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One-sided Lipschitz observer design for circadian models

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Abstract— **This paper deals with observer designs to mathematical models of circadian rhythms which exist in every living organism. Two mathematical models are considered, with a 3rd order model for Neurospora, and a 7th order model for Mammals. The observer design is based on systems with Lipschitz nonlinearities. In particular, observers based on onesided Lipschitz condition are investigated, and the observers are then designed for both circadian models. Detailed analysis is performed for nonlinear functions in the models to show the one-sided Lipschitz observers can indeed be applied. Several simulations studies of proposed observers are carried out with the results shown in this paper.**

I. INTRODUCTION

Circadian rhythms exist in most of living species on the Earth as self-sustained, periodic oscillations, and govern the daily biological activities of these species. Physiological functions such as sleep-walk cycle, blood pressure, and heart rate are examples of circadian rhythms. Robustness to external environmental changes is a property of these rhythms. Circadian rhythms can be disrupted, and this phenomenon is known as circadian disorders. Lack of treatment of circadian disorders may lead to negatively impact to daily activities and health. Jet lag caused by transcontinental flight, and sleeping disorder caused by irregular sleep patterns are two well known examples of circadian disorders. Because of the importance of circadian rhythms to daily life, study of characteristics of circadian rhythms has attracted the attention from researchers in many years. Many results have been presented ([1], [2], [3]). Among those results, the identification of key genes which contribute to oscillations of circadian rhythms ([4], [5], [6], [7]), and the development of circadian models ([8], [9], [10], [11]), are most successfully achieved results.

With the existence of the circadian models, different areas of research studies of circadian rhythms have been carried out, e.g. analyses of amplitude under light constraints [12], entrainment in light/dark cycle [13], robustness analysis [14], and sensitivity analysis ([15], [16]). A result has presented the application of observer to Neurospora model [17]. In control theory, observers are designed to estimate the unknown state variables in both linear and nonlinear systems. Therefore, they are often used for control implementations when unmeasured state variables are needed, e.g. [18]. Besides, using observer also helps to reduce number of output measurements. Reduction of measurements by using observers has not been much considered in system biology, especially to circadian models. This may due to the complexities of circadian models which are difficult for nonlinear observer design. It may also due to lack of right methods for observer designs in the past. Nevertheless, in recent years, some new methods of observer designs have been developed such as reduced order observer[19], and one-sided Lipschitz observer design [20]. An observer is called one-sided Lipschitz observer if its design is based on systems with one-sided Lipschitz nonlinearities. Since mathematical models of Neurospora and mammalian rhythms consist of nonlinear functions which are one-sided Lipschitz nonlinearities, therefore, in this paper, we propose one-sided Lipschitz observer to these models. The proposed observer design is based on new result obtained in [20] for one-sided Lipschitz observer.

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II. CIRCADIAN MODELS

A. Neurospora

A 3rd order model from [8] that describes molecular mechanism of circadian rhythms in Neurospora is considered. This model is based on the negative feedback exerted by FRQ proteins on the expression of frq gene. Its mechanism consists of the transcription, translation, and inhibition processes. Transcription of frq gene yields messenger RNA (mRNA), and the translation of which synthesize FRQ protein. Given that there are not complexes between FRQ protein and other proteins, and the FRQ protein is not phosphorylated [8], the synthesized FRQ proteins are then transferred back into nucleus where these proteins inhibit the transcription of frq gene. New transcription of frq gene restarts the cycle. Dynamics of these variables are governed by the following set of differential equations:

$$\begin{aligned} \dot{x}_1 &= v_s \frac{K_i^n}{K_i^n + x_3^n} - v_m \frac{x_1}{K_M + x_1} \\ \dot{x}_2 &= k_s x_1 - v_d \frac{x_2}{K_d + x_2} - k_1 x_2 + k_2 x_3, \qquad (1) \\ \dot{x}_3 &= k_1 x_2 - k_2 x_3 \end{aligned}$$

