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Observer Design for Dynamical Model of the Operation of the Hypothalamus - Pituitary - Thyroid (HPT) Axis in Autoimmune Thyroiditis

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ABSTRACT: *An observer construction method for semilinear descriptor systems of the form* $E\dot{x} = Ax + f(x)$*, where* E *(singular),* A *are linear operators and* f *is a nonlinear function, is studied. Using a new approach, based on matrix theory, it is shown that an observer may be designed under certain conditions on system operators if one linear matrix inequality (LMI) is satisfied. The dynamical Model of the Operation of the HPT Axis in Autoimmune Thyroiditis is rewritten in the semilinear descriptor system form and then using proposed observer all the states are estimated. Numerical simulations are presented to demonstrate the effectiveness of the proposed approach.*

KEYWORDS-*semilinear descriptor system, LMI, HPT axes*

I. INTRODUCTION

The thyroid stimulating hormone (TSH) is synthesized and secreted into the blood by the pituitary gland. In response to TSH, the thyroid gland secretes thyroxine (T4) into the blood, in which 99 percent of T4 binds to proteins in blood serum and the remaining 1 percent circulates as free thyroxine (FT4). This in turn inhibits the secretion of TSH in the pituitary gland the secretion of TSH in the pituitary gland. This mechanism is called a negative feedback control through the hypothalamus-pituitary-thyroid (HPT) axis. The existence of the negative feedback control is to maintain the adequate levels of FT4 in the blood, which referred to a set point of the HPT axis. The set point of the HPT axis varies greater between individuals than in the same individual sampled repeatedly over time [1]. Autoimmune thyroiditis is a complex disorder in which the immune system attacks the thyroid gland with both proteins and immune cells. More precisely, the immune system produces proteins (thyroid peroxidase anti-bodies (TPOAb) and thyroglobulin antibodies (TGAb)) against the thyroid follicle cell membrane proteins (thyroid peroxidase (TPO) and thyroglobulin (TG)) in the blood. These proteins induce thyroid follicle cell lysis by binding with TPO and TG respectively. Thus, autoimmune thyroiditis interrupts the normal thyroid operation and eventually disrupts feedback control. Consequently, one develops symptoms (like, goiter), signs (like, hyperactivity), and some clinical conditions, like, euthyroidism (normal FT4 and TSH levels in the blood), subclinical hypothyroidism (normal FT4, but TSH above normal levels),overt (clinical) hypothyroidism (underactive thyroid gland- low FT4 levels and TSH above nor-mal levels) or hashitoxicosis (transient hyper to hypothyroidism). Hashitoxicosis is a life-threatening abnormal clinical condition.

Since the famous work of Danziger and Elmergreen [2, 3], many authors have discussed mathematical models related to the thyroid- pituitary system. We refer to the work of Roston [4], Rashevsky [5], Norwich and Reiter [6], Distefano and Stear [7], and Degon at el. [8]. In this paper, we discuss the following model, which is adopted from recent work of Pandiyan [9] where author has analyzed the dynamical behavior of operations of the HPT axis in autoimmune thyroiditis.

$$\varepsilon \frac{dTSH}{dt} = \frac{k_1}{k_2} - \frac{k_1 FT4}{k_2(k_a + FT4)} - TSH, \qquad (1a)$$

$$\frac{dFT4}{dt} = \frac{k_3 T\ TSH}{(k_d + TSH)} - k_4 FT4, \qquad (1b)$$

$$\frac{dT}{dt} = k_5\left(\frac{TSH}{T} - N\right) - k_6 Ab\ T, \qquad (1c)$$

$$\frac{dAb}{dt} = k_7 Ab\ T - k_8\,\mathrm{Ab}, \qquad (1c)$$

where $k_1, k_2, k_3, k_4, k_5, k_6, k_7, k_8, k_a, k_d$ and N are suitable constants and $\varepsilon << 1$ is very small positive constant. Small ε suggests that the model is on different time scale and can be considered as a descriptor system in whole. We redefine the model variables as follows

- $TSH(t) =$ Concentration of thyroid stimulating hormone(mU/L) at time t in blood.
- $FT4(t) =$ Concentration of free thyroxine (pg/mL) at time t in blood.
- $T(t) =$ the functional size of thyroid gland (active part of the gland) (L) at time t.
- $Ab(t) =$ Concentration of (unbound) anti-thyroid antibodies(U/mL) at time t in blood.

