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Nonlinear Time-Delayed Quorum Sensing System: State Estimation via a Robust Observer ⋆

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Abstract: This paper proposes an innovative method to estimate the states in a nonlinear time-delayed quorum sensing (QS) model using an extended Kalman filter (EKF) observer. By addressing the inherent time delays in QS system which arise as a delayed response of bacteria to population fluctuations, the study introduces variable structure dynamical estimators, specifically the EKF, to approximate missing states based on available measurements. The EKF observer is applied to estimate four out of five internal non-measurable nonlinear states in a time-delayed QS model. This is the first attempt to utilize the EKF state estimation in nonlinear time delay QS models. The research contributes to the understanding of QS systems, provides insights into the communication dynamics inside biological systems, and offers a practical solution for estimating states in realistic scenarios.

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

1. INTRODUCTION

Quorum sensing (QS) describes the regulation of biological organisms gene expressions in response to changes in the population density sensed by certain signaling molecules called *autoinducers*. There exist diverse QS systems, but those regulated by autoinducers acyl homoserine lactones (AHLs) are particularly important. For instance, some QS circuits moderated by AHL molecules are used to explain some human pathogens virulence, as in the case of the *Pseudomonas aeruginosa*, (Lazdunski et al., 2004), *Streptococcus pneumoniae* (Karlsson et al., 2007), and *Staphylococcus aureus* (Lyon and Novick, 2004), to name a few. When concentration of AHL reaches certain threshold, different expressions of specific genes are triggered through the action of diverse proteins. Between them, certain class of intracellular protease called *LuxI* and a type of lactonase named *AiiA* are particularly important since it is well known that they participate in the synthesis and hydrolisis of AHL, respectively. The collective result obtained by the interplay of the aforementioned substances is that populations can achieve physiological and regulatory functions that cannot be reached by a single individual.

In general, QS regulatory circuits assume the *instantaneous* production, release, recognition, and response to autoinducers. However, there exist inherent time delays due to transcription and translation processes that have increasingly been taken into account in the models. For instance, in Barbarossa et al. (2010) a time delay was introduced to consider a lagged activation of lactonase which prompts autoiducers communication. In Zhang et al. (2016) a model of *Escherichia coli* gene regulatory network is affected by introducing time delays in transcription and translation processeses. A translation delay of 1-3 min is used to synthesize certain protein from mRNA in Honkela et al. (2015) or a transcriptional delay of 10-20 min is present between the action of a gene factor and maduration of corresponding mRNA (Monk (2020)).

It has been widely recognized that a better understanding of the QS system for using it in the solution of human health problems depends on full knowledge of diverse model variables and some capabilities to measure them. In this sense, for instance, *LuxI* can be quantified using methods such as Western blotting, enzyme-linked immunosorbent assay (ELISA), and fluorescence-based approaches like fluorescence resonance energy transfer

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(FRET). In addition, biosensors have been developed to measure the concentration of autoinducers and *LuxI* in real-time. Biosensors are devices which utilize receptor molecules coupled with transducers like green fluorescent protein (GFP) or luciferase reporter genes, to convert the binding events into measurable signals. It is important to mention that *LuxI* is relatively easier to measure compared to some other substances, because it is a protein whose concentration can be detected using specific antibodies or fluorescence-based assays.

The measurement of QS related substances is always a challenge as they depend on several chemical and physical reactions whose estimation show practical limitations. To complement the measuring process, variable structure dynamical estimators could be designed to estimate missing states and/or parameters once a linear or a nonlinear time delay model is at hand (Richard (2003)). For instance, in Marquez-Martinez et al. (2000) and Batmani and Khaloozadeh (2014) some change of coordinates is designed to give a nonlinear time delay system a linear-like structure where linear estimation techniques accomplish approximation of states and parameters. 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. Although the aforementioned techniques are widely applied in control systems, estimation of variables in time delay QS models is still an open problem.

Contribution. In this work the estimation of four out of five internal states in a nonlinear time-delayed QS model using an EKF is accomplished. Selection of known states is supported on the physical measuring capabilities of QS substances. With base on standard chemical experiments this paper suggests that only the *LuxI* protein can be effectively measured. Local stability and convergence of the estimation error dynamics is reached.