where x_1 denotes concentration of frq mRNA, x_2 denotes concentration of FRQ protein outside nucleus, and x_3 represents concentration of nucleus FRQ protein. States x_1, x_2, and x_3 are assumed to be positive values. The parameters have their values as: $v_s = 1.6nM.h^{-1}$, $K_i = 1nM$, n=4, $v_m = 0.7nM.h^{-1}$, $K_M = 0.4nM$, $k_s = 1h^{-1}$, $v_d = 4nM.h^{-1}$, $K_d = 1.4nM$, $k_1 = 0.3h^{-1}$, $k_2 = 0.15h^{-1}$.

B. Mammals

Circadian model of mammals is a 7th order model, and is proposed in [11] to investigate negative and positive feedback in mammalian circadian oscillator. Similar to Neurospora model, this model describes molecular mechanism of mammalian circadian rhythms. In mammals, $Per2$ gene, Cry gene, and $Bmal1$ gene have been identified as part of circadian oscillations. Therefore, oscillatory mechanism of this model consists of oscillations of PER2, CRY, and BMAL1 proteins. $Clock$ gene has also been identified as part of circadian oscillations in mammals. The expression of $Clock$ gene, CLOCK protein, together with the expression of $Bmal1$ gene, BMAL1 protein, are phosphorylated to form a heterodimer which activates the transcriptions of $Per2$ and Cry genes [11]. However, since CLOCK protein is expressed at a constant level [21], only oscillation of BMAL1 protein is considered [11]. Furthermore, the heterodimer BMAL1/CLOCK which activates the transcriptions of $Per2$ and Cry genes is now replaced by BMAL1*. BMAL1* is considered as a phosphorylated form of BMAL1 ([11], [22]), or as a complex with CLOCK protein ([11], [23]). The mechanism starts with the activation of BMAL1* to the transcription of $Per2$ to produce $Per2$ mRNA, and the transcription of Cry genes to produce Cry mRNA. However, in this mechanism, the expressions of $Per2$ gene and Cry gene, which are mRNAs of $Per2$ and Cry, and their proteins, are represented by the same variables [11]. Dynamics of involved mRNAs and proteins are described by the following set of differential equations:

$$\begin{aligned}
\dot{x}_1 &= \frac{v_{1b}(x_7+c)}{k_{1b}(1+(\frac{x_3}{k_{1i}})^p)+x_7+c} - k_{1d}x_1 \\
\dot{x}_2 &= k_{2b}x_1^q - (k_{2d}+k_{2t})x_2 + k_{3t}x_3 \\
\dot{x}_3 &= k_{2t}x_2 - (k_{3t}+k_{3d})x_3 \\
\dot{x}_4 &= \frac{v_{4b}x_3^r}{k_{4b}^r+x_3^r} - k_{4d}x_4, \\
\dot{x}_5 &= k_{5b}x_4 - (k_{5d}+k_{5t})x_5 + k_{6t}x_6 \\
\dot{x}_6 &= k_{5t}x_5 - (k_{6t}+k_{6d}-k_{6a})x_6 + k_{7a}x_7 \\
\dot{x}_7 &= k_{6a}x_6 - (k_7+k_{7d})x_7
\end{aligned} \tag{2}$$

