Interval observer for sequestered erythrocytes in malaria

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***Abstract*—For malaria patients, a usual observation problem consists in estimation of sequestered parasites *Plasmodium falciparum* from measurements of circulating ones. The model of an infected patient is rather uncertain, and for all rates (death, transition, recruitment and infection) in the model it is assumed that only intervals of admissible values are given. In addition, the measurements of the concentration of circulating parasites are subjected by a bounded noise, while some parameters, like the rate of infection of blood cells by merozoites, are completely unknown and highly time-varying. In order to evaluate the concentration of sequestered parasites, an interval observer is designed, which provides intervals of admissible value for that concentration, with the interval width proportional to the model uncertainty. Stability of the proposed observer can be verified by a solution of LMI. The efficiency of the observer is demonstrated in simulation for a model and for real measured data.**

I. Introduction

Malaria is an important disease causing at least one million deaths around the world each year (with ninety percents among children in Africa), and it is spreed by the *Plasmodium* parasite. The most dangerous type of malaria is summoned by the most virulent species called *Plasmodium falciparum*. Sequestration is one of the characteristics of *Plasmodium falciparum*, which is related with the *Plasmodium* life cycle. The cycle begins when a parasite enters the human body through the bite of an infected mosquito, after which it migrates to the liver and starts to multiply within. The free forms resulting from this multiplication (called merozoites) are able to invade the red blood cells (erythrocytes). The infected erythrocytes are matured during the erythrocytic cycle. At roughly the middle stage of trophozoite development (in 24 hours), molecules on the surface of infected erythrocytes can link to receptors of endothelial cells. This bind has the effect of holding infected erythrocytes within vessels of organs (such as the brain), where they remain until the rupture of the erythrocyte and the release of merozoites. This period of attachment is called sequestration and during it, the infected erythrocytes are not detectable in the blood flow, they are "sequestered". Also it is widely accepted that antimalarial drugs act differently depending on the stage of parasite development [11], [10].

In practice, to know the stage of infection for a patient, the total parasite concentration $\sum_{i=1}^{n} y_i$ in the bloodstream is needed, where y_i represent population of parasites of certain age, from the youngest y_1 till the oldest y_n, $n < 1$ determines the grid of age differentiation. However, only the presence of peripheral infected erythrocytes, *i.e.* the young parasites $y_1 + y_2 + ...y_k$ for some $k < n$, also called circulating, can be detected on peripheral blood smears and the other ones (sequestered $y_{k+1}, ...y_n$), which are hidden in some organs like brain and heart, cannot be observed. Nowadays, there is no clinical method of measuring the sequestered infected cells directly, and the measurements of circulating parasites are rather costly and corrupted by noise.

That is why the estimation of sequestered parasite population is an important challenge, with many authors having studied this problem [11], [10], [16], [1]. In this work an interval observer is designed in order to estimate the interval for sequestered parasite population, which is admissible for given uncertainty in patient model. In the presence of uncertainty, which has an important impact in this application, design of a conventional estimator, converging to the ideal value of the state, cannot be realized. In this case an interval estimation becomes more feasible: an observer can be constructed that, using input-output information, evaluates the set of admissible values (interval) for the state at each instant of time. The interval length is proportional to the size of the model uncertainty (it has to be minimized by tuning the observer parameters). There are several approaches to design interval/set-membership estimators [12], [14], [17].

K.H. Degue is with the department of Electrical Engineering, Polytechnique Montreal, QC H3T-1J4, Canada and GERAD, QC H3T- 1J4, Montreal, Canada.

D. Efimov is with Non-A team @ Inria, Parc Scientifique de la Haute Borne, 40 avenue Halley, 59650 Villeneuve d'Ascq, France, CRIStAL (UMR-CNRS 9189), Ecole Centrale de Lille, BP 48, Cité Scientifique, 59651 Villeneuve-d'Ascq, France and with Department of Control Systems and Informatics, University ITMO, 49 av. Kronverkskiy, 197101 Saint Petersburg, Russia.

