

# Robust Observer to estimate states and parameters of Nonlinear Quorum Sensing Dynamics with Time Delay <sup>★</sup>

Flores-Pérez, A. <sup>\*</sup> Breña-Medina, Víctor <sup>\*\*</sup>  
González-Olvera, Marcos A. <sup>\*\*\*</sup>

<sup>\*</sup> *Universidad Nacional Autónoma de México, Facultad de Ingeniería  
(e-mail: afloresperez@comunidad.unam.mx).*

<sup>\*\*</sup> *Instituto Tecnológico Autónomo de México (e-mail:  
victor.brena@itam.mx)*

<sup>\*\*\*</sup> *Universidad Autónoma de la Ciudad de México, Plantel San  
Lorenzo Tezonco, (e-mail: marcos.angel.gonzalez@uacm.edu.mx)*

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**Abstract:** Quorum sensing (QS) is a self organization process in bacteria colonies where certain collective action is performed blue when a population density threshold is reached. Some medically relevant behaviors of bacteria are known to be described by QS dynamics such as virulence or antibiotics resistance. Estimation of states and parameters in QS model is important to address such medical issues but difficult in scenarios where measurements are limited and internal activation delay times are considered. In this paper an extended Kalman filter is applied to estimate two unknown states and a nonlinear parameter of a time delay QS (TDQS) system. To the author's knowledge this is the first extended Kalman filter applied to estimate state variables of QS in its delayed version. In this work it is shown how, by measuring only one of the states of the TDQS, the rest of the variables can be estimated, as well one nonlinear parameter.

*Keywords:* QS System, Time-delay systems, Extended Kalman Filter.

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## 1. INTRODUCTION

Quorum sensing (QS) is a collective behavior shown by several classes of bacteria in which each member of a colony performs a cooperative agreement by sensing certain cell-to-cell signaling molecules called *autoinducers* whose concentration depends on the population density (Miller and Bassler (2001); Waters and Bassler (2005)). QS mechanism was proposed in the early 1970s to explain the bioluminescence phenomena in marine bacteria species *Vibrio fischeri* (Nealson et al. (1970)) and has been used to explain some other important social bacterial behavior such as symbiosis, competence, virulence, motility, sporulation, biofilm formation, and antibiotic production and resistance (Miller and Bassler (2001); McClean et al. (1997); Nadell et al. (2008)).

The QS mathematical modeling has been addressed from different approaches along the last decades. These models have taken into account autoinduction or bacterial density thresholds, as well as up- and down-regulated populations by autoinducers, see Pérez-Velázquez et al. (2016). These

models have focused on cellular-intracellular autoinducer interactions or, on the other hand, cell response to QS dynamics. In Harris-Heredia (2019), a QS model is proposed which gathers such a these ingredients as well as not only activation features but also deactivation ones by means of an on-and-off switch functional. To do so, they consider a generalised Gierer-Meinhardt dynamics with saturation, and perform a desingularization method in order to capture biological relevant dynamical aspects.

Like in many other biological systems, time delays are specially expected in QS since it involves several transcription factors playing key roles on the gene network dynamics, which may take several minutes to promote expression of genes as well as correspondent mRNA; see, for instance, Chen et al. (2020); Monk (2020); Jiang et al. (2020) and references therein. Although stability changes due to time delays for systems in nature are well known (Hutchinson et al. (1948)) their effects in QS model have remain partially unveiled. For instance, in Chen et al. (2019) it was demonstrated that time delay is a prerequisite to elicit oscillations in QS system whose amplitude and period are strongly related with the time delay length. This last behavior is a strong indicative that time delay is a bifurcation parameter whose variation affects stabil-

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ity of QS mechanism (Flores Pérez and Breña-Medina (2020)).

Until now, to the best of the author's knowledge, parameters estimation and variables measurements in QS have been done only by performing experimental data fitting (Ward et al. (2001)) with no considerations of delay times at all. Moreover, it has been recognized that several limitations exist on reaching satisfactory results. For instance, measurements can be taken only on certain time lapses of experiments, test conditions are difficult to reproduce and best parameters estimation require extensive experimental information (Ward et al. (2001)).