where x_1, x_2, and x_3 represent concentrations of $Per2/Cry$ mRNA, PER2/CRY complex protein in cytoplasm, and PER2/CRY complex in nucleus respectively. x_4 denotes concentration of $Bmal1$ mRNA. x_5 denotes concentration of BMAL1 protein in cyptoplasm, and x_6 represents nuclear BMAL1 protein. State x_7 represents the concentration of BMAL1*. All of state variables are assumed to be positive values. Values of parameters are given in [11] with: $v_{1b} = 9nM.h^{-1}$, $k_{1b} = 1nM$, $k_{1i} = 0.56nM$, $c = 0.01nM$, $p = 8$, $k_{1d} = 0.12h^{-1}$, $k_{2b} = 0.3nM^{-1}.h^{-1}$, $q = 2$, $k_{2d} = 0.05h^{-1}$, $k_{2t} = 0.24h^{-1}$, $k_{3t} = 0.02h^{-1}$, $k_{3d} = 0.12h^{-1}$, $v_{4b} = 3.6nM.h^{-1}$, $k_{4b} = 2.16nM$, $r = 3$, $k_{4d} = 0.75h^{-1}$, $k_{5b} = 0.24h^{-1}$, $k_{5d} = 0.06h^{-1}$, $k_{5t} = 0.45h^{-1}$, $k_{6t} = 0.06h^{-1}$, $k_{6d} = 0.12h^{-1}$, $k_{6a} = 0.09h^{-1}$, $k_{7a} = 0.003h^{-1}$, $k_{7d} = 0.09h^{-1}$.

III. Observer

Consider the class of nonlinear system which is described by:

$$\begin{aligned}
\dot{x} &= Ax + \varphi(x,u), \\
y &= Cx
\end{aligned} \tag{3}$$

where $x \in \mathbb{R}^n, u \in \mathbb{R}^p, A \in \mathbb{R}^{n\times n}, C \in \mathbb{R}^{m\times n}, y \in \mathbb{R}^m$, and $\varphi(x,u) \in \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$ are nonlinear functions. If $\varphi(x,u)$ satisfies Lipschitz condition described by

$$\|\varphi(x,u) - \varphi(\hat{x},u)\| \leq \gamma \|x-\hat{x}\|, \forall x,\hat{x} \in \mathbb{R}^n, \tag{4}$$

where γ is Lipschitz constant, $\varphi(x,u)$ is called Lipschitz nonlinearity. Another condition is called one-sided Lipschitz condition which is described by

$$< f(x,u) - f(\hat{x},u), x-\hat{x} > \leq \upsilon_p \|x-\hat{x}\|, \forall x,\hat{x} \in \mathbb{R}^n, \tag{5}$$

where υ_p, which may be negative value, is one-sided Lipschitz constant. In addition, $f(x,u) = P\varphi(x,u)$, where P is positive definite matrix, and $< .,. >$ is an Euclidean product on $\mathbb{R}^n$. If $\varphi(x,u)$ satisfies (5), $\varphi(x,u)$ is called one-sided Lipschitz nonlinearity.

For nonlinear system (3), observer design has its form described by:

$$\dot{\hat{x}} = A\hat{x} + \varphi(\hat{x},u) + L(y - C\hat{x}), \tag{6}$$

where L is observer gain with $L \in \mathbb{R}^{n\times m}$. If $\varphi(x,u)$ satisfies (5), observer design is given in [24]:

Lemma 1: If a gain L is chosen such that $(A-LC)$ is stable and the following inequality

$$(A-LC)^T P + P(A-LC) + 2\upsilon_p I < 0 \tag{7}$$

is satisfied, where P is a positive definite matrix, and υ_p is one-sided Lipschitz constant of $f(x,u) = P\varphi(x,u)$ such that (5) holds, the observer (6) yields asymptotically convergence estimate for system (3).

However, condition for existence of observer gain L such that (7) admits a positive definite matrix solution P, and how to obtain value of this gain L are not shown in [24]. This problem is solved by new result of one-sided Lipschitz observer design in [20]. This new observer design is given through a theorem and a corollary:

Theorem 1: For a nonlinear system (3) which satisfies one-sided Lipschitz condition (5), a gain matrix L can be chosen such that the inequality (8) has a positive definite matrix if and only if there exists a positive constant σ such that P satisfies the following condition

$$A^T P + PA - \sigma C^T C + 2\upsilon_p I < 0, \tag{8}$$

where υ_p is one-sided Lipschitz constant of $P\varphi(x,u)$ with respect to x.