A. Iggidr is with Inria and Université de Lorraine and CNRS, MASAIE, Institut Élie Cartan de Lorraine (IECL, UMR CNRS 7502), ISGMP Bat. A, Ile de Saulcy, Metz Cedex 01 57045, France.

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This work is devoted to interval observers, which form a subclass of set-membership estimators and whose design is based on the monotone systems theory [17], [15], [19], [18], [6]. Since the estimated variables take positive values (all elements of the state vector for infected patient are concentrations), then the obtained estimates also should take positive values only, which poses an additional constraint to satisfy in this rather complex estimation problem.

The outline of this paper is as follows. After preliminaries in Section II, the problem statement is given in Section III. The interval observer design is presented in Section IV. Numerical experiments with really measured data and selected model are described in Section V.

II. Preliminaries

The real numbers are denoted by $\mathbb{R}$, $\mathbb{R}_+ = \{\tau \in \mathbb{R} : \tau \geq 0\}$. Euclidean norm for a vector $x \in \mathbb{R}^n$ will be denoted as $|x|$, and for a measurable and locally essentially bounded input $u : \mathbb{R}_+ \to \mathbb{R}$ the symbol $||u||_{[t_0,t_1]}$ denotes its L_∞ norm:

$$||u||_{[t_0,t_1]} = ess \sup_{t\in[t_0,t_1]} |u(t)|,$$

if $t_1 = +\infty$ then we will simply write $||u||_\infty$. We will denote as $\mathcal{L}_\infty$ the set of all inputs u with the property $||u||_\infty < \infty$. The symbols I_n, $E_{n\times m}$ and E_p denote the identity matrix with dimension $n \times n$, the matrix with all elements equal 1 with dimensions $n \times m$ and $p \times 1$, respectively.

A. Interval relations

For two vectors $x_1, x_2 \in \mathbb{R}^n$ or matrices $A_1, A_2 \in \mathbb{R}^{n\times n}$, the relations $x_1 \leq x_2$ and $A_1 \leq A_2$ are understood elementwise. The relation $P \prec 0$ ($P \succ 0$) means that the matrix $P \in \mathbb{R}^{n\times n}$ is negative (positive) definite. Given a matrix $A \in \mathbb{R}^{m\times n}$, define $A^+ = \max\{0, A\}$, $A^- = A^+ - A$ (similarly for vectors) and denote the matrix of absolute values of all elements by $|A| = A^+ + A^-$.

Lemma 1. [6] *Let $x \in \mathbb{R}^n$ be a vector variable, $\underline{x} \leq x \leq \overline{x}$ for some $\underline{x}, \overline{x} \in \mathbb{R}^n$.*

(1) *If $A \in \mathbb{R}^{m\times n}$ is a constant matrix, then*

$$A^+\underline{x} - A^-\overline{x} \leq Ax \leq A^+\overline{x} - A^-\underline{x}. \tag{1}$$

(2) *If $A \in \mathbb{R}^{m\times n}$ is a matrix variable and $\underline{A} \leq A \leq \overline{A}$ for some $\underline{A}, \overline{A} \in \mathbb{R}^{m\times n}$, then*

$$\begin{aligned}\underline{A}^+\underline{x}^+ - \overline{A}^+\underline{x}^- - \underline{A}^-\overline{x}^+ + \overline{A}^-\overline{x}^- \leq Ax \\ \leq \overline{A}^+\overline{x}^+ - \underline{A}^+\overline{x}^- - \overline{A}^-\underline{x}^+ + \underline{A}^-\underline{x}^-.\end{aligned} \tag{2}$$

Furthermore, if $-\overline{A} = \underline{A} \leq 0 \leq \overline{A}$, then the inequality (2) can be simplified: $-\overline{A}(\overline{x}^+ + \underline{x}^-) \leq Ax \leq \overline{A}(\overline{x}^+ + \underline{x}^-)$.