To address this problem, variable structure dynamical estimators have been designed to "reconstruct" missing states and/or parameters from available measurements in linear and nonlinear time delay systems with an important variety of successful applications but many open problems to face (Karafyllis et al. (2016), Richard (2003)). For instance, to deal with state/parameter estimation for nonlinear systems with constant time delays in states, in Marquez-Martinez et al. (2000) and Batmani and Khaloozadeh (2014) some change of coordinates is sought in order to transform the nonlinear time delay system into a linear-like model for which linear design tools accomplish the construction of a stable observer. However, as in other control problems, such adequate transformations are difficult to find. A control systems approach is addressed in Raff and Allgower (2006) and Hugues-Salas and Shore (2010) where an extended Kalman filter (EKF) based observer is designed. The basic idea here is to introduce appropriate gains in a modified Riccati equation as proposed in Reif et al. (1998) to compensate constant time delays influences to reach local stability of the observation error dynamics.

*Contribution.* Upon applying the existing EKF observer reported in Raff and Allgower (2006) and Hugues-Salas and Shore (2010), we solved the problem of estimating one nonlinear parameter, which is related to the carrying capacity of the environment, and two out of three internal nonlinear states in a time delayed version of the QS model developed in Harris-Heredia (2019). To the best of the authors' knowledge, this is the first effort where EKF is used to realize parameters and states estimation of nonlinear time delay QS (TDQS) model.

This remaining manuscript is organized as follows: a summary of the particular models QS and TDQS addressed in this work are given in Section 2. The EKF based observer for general time delay nonlinear dynamics reported in Raff and Allgower (2006) and Hugues-Salas and Shore (2010) is summarized in Section 3, where its application to the TDQS model is also explained. Numerical results and discussion are detailed in Section 4. Finally, conclusions can be found in Section 5.

## 2. QUORUM SENSING NONLINEAR MODEL.

### 2.1 Non-delayed Quorum Sensing dynamics.

Bacteria conforming a population can be subdivided in two classes, *motile* and *static*, which correspond to subpopulations up- and down-regulated by autoinducers, respectively. Such categories are defined by the cell receptor responses to the autoinducers: if expression of certain particular gene is promoted, cell is classified as motile, otherwise, cell is static. Motile and static bacteria interact within a single compartment acting as activator or inhibitor, respectively, limited by the environment capacity and regulated by autoinducers production. This features are captured in the following model, which has been rescaled and desingularized in order to obtain dimensionless parameters as well as analyze possible singular states in phase space,

$$\dot{w}(t) = dv(t)(u(t) + v(t)) - cw(t)v(t), \quad (1a)$$

$$\dot{v}(t) = w(t)v(t)u^2(t) + a\epsilon v(t) - v^2(t), \quad (1b)$$

$$\dot{u}(t) = \frac{w(t)u^2(t)}{1 + Ku^2(t)} + av(t) - bu(t)v(t), \quad (1c)$$

where  $w(t)$  is the autoinducers concentration,  $v(t)$  corresponds to the density of static bacteria and  $u(t)$  to the density of motile bacteria, all of these variables are measured in datum per length (see Harris-Heredia (2019) for further details). Dimensionless constants  $a$  and  $a\epsilon$  capture category bacteria changes since motile and static can either switch or remain in their class. Parameter  $b$  is the decaying rate of the whole bacteria population,  $c$  and  $d$  describe the decaying and production rate of autoinducers, respectively. Notice that factor in (1c) given by the function

$$\frac{u^2(t)}{1 + Ku^2(t)}$$

comes from an auto-catalytic Hill functional, see Santillán (2014); which models the carrying capacity and may grow monotonically until certain limit defined by the value of  $K$  parameter is reached, which represents the saturation capacity of the environment and characterizes resources availability, for instance.

Finally, the parameters set values taken into account for simulations were  $a = 3/70$ ,  $\epsilon = 1/10$ ,  $b = 1.4$ ,  $c = 0.16$ ,  $d = 98/1875$  and  $K = 49/1125$  as it has been shown that these values give rise to coexistence of subpopulations expressed by self-sustained oscillations (Harris-Heredia (2019)).