Corollary 1: Consider nonlinear system (3) with condition (5). If there exists a positive value σ such that the following condition

$$A^T P + PA - \sigma C^T C + 2\upsilon_p I < 0 \tag{9}$$

is satisfied, where P is a positive definite matrix, and υ_p is one-sided Lipschitz constant. The observer (6) having $L = \frac{\sigma}{2} P^{-1} C^T$ as observer gain yields asymptotically convergence estimate for system (3).

Given that $\varphi(x,u)$ are Lipschitz nonlinearities, according to [20], instead of (9), linear matrix inequality (LMI) is modified with the form described by

$$A^T P + PA - \sigma C^T C + 2n \sum_{i=1}^{n} \gamma_i \lambda_i I < 0, \tag{10}$$

where γ_i indicates Lipschitz constants for each of Lipschitz nonlinear functions, n denotes number of state variables of the system, and λ_i are small positive real constants. Values of λ_i can be chosen such that $n \sum_{i=1}^{n} \gamma_i \lambda_i < (\sum_{i=1}^{n} \gamma_i^2)^{\frac{1}{2}}$.

IV. Main results

A. Preliminary

Simulation studies have been performed in MATLAB, and they are carried out with $x(0)$=$\begin{bmatrix} 1 & 1 & 1 \end{bmatrix}$ for Neurospora model, and $x(0)$=$\begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 \end{bmatrix}$ for mammalian model.

Lipschitz constants can be computed by using (4) or (5). Another useful tool for finding Lipschitz constants is mean value theorem. This theorem is described by

$$|f'(\zeta)| = \left| \frac{f(x) - f(\widehat{x})}{x - \widehat{x}} \right|, \tag{11}$$

where $\zeta \in [x, \widehat{x}]$. Value of Lipschitz constant is equivalent to maximum value of function $f'(\zeta)$.

Basing on (3), (1) has nonlinear functions $\varphi(x,u)$ as

$$\begin{aligned} \varphi_{1a}(x_1) &= -\upsilon_m \frac{x_1}{K_M + x_1} \\ \varphi_{1b}(x_3) &= \upsilon_s \frac{K_i^n}{K_i^n + x_3^n}, \\ \varphi_2(x_2) &= -\upsilon_d \frac{x_2}{K_d + x_2} \end{aligned}$$

and (2) has its nonlinear functions $\varphi(x,u)$ as

$$\begin{aligned} \varphi_1(x_3, x_7) &= \frac{\upsilon_{1b}(x_7 + c)}{k_{1b}(1 + \frac{x_3^p}{k_{1i}^p}) + x_7 + c} \\ \varphi_2(x_1) &= x_1^q \\ \varphi_4(x_3) &= \frac{\upsilon_{4b} x_3^r}{k_{4b}^r + x_3^r} \end{aligned}$$