B. Nonnegative continuous-time linear systems

A matrix $A \in \mathbb{R}^{n\times n}$ is called Hurwitz if all its eigenvalues have negative real parts, and it is called Metzler if all its elements outside the main diagonal are nonnegative. Any solution of the linear system

$$\begin{aligned}\dot{x} = Ax + B\omega(t),\ \omega : \mathbb{R}_+ \to \mathbb{R}^q_+,\ \omega \in \mathcal{L}^q_\infty, \\ y = Cx + D\omega(t),\end{aligned} \tag{3}$$

with $x \in \mathbb{R}^n$, $y \in \mathbb{R}^p$ and a Metzler matrix $A \in \mathbb{R}^{n\times n}$, is elementwise nonnegative for all $t \geq 0$ provided that $x(0) \geq 0$ and $B \in \mathbb{R}^{n\times q}_+$ [9], [20]. The output solution $y(t)$ is nonnegative if $C \in \mathbb{R}^{p\times n}_+$ and $D \in \mathbb{R}^{p\times q}_+$. Such dynamical systems are called cooperative (monotone) or nonnegative if only initial conditions in $\mathbb{R}^n_+$ are considered [9], [20].

For a Metzler matrix $A \in \mathbb{R}^{n\times n}$ its stability can be checked verifying a Linear Programming (LP) problem

$$A^{\mathrm{T}}\lambda < 0$$

for some $\lambda \in \mathbb{R}^n_+ \setminus \{0\}$, or Lyapunov matrix equation

$$A^{\mathrm{T}}P + PA \prec 0$$

for a *diagonal* matrix $P \in \mathbb{R}^{n\times n}$, $P > 0$ (in general case the matrix P should not be diagonal). The L_1 and L_∞ gains for nonnegative systems (3), *i.e.* the gains of transfer function from input to output in different norms, have been studied in [2], [5], for this kind of systems these gains are interrelated. The conventional results and definitions on L_2/L_∞ stability for linear systems can be found in [13].

C. A non-homogeneous sliding mode differentiator

Let $\tilde{y}(t) = y(t) + \nu(t)$ be a measured signal, where $y : \mathbb{R}_+ \to \mathbb{R}$ is a signal to be differentiated and $\nu \in \mathcal{L}_\infty$ is a bounded measurement noise, then a differentiator can be proposed [7]:

$$\begin{aligned}\dot{x}_1 &= -\alpha\sqrt{|x_1 - \tilde{y}(t)|}\mathrm{sign}(x_1 - \tilde{y}(t)) + x_2, \\ \dot{x}_2 &= -\varrho\,\mathrm{sign}(x_1 - \tilde{y}(t)) - \chi\,\mathrm{sign}(x_2) - x_2, \\ &\quad x_1(0) = \tilde{y}(0),\ x_2(0) = 0,\end{aligned} \tag{4}$$

where $x_1, x_2 \in \mathbb{R}$ are the state variables of the system (4), α, ϱ and χ are the tuning parameters with $\alpha > 0$ and $\varrho > \chi \geq 0$. The variable $x_1(t)$ serves as an estimate of the function $y(t)$ and $x_2(t)$ is an estimate of $\dot{y}(t)$, *i.e.* it provides the derivative estimate. Therefore, the system (4) has $\tilde{y}(t)$ as the input and $\hat{\dot{y}}(t) = x_2(t)$ as the output.

Lemma 2. [7] *Let $\dot{y}, \ddot{y}, \nu \in \mathcal{L}_\infty$, then there exist $\alpha > 0$ and $\varrho > \chi \geq 0$ such that $x_1, x_2 \in \mathcal{L}_\infty$ and there exist $T_0 > 0$, $c_1 > 0$ and $c_2 > 0$:*

$$|x_2(t) - \dot{y}(t)| \leq \sqrt{c_1||\nu||_\infty + \sqrt{c_2||\nu||_\infty}} \quad \forall t \geq T_0.$$

Estimates on $T_0 > 0$, $c_1 > 0$, $c_2 > 0$ and guidelines for tuning α, ϱ, χ can also be found in [7].