### 2.2 Time Delay Quorum Sensing model.

In order to capture delay effects on the QS dynamics to generate the TDQS model, we proposed that autoinducers concentration are produced by the entire population, but activation response from each subpopulation is delayed. As has been addressed earlier, factor of transcription in a gene network may take several minutes in comparison to

the time scale interaction of bacteria and autoinducers. In so doing, a modified QS model with a delay for  $w(t)$ , which model the delayed response to autoinducers concentration from bacteria subpopulation, in the  $u(t)$  and  $v(t)$  dynamics is

$$\begin{aligned}\dot{w} &= dv(t)(u(t) + v(t)) - cw(t)v(t), \\ \dot{v} &= w(t - \tau)v(t)u^2(t) + a\epsilon v(t) - v^2(t), \\ \dot{u} &= \frac{w(t - \tau)u^2(t)}{1 + Ku^2(t)} + av(t) - bu(t)v(t),\end{aligned}\quad (2)$$

where  $\tau = 52s$  is the time delay. Such value was determined by a previous bifurcation study of the TDQS system stability and it is known that it allows coexistence of population classes which is expressed by oscillations (Flores Pérez and Breña-Medina (2020)). In this work, states  $v(t)$ ,  $w(t)$  and  $K$  parameter will be estimated for the TDQS given in (2) in two scenarios:  $K$  constant and periodic time-dependent  $K(t) \geq 0$ , which may model periodical lack of resources.

### 3. ROBUST NONLINEAR OBSERVER OF THE TDQS SYSTEM.

#### 3.1 Extended Kalman filter for general nonlinear time delay systems.

Consider the following nonlinear time delay system

$$\begin{aligned}\dot{\mathbf{x}}(t) &= \mathbf{f}(\mathbf{x}(t), \mathbf{x}(t - \tau)), \\ \mathbf{x}(t) &= \boldsymbol{\psi}(t), t \in [-\tau, 0], \\ \mathbf{y}(t) &= \mathbf{C}\mathbf{x}(t),\end{aligned}\quad (3)$$

where  $\mathbf{x} \in \mathbb{R}^n$  is the state,  $\mathbf{x}(t - \tau)$  is the delayed state with  $\tau > 0$  the time delay,  $\mathbf{C} \in \mathbb{R}^{m \times n}$  is a constant matrix,  $\mathbf{y}(t) \in \mathbb{R}^m$  is the measured output and  $\boldsymbol{\psi}(t) \in \mathbb{R}^n, t \in [-\tau, 0]$  is the continuous initial value function vector. The following system is proposed to reconstruct missing states and parameters from available output

$$\begin{aligned}\dot{\hat{\mathbf{x}}}(t) &= \mathbf{f}(\hat{\mathbf{x}}(t), \hat{\mathbf{x}}(t - \tau)) + \mathbf{L}(t)(\mathbf{y}(t) - \mathbf{C}\hat{\mathbf{x}}(t)), \\ \hat{\mathbf{x}}(t) &= \boldsymbol{\xi}(t), t \in [-\tau, 0],\end{aligned}\quad (4)$$

where  $\hat{\mathbf{x}}(t)$  ( $\hat{\mathbf{x}}(t - \tau)$ ) is the state estimate of  $\mathbf{x}(t)$  ( $\mathbf{x}(t - \tau)$ ) and  $\boldsymbol{\xi}(t)$  is the initial condition function vector that has the same dimension as  $\boldsymbol{\psi}(t)$ . By following the procedures of the extended Kalman filter based estimators, take the following Taylor series expansion

$$\begin{aligned}\mathbf{f}(\mathbf{x}(t), \mathbf{x}(t - \tau)) - \mathbf{f}(\hat{\mathbf{x}}(t), \hat{\mathbf{x}}(t - \tau)) &= \\ &= \mathbf{A}(t)(\mathbf{x}(t) - \hat{\mathbf{x}}(t)) + \mathbf{A}_\tau(t)(\mathbf{x}(t - \tau) - \hat{\mathbf{x}}(t - \tau)) + \dots \\ &\quad \boldsymbol{\varphi}(\mathbf{x}(t), \mathbf{x}(t - \tau), \hat{\mathbf{x}}(t), \hat{\mathbf{x}}(t - \tau)),\end{aligned}$$