The remaining manuscript is organized as follows: a summary of the particular time delay QS (TDQS) model addressed in this work is given in Section 2. The EKF based observer for general time delay nonlinear dynamics reported in Raff and Allgower (2006) 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 TIME DELAY SYSTEM

A biochemical model of QS which describes the relationship between AHL, LuxI and AiiA proteins in the *Vibrio fischeri* and *Bacillus thuringiensis*, that take into account the time delay dynamics of the internal AHL, has been proposed by Chen et al. (2020), based on the analysis by Prindle et al. (2014), and is given by the model:

$$
\begin{aligned}
\dot{x} &= k_1\left(k_2+\frac{k_3\left(\frac{z(t-\tau)}{k_4}\right)^4}{1+\left(\frac{z(t-\tau)}{k_4}\right)^4}\right)-\frac{k_5\frac{x(t)}{k_6}}{1+\frac{x(t)}{k_6}+\frac{y(t)}{k_7}},\\
\dot{y} &= k_8\left(k_2+\frac{k_3\left(\frac{z(t-\tau)}{k_4}\right)^4}{1+\left(\frac{z(t-\tau)}{k_4}\right)^4}\right)-\frac{k_9\frac{y(t)}{k_7}}{1+\frac{x(t)}{k_6}+\frac{y(t)}{k_7}},\\
\dot{z} &= \frac{k_{10}y(t)\frac{w(t)}{k_{11}}}{1+\frac{w(t)}{k_{11}}}-\frac{k_{12}x(t)\frac{z(t)}{k_{13}}}{1+\frac{z(t)}{k_{13}}}+D(p(t)-z(t)),\\
\dot{p} &= -\frac{d}{1-d}D(p(t)-z(t))-\mu p(t),\\
\dot{w} &= S_0-w(t)-\frac{k_{10}y(t)\frac{w(t)}{k_{11}}}{1+\frac{w(t)}{k_{11}}}.
\end{aligned}
\tag{1}
$$

where x, y, z, p, w denote the intracellular concentrations of AiiA, LuxI, internal AHL, external AHL and AHL substrate, respectively. Parameters k_1 and k_8 denote the AiiA copy number and the LuxI copy number, d is the cell density, k_{10} represents the AHL synthesis rate by LuxI. Difference multiplied by D describe the diffusion across the membrane where $p(t)$ describes the dilution of external AHL. Factors multiplied by k_5 and k_9 represents the enzymatic degradation of LuxI and AiiA, respectively. k_2, k_3, k_4 denote Lux promoter basal production, Lux promoter AHL induced production and AHL promoter binding affinity, respectively. k_6 is AiiA binding affinity to ClpXP, k_7 LuxI binding affinity to ClpXP, k_{11} AHL substrate binding affinity to LuxI, and k_{13} is AHL binding affinity to AiiA. S_0 stands for basal AHL substrate production, and k_{12} is the AHL degradation rate by AiiA. In this model, time delays due to transcription, translation, and maturation of functional AiiA and LuxI proteins are condensed in a unique time delay τ.

This model is useful to obtain a comprehensive understanding of QS systems, and allows to: obtain an accurate representation of the biological processes involved, provide insights into protein production kinetics, enable predictions and simulations, aid parameter estimation, and facilitate the study of time-dependent phenomena. By considering the temporal dynamics and sequence of events in protein production, this model enhances our understanding of QS dynamics and aids in experimental design and optimization.

2.1 Discussion on the experimental measurements of the variables in the QS model

One of the most widely used techniques for real-time concentration measurement of autoinducers is surface plasmon resonance (SPR). SPR allows for label-free detection of molecules by monitoring changes in the refractive index near a metal surface. It has been used to measure the binding of autoinducers to their receptors, as well as to quantify the concentration of autoinducers in solution. Other techniques for autoinducer detection include