The above model is based on the following assumptions

- Anti-thyroid antibodies attack the thyroid follicle cells whereby the gland stimulates more activity of the immune response. The damaged part of the gland is no longer functional (active) in secreting thyroid hormones.

- TSH stimulates the functional (active) part of the thyroid gland for growth and hormonal secretion.
- TSH disappears from the blood through a non-specific excretion mechanism.
- TSH distributes uniformly throughout the functional part of the gland. The hypothalamus pituitary function is intact.
- The blood concentration of iodine is sufficient for synthesis of hormonal production.
- The total TSH receptor concentration in the gland is approximately constant since the TPOAb and TGAb do not attack the TSH receptors.

In this paper, we design an observer for the states of the system (1), if we have the following output equation

$$y = TSH, \tag{2}$$

i.e., the problem is to estimate all the state variables of the model (1) if only the TSH values are available. Thus, the problem is to design an observer for the system (1)-(2). An observer is a proposed dynamical system to estimate the state of given dynamical system using only the measured output and known input of the latter. The observe design problem has been discussed for linear and semilinear normal systems in very details and now a days mathematicians and engineers are extending these approaches to descriptor systems. For example, in [10], author has considered a nonlinear observer for a class of continuous nonlinear descriptor systems with unknown inputs and faults. Koenig [11] has designed full-order observers for nonlinear descriptor systems with unknown input, when the spectral domain of the unknown inputs is unknown or in low frequency range. Apart from these, the observer design approach has been used on some biological problems too. In [12], a nonlinear mathematical model of the phytoplanktonic growth has been developed and then observed for the states.

II. PROBLEM DESCRIPTION AND ITS MATHEMATICAL FORMULATION

The problem is to design an observer for the states of the system (1) which has the output as described by the equation (2). To achieve the goal, first we assume $\varepsilon = 0$ and write the system (1)-(2) in the following descriptor form

$$E\dot{x} = Ax + f(x) \qquad \text{3(a)}$$

$$y = Cx \qquad \text{3(b)}$$

where

$$E = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}, \quad x = \begin{bmatrix} TSH \\ FT4 \\ T \\ Ab \end{bmatrix}$$

$$A = \begin{bmatrix} -1 & 0 & 0 & 0 \\ 0 & -k_4 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & -k_8 \end{bmatrix},$$

$$f(x)=\begin{bmatrix} \frac{k_1}{k_2}-\frac{k_1 FT4}{k_2(k_a+FT4)} \\ \frac{k_3 TTSH}{K_d+TSH} \\ k_5(\frac{TSH}{T}-N)-k_6 AbT \\ k_7 AbT \end{bmatrix}, \text{ and}$$

$$C=\begin{bmatrix}1 & 0 & 0 & 0\end{bmatrix}.$$

It can be checked immediately that the following equation is satisfied by the system (3)

$$Rank\begin{bmatrix}E \\ C\end{bmatrix}=n, \quad (4)$$

where $n=4$ is the order of the system (1). Now using the algorithm 1, a full column rank matrix R is constructed such that the system (3) is equivalent to the following descriptor system

$$\tilde{E}\dot{x}=\tilde{A}x+Rf(x) \quad 5(a)$$

$$y=Cx \quad 5(b)$$

where $\tilde{E}=RE$ and $\tilde{A}=RA$. Here equivalent means both system (3) and system (5) have the same solution for a given initial condition.