where, according to Raff and Allgower (2006), a linearization term in the time delay is considered since

$$\begin{aligned}\mathbf{A}(t) &\triangleq \left[ \frac{\partial \mathbf{f}(\mathbf{x}(t), \mathbf{x}(t - \tau))}{\partial \mathbf{x}(t)} \right] \Bigg|_{\substack{\mathbf{x}(t) = \hat{\mathbf{x}}(t) \\ \mathbf{x}(t - \tau) = \hat{\mathbf{x}}(t - \tau)}}, \\ \mathbf{A}_\tau(t) &\triangleq \left[ \frac{\partial \mathbf{f}(\mathbf{x}(t), \mathbf{x}(t - \tau))}{\partial \mathbf{x}(t - \tau)} \right] \Bigg|_{\substack{\mathbf{x}(t) = \hat{\mathbf{x}}(t) \\ \mathbf{x}(t - \tau) = \hat{\mathbf{x}}(t - \tau)}}\end{aligned}\quad (5)$$

and  $\boldsymbol{\varphi}(\cdot)$  encompasses the higher order terms. The observer gain matrix  $\mathbf{L}(t)$  is computed as

$$\mathbf{L}(t) = \mathbf{P}(t)\mathbf{C}\mathbf{R}^{-1},\quad (6)$$

with  $\mathbf{R} \in \mathbb{R}^{m \times m}$  a positive definite constant matrix and  $\mathbf{P}(t)$  is the solution of the modified Riccati matrix

$$\begin{aligned}\dot{\mathbf{P}}(t) &= (\mathbf{A}(t) - \mathbf{L}(t)\mathbf{C})\mathbf{P}(t) + \mathbf{P}(t)(\mathbf{A}^T(t) - \beta\mathbf{I}) \\ &\quad + \mathbf{Q} + \gamma\mathbf{A}_\tau(t)\mathbf{A}_\tau^T(t),\end{aligned}\quad (7)$$

where  $\beta$  and  $\gamma$  positive constants and  $\mathbf{Q} \in \mathbb{R}^{n \times n}$ ,  $\mathbf{Q}$  a constant positive definite matrix. In addition, the following assumptions are in order.

#### Assumptions

- (i) There exist constants  $\delta, \rho > 0$  such that

$$\delta\mathbf{I} \leq \mathbf{P}(t) \leq \rho\mathbf{I}.$$

- (ii) There exist constants  $\mu, \nu > 0$  such that

$$\begin{aligned}\|\boldsymbol{\varphi}(\mathbf{x}(t), \mathbf{x}(t - \tau), \hat{\mathbf{x}}(t), \hat{\mathbf{x}}(t - \tau))\| &\leq \\ \mu\|\mathbf{x}(t) - \hat{\mathbf{x}}(t)\|^2 + \nu\|\mathbf{x}(t - \tau) - \hat{\mathbf{x}}(t - \tau)\|^2.\end{aligned}$$

The following lemma demonstrated formally in Hugues-Salas and Shore (2010) establishes the observer for a general nonlinear time delay system.

*Lemma 1.* (Hugues-Salas and Shore (2010)) Consider the nonlinear time-delay system (3) and its proposed observer given in (4)-(7). Let the assumptions (i) and (ii) hold. Then the system (4)-(7) is a local observer of (3), *i.e.* the reconstruction error  $\mathbf{x}(t) - \hat{\mathbf{x}}(t)$  is locally stable.

*Remark 1.* Modified Riccati equation (7) differs from the classical equation by the introduction of two terms,  $\beta\mathbf{I}$  and  $\gamma\mathbf{A}_\tau\mathbf{A}_\tau^T$ . According to Reif et al. (1998),  $\beta$  gives to the observer a prescribed degree of stability which can be used to compensate the influence of noise in the measurements. Delay jacobian term in the Taylor expansion was pointed out by Raff and Allgower (2006). To compensate this term,  $\gamma$  is introduced in order to reduce its action in the error dynamics. This combination allows to generate a robust observer which deals with noise and nonlinear delay terms. Regarding global stability, it depends on the unboundedness of matrix  $\mathbf{P}$ , but given assumption (i), only local stability can be achieved (for further details see Hugues-Salas and Shore (2010)).