enzyme-linked immunosorbent assays (ELISAs), fluorescence resonance energy transfer (FRET), and mass spectrometry (MS). For LuxR and LuxI, the concentration can be measured using a variety of techniques. The most common method is Western blotting, which involves the separation of proteins using gel electrophoresis, followed by transfer to a membrane and detection with specific antibodies. This technique has been used to measure the concentration of LuxR and LuxI in various bacterial strains. Another method is enzyme-linked immunosorbent assay (ELISA), which uses specific antibodies to detect and quantify the protein of interest. Fluorescence-based methods such as fluorescence resonance energy transfer (FRET) and Förster resonance energy transfer (FRET) have also been used to measure the concentration of LuxR and LuxI. In addition to these traditional techniques, biosensors have been developed to measure the concentration of autoinducers, LuxR, and LuxI in real time. Biosensors are analytical devices that detect and respond to specific biological or chemical molecules. They have been developed for a wide range of applications, including environmental monitoring, food safety, and medical diagnostics. Biosensors for QS typically consist of a receptor molecule that recognizes the autoinducer or regulatory protein of interest, coupled with a transducer that converts the binding event into a measurable signal. Several biosensors have been developed for the detection of autoinducers. One example is the LuxR-based biosensor, which utilizes LuxR as the receptor molecule and a green fluorescent protein (GFP) reporter gene as the transducer. The binding of autoinducers to LuxR activates the expression of the GFP gene, resulting in fluorescence that can be measured in real time. Another biosensor is based on the LuxI/LuxR QS system and uses LuxI as the receptor molecule and a luciferase reporter gene as the transducer. The binding of autoinducers to LuxI results in the synthesis of a substrate for luciferase, which produces light that can be measured in real time. Biosensors have also been developed for the detection of LuxR and LuxI. One example is the use of split-luciferase complementation assays, which involve the co-expression of two non-functional fragments of luciferase fused to LuxR or LuxI. When LuxR or LuxI is present at high concentrations, it brings the two fragments of luciferase into proximity, resulting in complementation and the production of light that can be measured in real time. Overall, a variety of techniques have been developed for measuring the concentration of autoinducers, LuxR, and LuxI in real time. These techniques are essential for understanding the dynamics of QS and have a wide range of applications in basic research, biotechnology, and medicine.

2.2 Assumptions of the model

(1) The system (1) has a unique positive equilibrium point since from the biology point of view only positive equilibrium is of interest. Such equilibrium is denoted by $E^* = (x^*, y^*, z^*, p^*, w^*)$ and it is defined as the point which satisfies the equations set $\dot{x} = 0, \dot{y} = 0, \dot{z} = 0, \dot{p} = 0, \dot{w} = 0$ given from system (1) evaluated in $(x^*, y^*, z^*, p^*, w^*)$.
(2) From the discussion presented in Sect. 2.1, it is assumed that LuxI, *i.e.* the state y is the only measurable variable,
(3) The system parameters, as well as the time-delay are known,
(4) Variables x, w, p and w are not measurable.

Determining the concentration of autoinducer synthase enzyme LuxI has several advantages. Since LuxI produces the autoinducer molecule required for the signaling pathway, its activity directly correlates with QS activity. The study can focus and observe the QS processes of Gram-negative bacteria by concentrating on LuxI, measuring its concentration, sheds light on the regulatory mechanisms governing QS and the effects of environmental variables and cell density on LuxI expression and activity. Additionally, it makes it possible to quantitatively analyze QS dynamics, which makes it easier to research activation kinetics and how it affects bacterial behavior and population dynamics. Moreover, LuxI measurement has diagnostic implications as well because it may be connected to abnormal expression or poorly controlled QS. Therefore, in this work we focus on considering that LuxI as the only measurable variable.

3. NONLINEAR OBSERVER OF THE TDQS SYSTEM.

3.1 Extended Kalman filter for general nonlinear time delay systems.

From Raff and Allgower (2006), it is taken into consideration the class of nonlinear time delay systems in the form:

$$\begin{aligned} \dot{\mathbf{x}}(t) &= \mathbf{f}(\mathbf{x}(t), \mathbf{x}(t-\tau)), \\ \mathbf{x}(t) &= \boldsymbol{\psi}(t), t \in [-\tau, 0], \\ \mathbf{y}(t) &= \mathbf{C}\mathbf{x}(t), \end{aligned} \tag{2}$$

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 the missing states from a measurable output

$$\begin{aligned} \dot{\hat{\mathbf{x}}}(t) &= \mathbf{f}(\hat{\mathbf{x}}(t), \hat{\mathbf{x}}(t-\tau)) + \mathbf{L}(t)(\mathbf{y}(t) - \mathbf{C}\hat{\mathbf{x}}(t)), \\ \hat{\mathbf{x}}(t) &= \boldsymbol{\xi}(t), t \in [-\tau, 0], \end{aligned} \tag{3}$$