III. Estimation of the hidden erythrocytes

The dynamics of the parasitized erythrocytes is described by the following model [1]:

$$\begin{aligned} \dot{z}(t) &= A(t)z(t) + E\beta(t)x(t)m(t) + e_1\Lambda(t)\ \forall t \geq 0, \\ Y(t) &= Cz(t) + v(t), \end{aligned} \tag{5}$$

where $z = (x, y_1, \ldots, y_5, m)^{\mathrm{T}} \in \mathbb{R}^7_+$ is the state vector and $Y \in \mathbb{R}_+$ is the measured output, $v \in \mathcal{L}_\infty$ is the measurement noise, $||v||_\infty \leq V$ for some known $V > 0$; y_1 and y_2 correspond to the concentrations of free circulating parasitized erythrocytes and y_3, y_4, y_5 correspond to the sequestered ones; x is the concentration of healthy cells, and m is the concentration of merozoites; $\Lambda(t) \in \mathbb{R}_+$, $\Lambda \in \mathcal{L}_\infty$ represents recruitment of the healthy Red Blood Cells (RBC) and $\beta(t) \in \mathbb{R}_+$, $\beta \in \mathcal{L}_\infty$ is the rate of infection of RBC by merozoites. The variables $\beta(t)$ and $\Lambda(t)$ serve as exogenous uncertain inputs in (5). The time-varying matrix A and the constant matrices C, E, e_1 are defined as follows:

$$\begin{aligned} C &= [\ 0 \quad 1 \quad 1 \quad 0 \quad 0 \quad 0 \quad 0\ ], \\ E &= [\ -1 \quad 1 \quad 0 \quad 0 \quad 0 \quad 0 \quad -1\ ]^{\mathrm{T}}, \\ e_1 &= [\ 1 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0\ ]^{\mathrm{T}}, \end{aligned}$$

$$A = \begin{bmatrix} -\mu_x & 0 & 0 & 0 \\ 0 & -\mu_1 - \gamma_1 & 0 & 0 \\ 0 & \gamma_1 & -\mu_2 - \gamma_2 & 0 \\ 0 & 0 & \gamma_2 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ -\mu_3 - \gamma_3 & 0 & 0 & 0 \\ \gamma_3 & -\mu_4 - \gamma_4 & 0 & 0 \\ 0 & \gamma_4 & -\mu_5 - \gamma_5 & 0 \\ 0 & 0 & r\gamma_5 & -\mu_m \end{bmatrix},$$

where $\mu_x > 0$ is the natural death rate of healthy cells; $\mu_i > 0$ is the natural death rate of i^{th} stage of infected cells, $\gamma_i > 0$ is the transition rate from i^{th} stage to $(i+1)^{\text{th}}$ stage of infected cells, $i = 1, \ldots, 5$; $r > 0$ is the number of merozoites released by the late stage of infected cells, $\mu_m > 0$ is the natural death rate of merozoites.

For different patients the values of the parameters μ_x, μ_i, γ_i, r and μ_x are different and they are varying with time for a patient, that is why we assume that

$$\underline{A} \leq A(t) \leq \overline{A}$$

for some known $\underline{A}, \overline{A} \in \mathbb{R}^{7\times 7}$ and the instant value of $A(t)$ is unavailable. Such a hypothesis is rather natural since on-line identification of these parameters is complicated. Similarly for the healthy RBC recruitment $\Lambda(t)$, the values $\underline{\Lambda}, \overline{\Lambda} \in \mathbb{R}_+$ are given such that

$$\underline{\Lambda} \leq \Lambda(t) \leq \overline{\Lambda}\ \forall t \geq 0.$$

It is assumed that for $\beta(t)$ there is no confidence interval (its instant value is highly uncertain).

We suppose that $Y = y_1 + y_2 + v(t)$, *i.e.* the circulating *Plasmodium* concentration can be measured with a noise v, while it is required to estimate the sequestered one $Z = y_3 + y_4 + y_5$.

IV. Interval observer design

We define $w(t) = \beta(t)x(t)m(t)$ as a new unmeasurable variable, which can be considered as a new uncertain input for (5). Following [1] and using the equation (5), we can find:

$$w = ((CE)^{\mathrm{T}}CE)^{-1}(CE)^{\mathrm{T}}(\dot{Y} - CAz - Ce_1\Lambda)$$

where $\dot{Y}$ is the derivative of the output. Using Lemma 2 and differentiator (4), an estimate $\hat{\dot{Y}}$ of $\dot{Y}$ can be calculated such that for all $t \geq 0$:

$$\dot{Y}(t) = \hat{\dot{Y}}(t) + v'(t),$$

where $||v'||_\infty < V'$ for some known $V' > 0$.