#### 3.2 Application of the robust observer to TDQS model.

Even though that our model considers up- and down-regulated bacteria sub-populations, we may be able to measure one of such a sub-populations by means of key solution features of our system. In this work it is supposed that only  $u(t)$  is measurable, and  $w(t)$ ,  $v(t)$ , and parameter  $K(t)$  are unknown. For the sake of observation, the augmented state vector and delayed state vector are defined by  $\mathbf{x}(t)^T = (w(t), v(t), u(t), K(t))$ , and  $\mathbf{x}(t - \tau)^T = (w(t - \tau), v(t), u(t), K(t))$ , respectively.  $\hat{\mathbf{x}}(t) = (\hat{w}(t), \hat{v}(t), \hat{u}(t), \hat{K}(t))^T$  and  $\hat{\mathbf{x}}(t - \tau) = (\hat{w}(t - \tau), \hat{v}(t), \hat{u}(t), \hat{K}(t))^T$ . The augmented system is given by (3) with

$$\mathbf{f}(\mathbf{x}(t), \mathbf{x}(t - \tau)) = \begin{pmatrix} d(u(t) + v(t)) - cw(t) \\ w(t - \tau)v(t)u^2(t) + a\epsilon v(t) - v^2(t) \\ \frac{w(t - \tau)u^2(t)}{1 + \hat{K}(t)u^2(t)} + av(t) - bu(t)v(t) \\ \hat{K}(t) \end{pmatrix}$$

where last row corresponds to  $\dot{K}(t) = 0$  when  $K$  constant.  $\mathbf{f}(\hat{\mathbf{x}}(t), \hat{\mathbf{x}}(t - \tau))$  is obtained by substituting  $\mathbf{x}(t) \rightarrow \hat{\mathbf{x}}(t)$   $\mathbf{x}(t - \tau) \rightarrow \hat{\mathbf{x}}(t - \tau)$ .

As it was previously mentioned, only  $u(t)$  is measurable, then output function of system (3) is given by  $y(t) = \mathbf{C}\mathbf{x}(t) = (0 \ 0 \ 1 \ 0)\mathbf{x}(t)$ , and the observer has the form (4)-(7) with numerical gains and initial conditions given in the following section.

#### 4. NUMERICAL RESULTS AND DISCUSSION

##### 4.1 Open loop TDQS system behavior.

Time evolution of states  $w(t)$ ,  $v(t)$ ,  $u(t)$  when  $K$  is constant and time varying for the TDQS system are depicted in Fig. 1. Time varying  $K(t)$  represents a possible periodic lack of resources and is given in the simulation by  $K(t) = 49/1125 + 0.04\sin(0.005t)$ . Initial state in the system was  $(w(t), v(t), u(t))^T = (3/10, 0.1, 0.1)$ ,  $t \in [-\tau, 0]$ ,  $\tau = 52$ , for both cases. It is important to notice that oscillatory responses match with the results given in Chen et al. (2019) and Zhang et al. (2016) where non vanishing periodic solutions were related with the time delay introduction. Notice how dynamics of the TDQS system is not so affected by introduction of the time dependent  $K(t)$  and only slight differences appear in the behavior of the states.

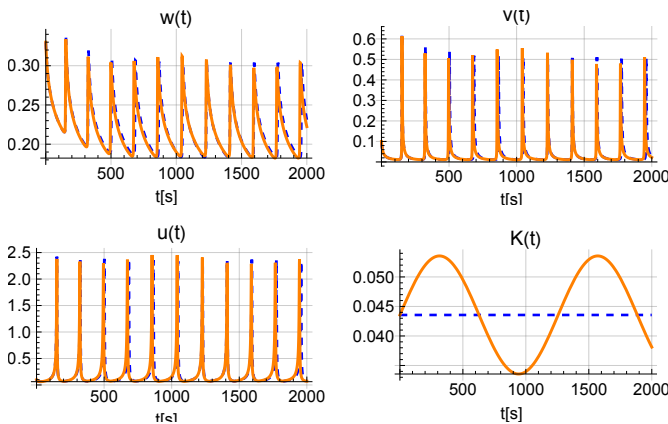


Fig. 1. Dynamic behavior of the TDQS system states with a constant value  $K$  (blue dotted line) and with a time-varying  $K(t)$  (solid orange line).