Algorithm 1

1. Carry out the singular value decomposition (SVD) of matrix $C=U_1\begin{bmatrix}D_1 & 0 \\ 0 & 0\end{bmatrix}V_1^T$.
2. Calculate $P=V_1\begin{bmatrix}D_1^{-1} & 0 \\ 0 & I_{n-r}\end{bmatrix}$.
3. Calculate $E_1=EP\begin{bmatrix}0_{r\times(n-r)} \\ I_{n-r}\end{bmatrix}$, where $r=rank(C)$.
4. Carry out the SVD of matrix $E_1=U_2\begin{bmatrix}D_2 \\ 0\end{bmatrix}V_2^T$.
5. Calculate $R_0=\begin{bmatrix}0 & I_{m+r-n} \\ V_2 D_2^{-1} & 0\end{bmatrix}U_2^T$.
6. Calculate $R=P\begin{bmatrix}0_{(n-m)\times m} \\ R_0\end{bmatrix}$.

It is easy to verify that the system (3) satisfies the equation (4), the system (5) satisfies the following property

$$rank\begin{bmatrix}1-\tilde{E} \\ C\end{bmatrix}=rank(C)=1. \quad (6)$$

Mathematically, the problem is to construct matrices N, L and M of compatible dimensions such that that the following normal system becomes a full-order observer (i.e., $\hat{x} \to x$ as $t \to \infty \forall z(0), x(0) \in \mathbf{R}^n)$ for the system (5).

$$\dot{z} = Nz + Ly + Rf(\hat{x}) \quad 7(a)$$

$$\hat{x} = z + My \quad 7(b)$$

Since (3) and (5) are equivalent systems, observer for the system (5) works for the system (3) also.

III. METHODOLOGY

From the system (5) and (7), it is clear that error vector

$$\begin{aligned} e &= x - \hat{x} \\ &= x - z - MCx \\ &= (I - MC)x - z \\ &= \tilde{E}x - z \end{aligned} \quad (8)$$

gives the dynamics

$$\begin{aligned} \dot{e} &= \tilde{E}\dot{x} - \dot{z} \\ &= \tilde{A}\dot{x} + Rf(x) - (Nz + LCx + Rf(\hat{x})) \\ &= (\tilde{A} - LC)x - N(\tilde{E}x - e) + R\Delta f \\ &= Ne + (\tilde{A} - LC - N\tilde{E})x + R\Delta f \\ &= Ne + (\tilde{A} - LC - N + NMC)x + R\Delta f \\ &= Ne + R\Delta f \end{aligned} \quad (9)$$

Where $\Delta f = f(x) - f(\hat{x})$. In order to write the equations (8) and (9) in above form, we have used the following equation:

$$\tilde{E} = I - MC \quad (10)$$

$$N = \tilde{A} - KC \quad (11)$$

$$K = L - NM \quad (12)$$

Thus, the design problem of the observer (7) now boils down to finding the matrices K, N and L so that the above equations (10), (11) and (12) are satisfied with the stability of matrix N Now, to show the existence of matrix K such that matrix N (in equation (11)) is stable, consider a matrix $P > 0$ and a Lyapunov function $V = e^T Pe$. Since $P > 0$, we have $V > 0$. Moreover,

$$\begin{aligned} \dot{V} &= \dot{e}^T Pe + e^T P\dot{e} \\ &= (Ne + R\Delta f)^T Pe + e^T P(Ne + R\Delta f) \\ &= e^T N^T Pe + \Delta f^T R^T Pe + e^T PNe + e^T PR\Delta f \end{aligned} \quad (13)$$

Since for some $T > 0$, in time interval $(0, T)$ the nonlinear function satisfies the inequality $\Delta f^T \Delta f \le \lambda^2 e^T e$, where $\lambda > 0$ is some positive content. Therefore, by rearranging equation (13), we get

$$\dot{V} \quad \leq \quad e^T(N^TP+PN)e+\Delta f^TR^TPe+e^TPNe \;+\; e^TPR\Delta f+\lambda^2e^Te-\Delta f^T\Delta f$$

$$\dot{V} \quad \leq \quad \begin{bmatrix} e^T & \Delta f^T \end{bmatrix}\begin{bmatrix} N^TP+PN+\lambda^2 I & PR \\ R^TP & -I \end{bmatrix}\begin{bmatrix} e \\ \Delta f \end{bmatrix}$$

Now for $\dot{V}<0$,

$$\begin{bmatrix} N^TP+PN+\lambda^2 I & PR \\ R^TP & -I \end{bmatrix}<0 \tag{14}$$

