pmatrix} z + \begin{pmatrix} \mu_x - \gamma_1 - \mu_1 \\ 0 \\ \gamma_1 \\ -\gamma_1 - \mu_1 + \mu_m \end{pmatrix} y + \Lambda e_1 \quad (13a)$$

$$\hat{x} = z + Ey \quad (13b)$$

With this observer decoupled to β , we can estimate all vector states and then the total parasite load $y_1 + y_2$. Following (9), we use symbolic software Maple to implement the observer and then estimate β . We found the following estimations of β for different patients :

# Patient	$\beta (\times 10^{-6})$
S1204	0.49172
S1050	0.69842
G221	2.36547
G54	1.10660

It is worth to compare those results with some others in the literature. Hetzel and Anderson [9] found, for rodents, β between $1.872 \times 10^{-6}(\text{cells}/\mu\text{l})^{-1} \text{ day}^{-1}$ and $7.329 \times 10^{-6}(\text{cells}/\mu\text{l})^{-1} \text{ day}^{-1}$. Gravenor et al. in [7] consider the model (1) and with a quasi steady-state assumption and by using clinical data, estimated $\beta = 3.4833 \times 10^{-6}(\text{cells}/\mu\text{l})^{-1} \text{ day}^{-1}$. However as stated by the authors, those assumptions are simplifying. By exploiting clinical data of parasitaemia used in [7] in our method, we find $\beta = 6.2734 \times 10^{-6}(\text{cells}/\mu\text{l})^{-1} \text{ day}^{-1}$. According to [7], in order for the model to predict standard clinical parasitaemia, β would have to be less than $10^{-6}(\text{cells}/\mu\text{l})^{-1} \text{ day}^{-1}$ (In fact $\beta/\mu_m < 10^{-3}$ in their units). Our results suit their claiming. Stating which of those different values of β are better estimation than another is a very difficult task. However our method is easy to handle and can be used for any set of data. Our aim here is also to show how techniques from control theory are useful to estimate parameter of epidemic models.

6 Conclusion and discussions

A method to estimate the total parasitaemia within a malaria patient and the infection rate β has been given. This method is independent of any set of data.

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615 rue du Jardin Botanique
CS20101
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