Note that $CE = 1$ in (5), let $0 \leq \underline{z}(t) \leq z(t) \leq \overline{z}(t)$ for all $t \geq 0$ and some $\underline{z}, \overline{z} \in \mathbb{R}^7$, then using Lemma 1 we obtain the following relations for all $t \geq 0$:

$$\underline{w}(t) \leq w(t) \leq \overline{w}(t),$$

where $\underline{w} = \hat{\dot{Y}} - V' - Ce_1\overline{\Lambda} - (C\overline{A})^+\overline{z} + (C\overline{A})^-\underline{z}$ and $\overline{w} = \hat{\dot{Y}} + V' - Ce_1\underline{\Lambda} - (C\underline{A})^+\underline{z} + (C\underline{A})^-\overline{z}$.

Following [3], the equations of an interval observer for (5) take the form:

$$\begin{aligned} \dot{\underline{\zeta}}(t) &= \underline{A}\underline{\zeta}(t) + e_1\underline{\Lambda} + E^+\underline{w}(t) \\ &\quad -E^-\overline{w}(t) + \underline{L}(Y(t) - C\underline{\zeta}(t)) - |\underline{L}|V, \\ \dot{\overline{\zeta}}(t) &= \overline{A\zeta}(t) + e_1\overline{\Lambda} + E^+\overline{w}(t) \\ &\quad -E^-\underline{w}(t) + \overline{L}(Y(t) - C\overline{\zeta}(t)) + |\underline{L}|V, \\ &\quad \underline{z}(t) = \max\{0, \underline{\zeta}(t)\}, \\ &\quad \overline{z}(t) = \max\{0, \overline{\zeta}(t)\}, \end{aligned} \tag{6}$$

where $\underline{z} \in \mathbb{R}^7$ and $\overline{z} \in \mathbb{R}^7$ are respectively the lower and the upper interval estimates for the state z; $\underline{\zeta}, \overline{\zeta} \in \mathbb{R}^7$ is the state of (6). The following restrictions are imposed on (6).

Assumption 1. *There exist matrices $\overline{L} \in \mathbb{R}^{7\times 1}$, $\underline{L} \in \mathbb{R}^{7\times 1}$ such that the matrices $(\overline{A} - \overline{L}C)$ and $(\underline{A} - \underline{L}C)$ are Metzler.*

Assumption 1 fixes the principal conditions to satisfy for positivity of the error dynamics (due to the structure of A this condition is always satisfied for $\overline{L} = \underline{L} = 0$).

Theorem 1. *Let Assumption 1 be satisfied. Then for all $t \in \mathbb{R}_+$ the estimates $\underline{z}(t)$ and $\overline{z}(t)$ given by (6) yield the relations:*

$$0 \le \underline{z}(t) \le z(t) \le \bar{z}(t) \quad \forall t \ge 0, \tag{7}$$

provided that $0 \le \underline{z}(0) \le z(0) \le \bar{z}(0)$. If in addition, there exists a diagonal matrix $P \in \mathbb{R}^7$ and $\gamma > 0$ such that

$$\mathcal{A}^T P + P\mathcal{A} + P(\gamma^{-2} I_7 + FF^T)P + 2I_7 \preceq 0$$

for

$$\mathcal{A} = \begin{bmatrix} (A - \underline{L}C) & 0 \\ 0 & (A - \overline{L}C) \end{bmatrix},$$
$$F = \begin{bmatrix} E^+(C\overline{A})^- + E^-(C\underline{A})^+ & -E^+(C\overline{A})^+ - E^-(C\underline{A})^- \\ -E^+(C\underline{A})^+ - E^-(C\overline{A})^- & E^+(C\underline{A})^- + E^-(C\overline{A})^+ \end{bmatrix},$$

then $\underline{z}, \bar{z} \in \mathcal{L}^7_\infty$ ($\underline{\zeta}, \bar{\zeta} \in \mathcal{L}^7_\infty$ and the transfer function $\begin{bmatrix} e_1\underline{\Lambda} + \underline{L}Y(t) - |\underline{L}|V \\ e_1\overline{\Lambda} + \overline{L}Y(t) + |\overline{L}|V, \end{bmatrix} \to \begin{bmatrix} \underline{\zeta} \\ \bar{\zeta} \end{bmatrix}$ has L_∞ gain less than γ).