B. Choice of output values

In literature, outputs of the mathematical models of Neurospora and Mammals are not clearly specified. Thus, in this paper, we choose the outputs for these models. In order to use observers, observability has to be guaranteed, that is, matrix (C, A) is observable. This condition is compulsory condition applied to both models. To Neurospora model, given that matrix (C, A) is observable, and values of C are kept as simple as possible, C can be chosen as: C=$\begin{bmatrix} 0 & 1 & 0 \end{bmatrix}$, C=$\begin{bmatrix} 0 & 0 & 1 \end{bmatrix}$, C=$\begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$, C=$\begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix}$, C=$\begin{bmatrix} 1 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix}$. Oscillations of circadian rhythms are caused by oscillations of proteins leading to the required measurements of dynamics of proteins. In other words, oscillations of mRNAs are less important than oscillations of proteins. Thus, the measurements of mRNAs can be reduced. As a result, values of C are left to C=$\begin{bmatrix} 0 & 1 & 0 \end{bmatrix}$, C=$\begin{bmatrix} 0 & 0 & 1 \end{bmatrix}$, C=$\begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$. Since value of state variable x_3, dynamic of nuclear FRQ protein, is required for computation of Lipschitz constant of nonlinear function $\varphi_{1b}(x_3)$, x_3 is compulsory value that can not be reduced. Therefore, values of C are left to C=$\begin{bmatrix} 0 & 0 & 1 \end{bmatrix}$, C=$\begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$. These values are chosen output values for Neurospora model. The same procedure of selection of output values C is applied to mammalian model. A set of values C are chosen such that matrix (C, A) is observable. Since the dynamics of mRNAs are less important than dynamics of proteins, their measurements can be reduced. However, since value of state variable x_1, dynamic of $Per2/Cry$ mRNA, will be used for the computaion of Lipschitz constant of nonlinear function $\varphi_2(x_1)$ in mammalian model, this value has to be measurable. In addition, values of x_3 and x_7, which are dynamics of nuclear PER2/CRY complex protein, and BMAL1* respectively, are also used to obtain Lipschitz constants of nonlinear functions $\varphi_1(x_3, x_7)$ and $\varphi_4(x_3)$. Therefore, these values have to be measurable. Given that value of C is kept as simple as possible, C can be chosen as: C=$\begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$.

C. Neurospora model

According to Lipschitz condition (4), we have

$$\begin{aligned}\left\|-v_m\frac{x_1}{K_M+x_1}+v_m\frac{\hat{x}_1}{K_M+\hat{x}_1}\right\| &\leq \frac{v_m}{K_M}\|x_1-\hat{x}_1\|\\ \left\|-v_d\frac{x_2}{K_d+x_2}+v_d\frac{\hat{x}_2}{K_d+\hat{x}_2}\right\| &\leq \frac{v_d}{K_d}\|x_2-\hat{x}_2\|\end{aligned}$$

Values of Lipschitz constants are obtained with $\gamma_{1a}=\frac{v_m}{K_M}$=1.01 for $\varphi_{1a}(x_1)$, and $\gamma_2=\frac{v_d}{K_d}$=10.7962 for $\varphi_2(x_2)$. Lipschitz constant of nonlinear function $\varphi_{1b}(x_3)$ is not straightforward to obtain by using (4). Instead of (4), this value is calculated by using (11). According to (11),

$$|f'(\zeta)|=\left|-\frac{n\zeta^{n-1}}{\left(K_i^n+\zeta^n\right)^2}\right|=\left|\frac{\varphi_{1b}(x_3)-\varphi_{1b}(\hat{x}_3)}{x_3-\hat{x}_3}\right|, \qquad (12)$$

where $\zeta\in[\min(x_3,\widehat{x}_3),\max(x_3,\widehat{x}_3)]$. Maximum value of $|f'(\zeta)|$ is equivalent to Lipschitz constant γ_{1b}, and this value is calculated by solving $|f''(\zeta)|$=0. Dynamic of state x_3, dynamic of nuclear FRQ protein, is known, and $x_3\in[0.6175,1.057]$. Maximum and minimum values of x_3 are then substituted to $|f''(\zeta)|$=0 to find maximum value of $|f'(\zeta)|$. The result has maximum value of $|f'(\zeta)|$ or Lipschitz constant $\gamma_{1b}=1.7043$ for $\varphi_{1b}(x_3)$. Then, we solve (10) to obtain σ=197.1422, $L=\begin{bmatrix}1.4721\\1.6396\\4.4247\end{bmatrix}$ in case of $C=\begin{bmatrix}0&0&1\end{bmatrix}$, and σ=50.0883, $L=\begin{bmatrix}0.8667&0.2354\\2.0833&-0.0152\\-0.0152&0.9276\end{bmatrix}$ for $C=\begin{bmatrix}0&1&0\\0&0&1\end{bmatrix}$. Error dynamics between the unmeasured states x_1, x_2 and their estimate are shown in Fig. 1 in case of $C=\begin{bmatrix}0&0&1\end{bmatrix}$. Error dynamic between the unmeasured states x_1 and its estimate is shown in Fig. 2 in case of $C=\begin{bmatrix}0&1&0\\0&0&1\end{bmatrix}$.