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

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

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

$$\mathbf{A}\left(t\right) \triangleq \left[\frac{\partial \mathbf{f}(\mathbf{x}\left(t\right),\mathbf{x}\left(t-\tau\right))}{\partial \mathbf{x}\left(t\right)}\right]\Bigg|_{\substack{\mathbf{x}\left(t\right)=\hat{\mathbf{x}}\left(t\right)\\ \mathbf{x}\left(t-\tau\right)=\hat{\mathbf{x}}\left(t-\tau\right)}},$$
$$\mathbf{A}_{\tau}\left(t\right) \triangleq \left[\frac{\partial \mathbf{f}(\mathbf{x}\left(t\right)\mathbf{x}\left(t-\tau\right))}{\partial \mathbf{x}\left(t-\tau\right)}\right]\Bigg|_{\substack{\mathbf{x}\left(t\right)=\hat{\mathbf{x}}\left(t\right)\\ \mathbf{x}\left(t-\tau\right)=\hat{\mathbf{x}}\left(t-\tau\right)}} \quad (4)$$

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

$$\mathbf{L}\left(t\right)=\mathbf{P}\left(t\right)\mathbf{C}\mathbf{R}^{-1}, \quad (5)$$

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

$$\begin{aligned}\dot{\mathbf{P}}\left(t\right)=&\left(\mathbf{A}\left(t\right)-\mathbf{L}\left(t\right)\mathbf{C}\right)\mathbf{P}\left(t\right)+\mathbf{P}\left(t\right)\left(\mathbf{A}^{T}\left(t\right)\right)\\&+\mathbf{Q}+\gamma\mathbf{A}_{\tau}\left(t\right)\mathbf{A}_{\tau}^{T}\left(t\right), \quad (6)\end{aligned}$$

where γ is a positive constant 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

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

(ii) The higher-order terms in the Taylor expansion given by $\boldsymbol{\varphi}(\cdot,\cdot,\cdot,\cdot)$ are such that there exist constants $\mu,\nu>0$ that

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

Remark 1. Assumption (ii) implies estimated variable is guaranteed to be within a region of validity in which $\mathbf{A}(t)$ and $\mathbf{A}_{\tau}(t)$ are representative of the nonlinear behavior among the trajectories of the observed state, which is conventional in the EKF.

Remark 2. Modified Riccati equation (6) differs from the classical equation by the introduction of the term $\gamma\mathbf{A}_{\tau}\mathbf{A}_{\tau}^{T}$. The delay jacobian term in the Taylor expansion was pointed out by Raff and Allgower (2006). To compensate this term, γ 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)).

From the previous discussion, the following lemma can be established:

Lemma 1. (Raff and Allgower (2006)) Consider the nonlinear time-delay system (2) and its proposed observer given in (3)-(6). Let the assumptions (i) and (ii) hold. Then the system (3)-(6) is a local observer of (2), *i.e.* the reconstruction error $\mathbf{x}(t)-\hat{\mathbf{x}}(t)$ is locally stable.

3.2 Application of the robust observer to TDQS model.

By applying the proposed EKF to (1), it is obtained, from (4):

$$\mathbf{A}(t)=(\mathbf{A}_1,\ \mathbf{A}_2,\ \mathbf{A}_3,\ \mathbf{A}_4,\ \mathbf{A}_5) \quad (7)$$

where

$$\mathbf{A}_1=\begin{pmatrix}\frac{k_5x}{k_6^2\left(\frac{x}{k_6}+\frac{y}{k_7}+1\right)^2}-\frac{k_5}{k_6\left(\frac{x}{k_6}+\frac{y}{k_7}+1\right)}\\ \frac{k_9y}{k_6k_7\left(\frac{x}{k_6}+\frac{y}{k_7}+1\right)^2}\\ -\frac{k_{12}z}{k_{13}\left(\frac{z}{k_{13}}+1\right)}\\ 0\\ 0\end{pmatrix} \quad (8)$$

$$\mathbf{A}_2=\begin{pmatrix}\frac{k_5x}{k_6k_7\left(\frac{x}{k_6}+\frac{y}{k_7}+1\right)^2}\\ \frac{k_9y}{k_7^2\left(\frac{x}{k_6}+\frac{y}{k_7}+1\right)^2}-\frac{k_9}{k_7\left(\frac{x}{k_6}+\frac{y}{k_7}+1\right)}\\ \frac{k_{10}w}{k_{11}\left(\frac{w}{k_{11}}+1\right)}\\ 0\\ -\frac{k_{10}w}{k_{11}\left(\frac{w}{k_{11}}+1\right)}\end{pmatrix} \quad (9)$$