Proof. Note that $z(t) \ge 0$ for all $t \ge 0$ and $z(t)$ is also bounded [1]. The equation (5) can be rewritten as follows:

$$\dot{z} = (A' - LC)z + (A(t) - A')z + Ew + e_1\Lambda + LY - Lv$$

for some $A' \in \mathbb{R}^{7\times 7}$ ($\underline{A}$ or $\overline{A}$) and $L \in \mathbb{R}^{7\times 1}$ ($\underline{L}$ or $\overline{L}$), then the dynamics of the errors $\underline{e}(t) = z(t) - \underline{\zeta}(t)$, $\overline{z}(t) = \overline{\zeta}(t) - z(t)$ obey the equations:

$$\begin{aligned} \dot{\underline{e}}(t) &= (\underline{A} - \underline{L}C)\underline{e}(t) + \underline{g}(t), \\ \dot{\bar{e}}(t) &= (\overline{A} - \overline{L}C)\overline{e}(t) + \overline{g}(t), \end{aligned} \tag{8}$$

where

$$\begin{aligned} \underline{g} &= (A(t) - \underline{A})z + Ew - E^+\underline{w} + E^-\overline{w} + \underline{L}v + |\underline{L}|V, \\ \overline{g} &= (\overline{A} - A(t))z + E^+\overline{w} - E^-\underline{w} - Ew - \overline{L}v + |\underline{L}|V. \end{aligned}$$

Under the introduced conditions, it can be inferred from Lemma 1 that $\underline{g}(t) \ge 0$, $\overline{g}(t) \ge 0$ $\forall t \ge 0$. From Assumption 1, we conclude that $\underline{e}(t) \ge 0$ and $\overline{e}(t) \ge 0$ ($\underline{g}, \overline{g}$ have the same property and $\underline{e}(0) \ge 0$ and $\overline{e}(0) \ge 0$ by conditions). That implies that the order relation $\underline{\zeta}(t) \le z(t) \le \bar{\zeta}(t)$ is satisfied for all $t \ge 0$, then (7) is true by construction of $\underline{z}, \overline{z}$ and due to nonnegativity of z.

In order to prove boundedness, let us define:

$$\zeta = [\underline{\zeta}^{\mathrm{T}}\ \overline{\zeta}^{\mathrm{T}}]^{\mathrm{T}},\ \epsilon = [\underline{\epsilon}^{\mathrm{T}}\ \overline{\epsilon}^{\mathrm{T}}]^{\mathrm{T}},$$
$$\underline{\epsilon} = Ce_1(E^-\underline{\Lambda} - E^+\overline{\Lambda}) + e_1\underline{\Lambda} + E\hat{\underline{Y}} - |E|V' + \underline{L}Y - |\underline{L}|V,$$
$$\overline{\epsilon} = Ce_1(E^-\overline{\Lambda} - E^+\underline{\Lambda}) + e_1\overline{\Lambda} + E\hat{\overline{Y}} + |E|V' + \overline{L}Y + |\underline{L}|V,$$

then dynamics of interval observer takes the form:

$$\dot{\zeta} = \mathcal{A}\zeta + F\max\{0, \zeta\} + \epsilon,$$

where the matrices $\mathcal{A}$ and F are defined in the theorem formulation and $\epsilon \in \mathcal{L}^{14}_\infty$ by construction. Consider a Lyapunov function $V(\zeta) = \zeta^{\mathrm{T}} P \zeta$, then