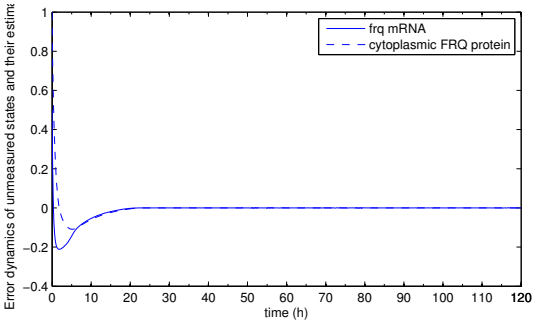

Fig. 1. Error dynamics of frq mRNA, FRQ protein and their estimate

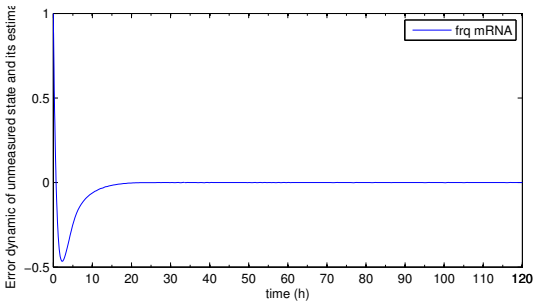

Fig. 2. Error dynamic of frq mRNA and its estimate

D. Mammalian model

Since $C=\begin{bmatrix}1&0&0&0&0&0&0\\0&0&1&0&0&0&0\\0&0&0&0&0&0&1\end{bmatrix}$, dynamics of states x_1, x_3, and x_7 are known. According to (11),

$$|f'(\zeta_1)|=\left|q\zeta_1^{q-1}\right|=\left|\frac{\varphi_2(x_1)-\varphi_2(\hat{x}_1)}{x_1-\hat{x}_1}\right|, \qquad (13)$$

where $\zeta_1\in[\min(x_1,\widehat{x}_1),\max(x_1,\widehat{x}_1)]$. Since x_1 is known, and oscillation of $x_1\in[0,1.518]$, therefore, $\zeta_1\in[0,1.518]$. With $q=2$, Lipschitz constant of $\varphi_2(x_1)$ is calculated as $\gamma_2=2*|\zeta_1|=3.038$. Value of Lipschitz constant of $\varphi_4(x_3)$ is calculated by using the same method applied to find Lipschitz constant of $\varphi_{1b}(x_3)$ in Neurospora model. This constant is obtained with $\gamma_2=0.864$. To nonlinear function $\varphi_1(x_3,x_7)$, according to (4),

$$\|\varphi_1(x_3,x_7)-\varphi_1(\hat{x}_3,\hat{x}_7)\|\leq\gamma_1\left\|\begin{array}{c}x_3-\hat{x}_3\\x_7-\hat{x}_7\end{array}\right\|, \qquad (14)$$

where γ_1 is Lipschitz constant. On the other hand, we have

$$\begin{aligned}&|\varphi_1(x_3,x_7)-\varphi_1(\hat{x}_3,x_7)+\varphi_1(x_3,x_7)-\varphi_1(x_3,\hat{x}_7)|\\ =\;&|f'(\zeta_2)(x_3-\hat{x}_3)+f'(\zeta_3)(x_7-\hat{x}_7)| \qquad (15)\end{aligned}$$

because according to (11),

$$\begin{aligned}|\varphi_1(x_3,x_7)-\varphi_1(\hat{x}_3,x_7)|&=|f'(\zeta_2)|\,|x_3-\hat{x}_3|\\ |\varphi_1(x_3,x_7)-\varphi_1(x_3,\hat{x}_7)|&=|f'(\zeta_3)|\,|x_7-\hat{x}_7|\end{aligned}$$