$$\mathbf{A}_3=\begin{pmatrix}0\\ 0\\ -D-\frac{k_{12}x}{k_{13}\left(\frac{z}{k_{13}}+1\right)}+\frac{k_{12}xz}{k_{13}^2\left(\frac{z}{k_{13}}+1\right)^2}\\ \frac{dD}{1-d}\\ 0\end{pmatrix} \quad (10)$$

$$\mathbf{A}_4=\begin{pmatrix}0\\ 0\\ D\\ -\frac{dD}{1-d}-\mu\\ 0\end{pmatrix} \quad (11)$$

$$\mathbf{A}_5=\begin{pmatrix}0\\ 0\\ \frac{k_{10}y}{k_{11}\left(\frac{w}{k_{11}}+1\right)}-\frac{k_{10}wy}{k_{11}^2\left(\frac{w}{k_{11}}+1\right)^2}\\ 0\\ -\frac{k_{10}y}{k_{11}\left(\frac{w}{k_{11}}+1\right)}+\frac{k_{10}wy}{k_{11}^2\left(\frac{w}{k_{11}}+1\right)^2}-1\end{pmatrix} \quad (12)$$

$$\mathbf{A}_\tau(t) = \begin{pmatrix} 0\ 0\ k_1\left(\frac{4k_3 z_\tau^3}{k_4^4\left(\frac{z_\tau^4}{k_4^4}+1\right)} - \frac{4k_3 z_\tau^7}{k_4^8\left(\frac{z_\tau^4}{k_4^4}+1\right)^2}\right) & 0\ 0 \\ 0\ 0\ k_8\left(\frac{4k_3 z_\tau^3}{k_4^4\left(\frac{z_\tau^4}{k_4^4}+1\right)} - \frac{4k_3 z_\tau^7}{k_4^8\left(\frac{z_\tau^4}{k_4^4}+1\right)^2}\right) & 0\ 0 \\ 0\ 0 \quad 0 \quad 0\ 0 \\ 0\ 0 \quad 0 \quad 0\ 0 \\ 0\ 0 \quad 0 \quad 0\ 0 \end{pmatrix} \tag{13}$$

4. NUMERICAL RESULTS

The proposed method was applied considering the parameters $k_1 = 1$, $k_2 = 0.6$, $k_3 = 3$, $k_4 = 0.1$, $k_5 = 15$, $k_6 = 1$, $k_7 = 0.2$, $k_8 = 4$, $k_9 = 8$, $k_{10} = 1$, $k_{11} = 25$, $k_{12} = 1$, $k_{13} = 0.1$, $D = 0.8$, $d = 0.1$, $\mu = 0.5$ and $S_0 = 50$ for the model, with an initial condition $\mathbf{x}(0) = (70, 100, 0.05, 0.01, 10)^T$, and $\mathbf{C} = (0, 1, 0, 0, 0)$, $\mathbf{Q} = \text{diag}(0.01, 0.01, 0.01, 0.01, 0.01, 100)$, $\mathbf{R}^{-1} = 0.01\mathbf{I}$, $b = 100$, $g = 100$. In Fig. 1 and 2 it can be seen how, even with only one measurement available, the observer effectively reconstructs the remaining states. In order to obtain a reasonable sense of its observability, the linearization of the system without time-delay was obtained around the equilibrium point given by $\mathbf{x}^* = (81.581, 122.371, 0.0891744, 0.0134603, 11.4832)$, resulting in an observable system. However, it is still an open question the observability analysis for the nonlinear system that considers the time-delay.

In order to test the robustness of the proposed algorithm, it was also considered that the LuxI measurement could only be obtained in samples of $T_s = 20s$ seconds, so a zero-order hold was considered as the input of the observer (that is $\mathbf{y}(t) = \mathbf{y}^*,\ t \in (t, t + T_s)$), where $\mathbf{y}^*$ is the sample of the state variable y in time t, that is maintained constant until the next sample is measured. In Fig. 3 and 4 it is shown how, even under these restrictive measuring conditions, the observer is still capable of reconstruct the rest of the states. In Fig. 5 it is shown how the matrix $\mathbf{P}(t)$ fulfills Assumption (i) during all the observation process, that also gives an insight on the reconstruction process as well as a numerical approximation on the observability of the system.