##### 4.2 States and parameter estimation of TDQS.

As it was stated before, it was supposed that only  $u(t)$  is measurable and estimation of the robust observer (4)-(7)

was applied to reconstruct  $w(t)$ ,  $v(t)$  and  $K$  constant in first place. Tuning parameters were  $\gamma = 100$ ,  $\beta = 10^{-4}$ ,  $\mathbf{Q} = 100\mathbf{I}$ ,  $\mathbf{R} = R = 1$ . Numerical results are shown in Fig. 2 and 3 where it can be seen that, even when only one state is measured, all other states and the unknown constant parameter  $K$  were successfully reconstructed.

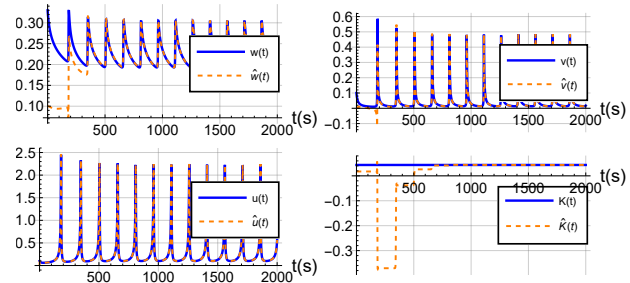


Fig. 2. Real states  $w(t)$ ,  $v(t)$  and real constant parameter  $K$  (blue line) and their estimations  $\hat{w}(t)$ ,  $\hat{v}(t)$ ,  $\hat{K}(t)$  (orange dotted line) reconstructed with observer (4)-(7).  $u(t)$  matches with  $\hat{u}(t)$ ,  $\forall t \geq 0$  since it was the measured state.

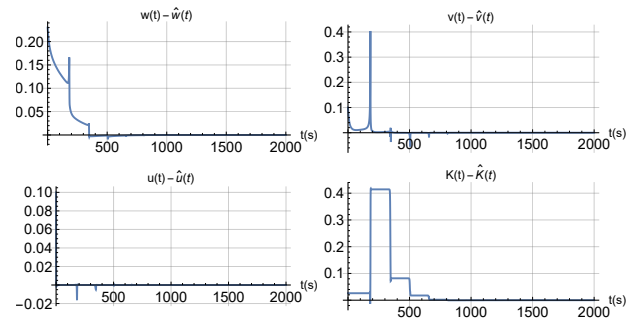


Fig. 3. Observer error results between real and estimated quantities for  $K$  constant.

In Fig. 4 and 5 the results for the state reconstruction of  $w(t)$ ,  $v(t)$  and the time-varying parameter  $K(t)$  are shown. Is noticeable that also the states and the parameter are estimated after  $\approx 500$  s.

In order to show that Assumption (i) is fulfilled, in Fig. 6 the maximum and minimum eigenvalues of the matrix  $\mathbf{P}(t)$  solution of the modified Riccati equation (7) are depicted. Notice that the matrix remains positive definite and bounded, so local stability of the estimation error is achieved.

As the term  $1 + \hat{K}(t)u^2(t)$  could cause a singularity, in Fig. 7 the value of this term is shown. It can be seen that during the observation process it does not become null. Nevertheless, as the observer is designed such that  $K$  remains constant, it still can catch the nonmeasurable states, as well  $\hat{K}$  remains close to the actual values of the parameter  $K$ .