$$\begin{aligned} \dot{V} &= \zeta^{\mathrm{T}}(\mathcal{A}^{\mathrm{T}}P + P\mathcal{A})\zeta + 2\zeta^{\mathrm{T}}P[F\max\{0,\zeta\} + \epsilon] \\ &\le \zeta^{\mathrm{T}}[\mathcal{A}^{\mathrm{T}}P + P\mathcal{A} + P(\gamma^{-2}I + FF^{\mathrm{T}})P + I]\zeta + \gamma^2\epsilon^{\mathrm{T}}\epsilon \\ &\le -\zeta^{\mathrm{T}}\zeta + \gamma^2\epsilon^{\mathrm{T}}\epsilon \end{aligned}$$

and the needed stability conclusion follows. □

The obtained interval estimates $\underline{z}, \overline{z}$ are nonnegative as the state z is. Note that the presented approach can be easily extended to higher/lower order models of parasitized erythrocytes (when age partition of erythrocytes has more/less than 5 levels as in (5)).

Remark 1. Using the results of [2], [5], the stability conditions for (6) can be expressed as a linear programming (LP) problem, then it is necessary to find $\lambda \in \mathbb{R}^{14}_+ \setminus \{0\}$ such that the following LP problem is feasible:

$$\begin{bmatrix} \mathcal{A}\lambda + |F|E_{14} \\ \lambda - E_{14} \end{bmatrix} < 0.$$

V. Simulation of the interval observer

In this section the result of numerical experiments are reported for the model (5) and with a real data measured for an infected patient.

A. Model experiments

In [1], for a patients without fever, *i.e.* at 37°C, the parameters of the matrix A have the following constant values:

$$\begin{aligned} \gamma_1 = 1.96, \gamma_2 = 3.78, \gamma_3 = 2.85, \gamma_4 = 1.76, \gamma_5 = 3.26; \\ \mu_1 = 0, \mu_2 = 1.86, \mu_3 = 0, \mu_4 = 0.1, \mu_5 = 0; \\ \mu_x = \frac{1}{120}, r = 16, \mu_m = 72. \end{aligned} \tag{9}$$

Assume that admissible deviations of these parameters from the nominal values given above are $\sigma\%$, then we can calculate the matrices $\underline{A}$ and $\overline{A}$. The nominal value of healthy RBC recruitment is $\Lambda_0 = \frac{5\times 10^6}{120}$ cellsμl^{-1}day^{-1} (as in [1], the unit of volume is micro-liter (μl) and the unit of time is day) with admissible deviations $\pm 20\%$, *i.e.*

$$0.8\Lambda_0 = \underline{\Lambda} \le \Lambda(t) \le \overline{\Lambda} = 1.2\Lambda_0\ \forall t \ge 0.$$