5. CONCLUSIONS

In this paper it was presented an method for estimating parameters and states in a nonlinear time-delayed quorum sensing model using an extended Kalman filter (EKF) observer that also addresses the the inherent time delays in QS systems as well as considerations for physically measurable states in realistic scenarios. The effectiveness of the proposed method was shown in different scenarios, considering that the measurements are not continuously available but only in determined time instants, and reaching a convergent estimation. Future work considers incorporating the time delays inherent to the measurement

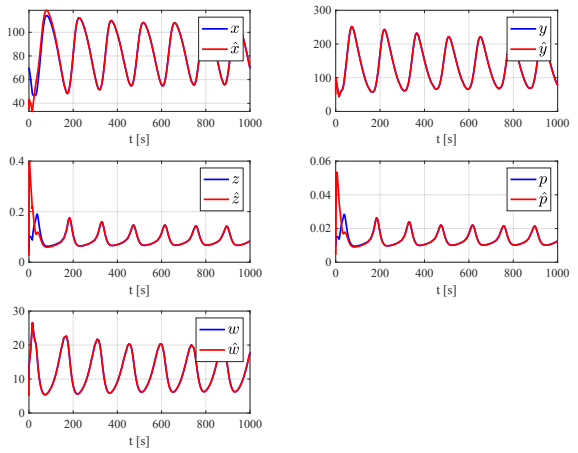

Fig. 1. Observer results to reconstruct the states using only the measurement of $LuxI$.

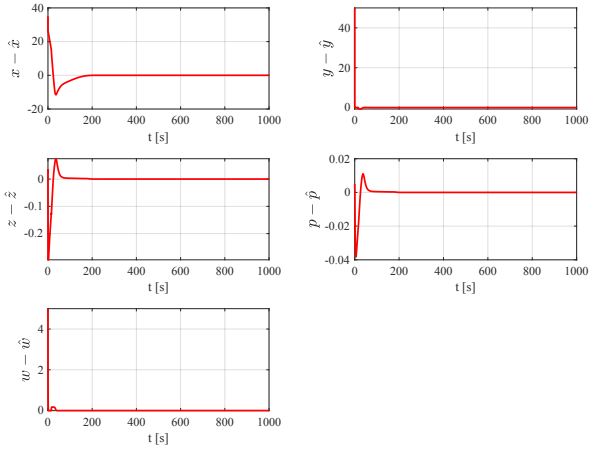

Fig. 2. Estimation error using only the measurement of $LuxI$.

process, added to the sampling effect, and also a parametric reconstruction. Also, it is still an open research field the analysis of the observability region of the nonlinear model.

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REFERENCES

Barbarossa, M.V., Kuttler, C., Fekete, A., and Rothballer, M. (2010). A delay model for quorum sensing of pseudomonas putida. *Biosystems*, 102(2-3), 148–156.

Batmani, Y. and Khaloozadeh, H. (2014). On the design of observer for nonlinear time-delay systems. *Asian Journal of Control*, 16(4), 1191–1201.

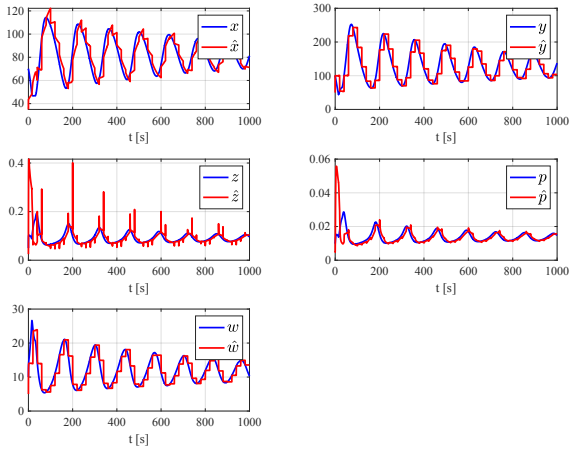

Fig. 3. Observer results to reconstruct the states using only the measurement of *LuxI* considering the time interval between measurements with a ZOH.