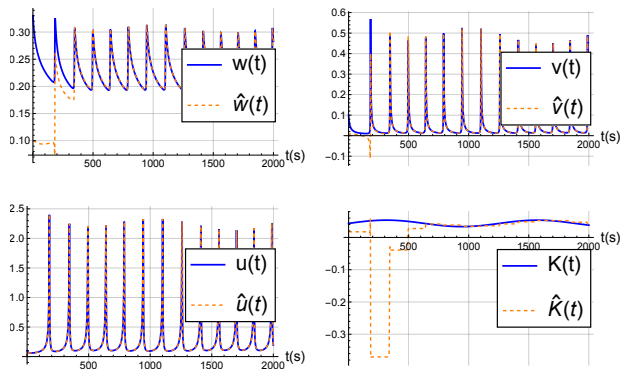


Fig. 4. Real states  $w(t)$ ,  $v(t)$  and real time varying parameter  $K(t)$  (blue line) and their estimations  $\hat{w}(t)$ ,  $\hat{v}(t)$ ,  $\hat{K}(t)$  (orange dotted line) reconstructed with observer (4)-(7).  $u(t)$  matches with  $\hat{u}(t)$ ,  $\forall t \geq 0$  since it was the measured state.

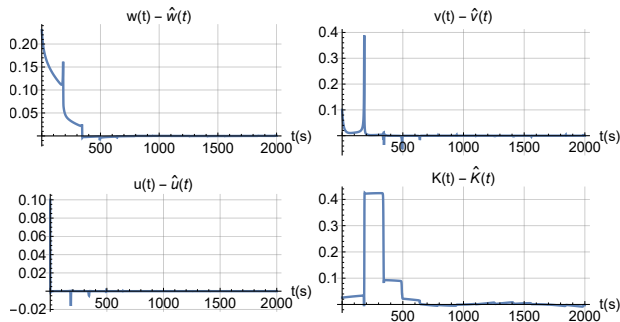


Fig. 5. Observer error results between real and estimated variables with time-varying  $K(t)$ .

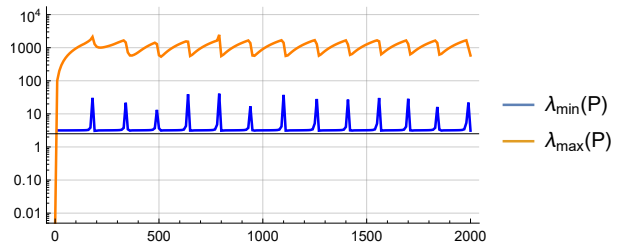


Fig. 6. Boundedness test of matrix  $\mathbf{P}(t)$  through time, in logarithmic scale, shown as the value of its minimum and maximum eigenvalues for the case of a time-varying parameter  $K(t)$ .

## 5. CONCLUSIONS

Quorum sensing is an organization process by which bacteria colonies manifest collective behaviors. Many processes such as symbiosis, competence, virulence, motility, sporulation, biofilm formation, antibiotic production and resistance are known to behave upon QS regulatory mechanisms. Hence, QS dynamics is relevant to be reconstructed in scenarios where measurements are limited and characteristic activation delay times are taken into

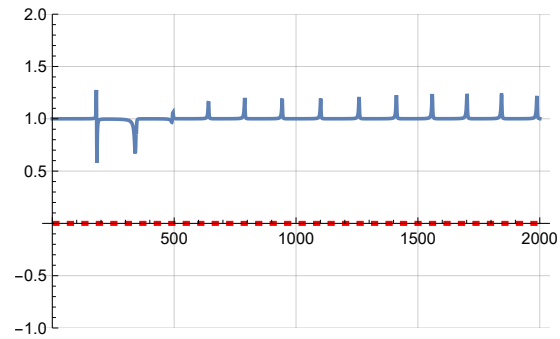


Fig. 7. Evaluation of the term  $1 + \hat{K}(t)\hat{u}^2(t)$  through time, considering possible singularities. In blue it is shown the value of  $K(t)$ , and in dotted red line the value of 0, that lead to the singularity.

account. In this work we showed how a TDQS model exhibit oscillations predicted in the literature, and how, by measuring only the density of motile bacteria, the autoinducer concentration and the density of static bacteria can be estimated. Estimation of a nonlinear parameter related with availability of resources in the environment was also possible. These results were obtained by applying an extended Kalman filter, which is robust to noise as well as nonlinear delay terms.

The conditions for estimation error stability are discussed in the context established by previous works, and numerical results were presented to show how such stability is achieved. Future work involves the explicit analytical stability for changes in the delay term, as well as explore a wider number of parameter reconstruction for experimental data, considering noisy measurements. As future work, observers can be applied to estimate states in models which describe important diseases in order to propose better control and therapy schemes.

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