with $\zeta_2\in[\min(x_3,\widehat{x}_3),\max(x_3,\widehat{x}_3)]$, and $\zeta_3\in[\min(x_7,\widehat{x}_7),\max(x_7,\widehat{x}_7)]$. Function $f'(\zeta_2)$ is differentiated function of $\varphi_1(x_3,x_7)$ with respect to x_3, and function $f'(\zeta_3)$ is differentiated function of $\varphi_1(x_3,x_7)$ with respect to x_7. Besides,

$$(15)\leq\left\|\begin{array}{c}f'(\zeta_2)\\f'(\zeta_3)\end{array}\right\|\left\|\begin{array}{c}x_3-\hat{x}_3\\x_7-\hat{x}_7\end{array}\right\| \qquad (16)$$

Therefore, inequality (16) is equivalent to inequality (14), and $\gamma_1=\sqrt{(\max(f'(\zeta_2)))^2+(\max(f'(\zeta_3)))^2}$. Maximum values of $f'(\zeta_2)$ and $f'(\zeta_3)$ are obtained by solving

$|f''(\zeta_2)|$=0 and $|f''(\zeta_3)|$=0. Nevertheless, in order to calculate maximum values of $f'(\zeta_2)$ and $f'(\zeta_3)$ by solving $|f''(\zeta_2)|$=0 and $|f''(\zeta_3)|$=0, values of states x_3 and x_7 are required. Dynamics of states x_3 and x_7 are known, and $x_3 \in [0.8, 1.861]$, $x_7 \in [0.85, 1.11]$. We substitute these values to solve $|f''(\zeta_2)|$=0, and $|f''(\zeta_3)|$=0. The results are obtained with $\max(f'(\zeta_2)) = 2.9909 \times 10^{-17}$ and $\max(f'(\zeta_3)) = 0.4906$. Lipschitz constant of nonlinear function $\varphi_1(x_3, x_7)$ has its value as $\gamma_1 = \sqrt{(2.9909 \times 10^{-17})^2 + (0.4906)^2} = 0.4906$. We then solve (10) to get σ=181.0579, $L = \begin{bmatrix} 0.3323 & 0 & 0 \\ 0 & -0.0402 & 0 \\ 0 & 0.4278 & 0 \\ 0 & 0 & -0.0022 \\ 0 & 0 & 0.0045 \\ 0 & 0 & 0.0155 \\ 0 & 0 & 0.3247 \end{bmatrix}$. Error dynamics between the unmeasured states x_2, x_4, x_5, x_6 and their estimate are shown in Fig. 3, Fig. 4, Fig. 5, and Fig. 6 .

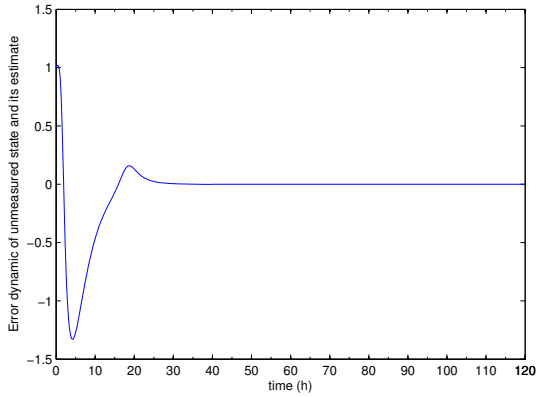

Fig. 3. Error dynamic of $Per2/Cry$ mRNA and its estimate

E. Discussion

The result obtained from [25] is used as standard result to judge the performance of one-sided Lipschitz observer. According to [25], with control of light input, the phase is restored and tracked within 40h. Therefore, we expect the desired performances of one-sided Lipchitz observer are also within 40h ($0 \leq \tau \leq 40$h) for both Neurospora and mammalian models. According to results depicted from Fig. 1 to Fig. 6, the performances of one-sided Lipschitz observer applied to both models satisfy the desired performances. Furthermore, the observer designed for Neurospora model has better performance than the one for mammalian model. This mainly due to the complexity in the mamalian model compared with a 3rd order one for Neurospora. Computation