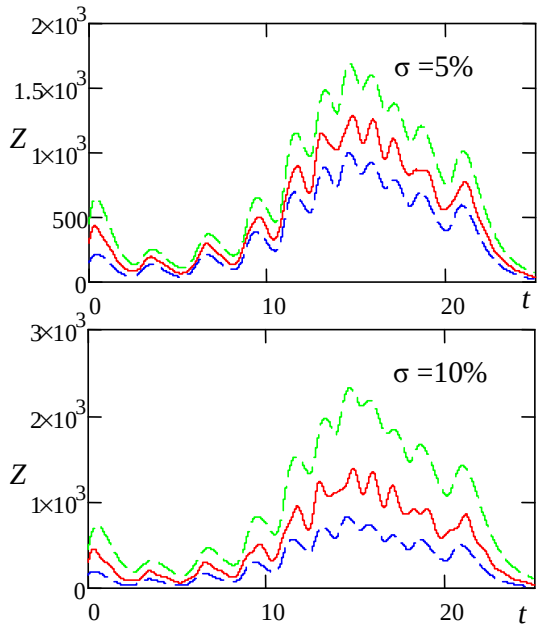

Figure 1. The results of interval estimation for sequestered parasites

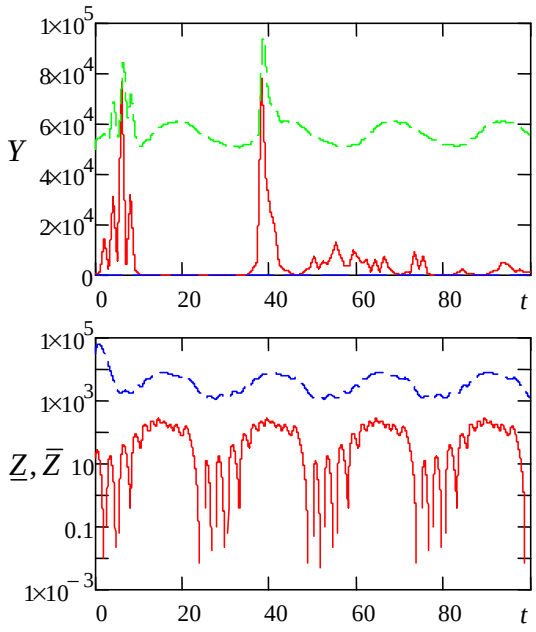

Figure 2. The results of interval estimation on real data

For simulations we selected:

$$\Lambda(t) = \Lambda_0(1 + 0.2\sin(2t)),$$
$$\beta(t) = 10^{-6}(1 + 0.25\sin(5t))e^{\mathrm{mod}^2(t,2.5+0.5\sin(0.25t))},$$
$$v(t) = V\sin(35t),\ V = 10,$$
$$A(t) = \sin^2(3t)\underline{A} + \cos^2(3t)\overline{A}.$$

Let $\underline{z}(0) = \frac{1}{3}\bar{z}(0) = [500\ 100\ 150\ 50\ 50\ 50\ 50]^{\mathrm{T}}$. For differentiator (4), $\alpha = 2 \times 10^3$, $\varrho = 3\alpha$ and $\chi = 0.25\alpha$, then $V' = 80V$ and

$$\underline{L} = \left(1 - \frac{\sigma}{100}\right)[0\ 0\ \gamma_1\ 0\ 0\ 0\ 0]^{\mathrm{T}},$$
$$\overline{L} = \left(1 + \frac{\sigma}{100}\right)[0\ 0\ \gamma_1\ 0\ 0\ 0\ 0]^{\mathrm{T}}$$

have been selected. The results of interval estimation of sequestered *Plasmodium* $Z(t)$ are shown in Fig. 1 for $\sigma = 5$ and $\sigma = 10$. As we can conclude, the size of uncertainty σ influences directly the estimation accuracy.

B. Real data experiments

The measured concentration of circulating parasites (peripheral *parasitaemia*, that is density of parasites in the blood) is taken from the data collected by the US Public Health Service at the National Institutes of Health laboratories in Columbia, South Carolina and Milledgeville, Georgia [4], [8], where malaria was used for therapy of neurosyphilis, and patients were inoculated through mosquito bite or infected blood (see also [1] for more details). The data of patient named S1204 is used in this work. As in [1] the parameters of the model have been selected the same as in (9). For differentiator (4), $\alpha = 3 \times 10^4$, $\varrho = 3\alpha$ and $\chi = 0.25\alpha$, with $V = 100$ and $V' = 6000$. The interval of uncertainty for $\Lambda(t)$ has been selected the same as previously. The level of the matrix A uncertainty σ has been adjusted in order to have correct interval estimates for the measured variable $Y(t)$, the obtained value is $\sigma = 31$, then the results of interval estimation for both variables, $Y(t)$ and $Z(t)$, are shown in Fig. 2 (the interval estimates for sequestered parasites, $\underline{Z}(t)$ and $\overline{Z}(t)$, are plotted in the logarithmic scale). As we can conclude, in order to have adequate interval estimates for $Y(t)$, the value of σ has been selected sufficiently big, which signalizes that the used model (5) with the parameters (9) are rather far from reality, then the interval estimates are rather approximate. From another side, this approach also allows the model accuracy to be evaluated by the measured data.

VI. Conclusion

An interval observer is proposed in this work in order to estimate the sequestered parasite population from the measured circulating parasites. It is assumed that almost all parameters and inputs of the model are uncertain (just intervals of admissible values are given) and the measurements are obtained with a noise. Despite of that the proposed observer demonstrates a reasonable accuracy of interval estimation, which is confirmed by numerical experiments.

In a future work the sampled-time kind of measurements can be taken into account.

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