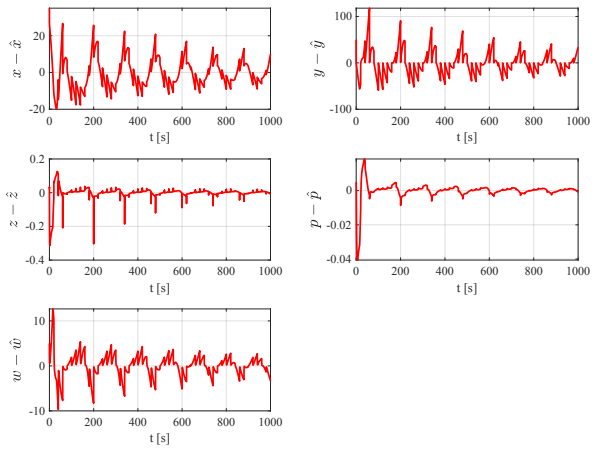

Fig. 4. Estimation error using only the measurement of *LuxI* considering the time interval between measurements with a ZOH.

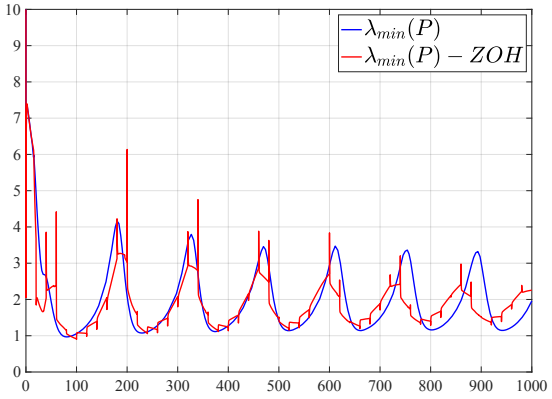

Fig. 5. Minimum eigenvalues for matrix $\mathbf{P}(t)$ both for the continuous measurments and considering a time interval between measurements using a ZOH.

Chen, M., Ji, J., Liu, H., and Yan, F. (2020). Periodic Oscillations in the Quorum-Sensing System with Time Delay. *International Journal of Bifurcation and Chaos*, 30(9). doi:10.1142/S0218127420501278.

Honkela, A., Peltonen, J., Topa, H., Charapitsa, I., Matarese, F., Grote, K., Stunnenberg, H.G., Reid, G., Lawrence, N.D., and Rattray, M. (2015). Genome-wide modeling of transcription kinetics reveals patterns of rna production delays. *Proceedings of the National Academy of Sciences*, 112(42), 13115–13120.

Hugues-Salas, O. and Shore, K.A. (2010). An extended kalman filtering approach to nonlinear time-delay systems: Application to chaotic secure communications. *IEEE Transactions on Circuits and Systems I: Regular Papers*, 57(9), 2520–2530.

Karlsson, D., Karlsson, S., Gustafsson, E., Normark, B.H., and Nilsson, P. (2007). Modeling the regulation of the competence-evoking quorum sensing network in streptococcus pneumoniae. *Biosystems*, 90(1), 211–223.

Lazdunski, A.M., Ventre, I., and Sturgis, J.N. (2004). Regulatory circuits and communication in gram-negative bacteria. *Nature Reviews Microbiology*, 2(7), 581–592.

Lyon, G.J. and Novick, R.P. (2004). Peptide signaling in staphylococcus aureus and other gram-positive bacteria. *Peptides*, 25(9), 1389–1403.

Marquez-Martinez, L., Moog, C., and Velasco-Villa, M. (2000). Observability and observers for nonlinear systems with time delays. *IFAC Proceedings Volumes*, 33(23), 109–114.

Monk, N. (2020). "oscillatory expression of hes1, p53, and nf-kappab driven by transcriptional time delays. *Curr. Biol.*, 13, 1409–1413.

Prindle, A., Selimkhanov, J., Li, H., Razinkov, I., Tsimring, L.S., and Hasty, J. (2014). Rapid and tunable post-translational coupling of genetic circuits. *Nature*, 508(7496), 387–391.

Raff, T. and Allgower, F. (2006). An ekf-based observer for nonlinear time-delay systems. In *2006 American control conference*, 4–pp. IEEE.

Richard, J.P. (2003). Time-delay systems: an overview of some recent advances and open problems. *automatica*, 39(10), 1667–1694.

Zhang, Y., Liu, H., and Zhou, J. (2016). Oscillatory expression in escherichia coli mediated by micrornas with transcriptional and translational time delays. *IET Systems Biology*, 10(6), 203–209.