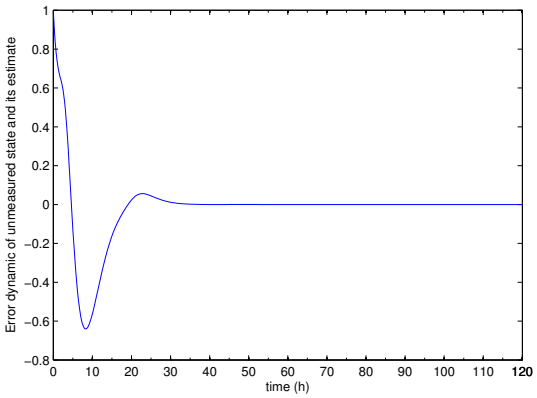

Fig. 4. Error dynamic of $Bmal1$ mRNA and its estimate

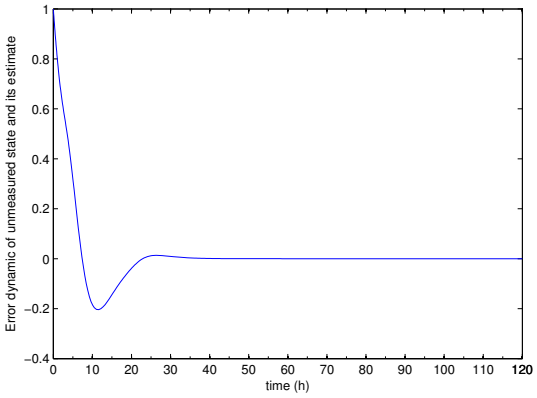

Fig. 5. Error dynamic of BMAL1 protein and its estimate

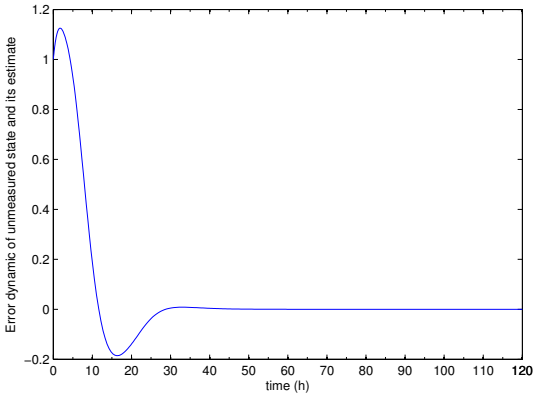

Fig. 6. Error dynamic of nuclear BMAL1 protein and its estimate

of Lipschitz constants may also be responsible for slower performance of observer designed for mammalian model than the one for Neurospora model. Different values of C may affect the performance of the observer. This is shown with slightly faster convergence of error dynamic of frq mRNA in Fig. 2 than dynamic of frq mRNA in Fig. 1. The reason may be due to fewer unmeasured state variables in case of C=$\begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$ than in case of C=$\begin{bmatrix} 0 & 0 & 1 \end{bmatrix}$, e.g. 1 unknown state variable for C=$\begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$ while 2 unknown state variables for C=$\begin{bmatrix} 0 & 0 & 1 \end{bmatrix}$, which affect the speed of estimation.

V. CONCLUSIONS

We have analyzed the nonlinearities in both circadian models of Neurospora and Mammals, and have shown that observers with one-sided Lipschitz nonlinearities can be applied. These observers have been designed for both models, and their performances have been evaluated by simulation studies. Detailed evaluation does show that both observers give asymptotic estimates of unmeasured state variables, and they provide a possibility of reducing measurements in biological study of circadian rhythms. Control designs for circadian models which are based on observer remains as topic for future research.

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