Using equations (11) and (14), we get,

$$\begin{bmatrix} (\tilde{A}-KC)^TP+P(\tilde{A}-KC)+\lambda^2 I & PR \\ R^TP & -I \end{bmatrix}<0$$

$$\begin{bmatrix} \tilde{A}^TP+P\tilde{A}-C^TK^TP-PKC+\lambda^2 I & PR \\ R^TP & -I \end{bmatrix}<0$$

$$\begin{bmatrix} \tilde{A}^TP+P\tilde{A}-C^T\tilde{K}^T-\tilde{K}C+\lambda^2 I & PR \\ R^TP & -I \end{bmatrix}<0, \tag{15}$$

where $\tilde{K}=PK$. The above LMI (15) has to be solved for $\tilde{K}$ in order to prove the stability of the error dynamics (9). Using this $\tilde{K}$, we can find K and thus matrix N. Now, by K, N and equation (12), matrix L can be calculated. Existence of M is simple implication of equation (10) whose solvability is determined by (6). With all thus calculated matrices K, N, L and M, the observer (7) can be designed.

IV. SIMULATION RESULTS

For the simulation purpose, we take the values for the system (3) as shown in the following table. This data has been taken from [9]. With above data, matrices E, A and C for the system (3) will become as follows

$$E=\begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix},$$

$$A=\begin{bmatrix} -1 & 0 & 0 & 0 \\ 0 & -0.099021 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -0.035 \end{bmatrix},$$

$$C=\begin{bmatrix} 1 & 0 & 0 & 0 \end{bmatrix}.$$

Table 1: Values of Parameters for the System (3)

Parameters	Values Used	Units
k_1	5000	$\frac{mU}{L*day}$
k_2	16.635	$\frac{1}{day}$
k_3	86	$\frac{pg}{mL*L*day}$

k_4	0.099021	$\frac{1}{day}$
k_5	1	$\frac{L^3}{mU*day}$
k_6	1	$\frac{mL}{U*day}$
k_7	1.3421	$\frac{1}{U*day}$
k_8	0.035	$\frac{1}{day}$
k_a	0.0434	$\frac{pg}{mL}$
k_d	0.0021	$\frac{mU}{L}$
N	66.7	$\frac{mU}{L^2}$

Since the system (3) satisfies the assumption (H1), by the algorithm 1, we calculate

$$R=\begin{bmatrix}-1&0&0&0\\0&1&0&0\\0&0&1&0\\0&0&0&1\end{bmatrix}.$$

Thus, system (5) is described by the matrices

$$\bar{E}=\begin{bmatrix}0&0&0&0\\0&1&0&0\\0&0&1&0\\0&0&0&1\end{bmatrix},$$

$$\bar{A}=\begin{bmatrix}1&0&0&0\\0&-0.099021&0&0\\0&0&0&0\\0&0&0&-0.035\end{bmatrix}.$$

By MATLAB LMI tool box, we ensure that LMI (15) is solvable for the system (5) as

$$\bar{K}=e+08\begin{bmatrix}2.412\\0\\0\\0\end{bmatrix} \text{ and}$$

$$P=e+06\begin{bmatrix}5.9208&0&0&0\\0&0.0026&0&0\\0&0&0&0\\0&0&0&0.0009\end{bmatrix}.$$

Thus,

$$K = P^{-1}\bar{K} = \begin{bmatrix} 407.3756 \\ 0 \\ 0 \\ 0 \end{bmatrix}.$$

Finally, we calculate from equations (10) and (12)

$$M = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \text{ and } L = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}.$$

Using the above matrices N, L, M and R , the observer is designed for the system (3). We have plotted the true and estimated values of the states in Figure 1-4 for arbitrary initial conditions $TSH(0) = 2, FT4(0) = 13, T(0) = 15, Ab(0) = 16$ for the system (3) and $z_1(0) = 10, z_2(0) = 24, z_3(0) = 5, z_4(0) = 20$ for the proposed observer (7). It can be seen from the graphs that estimated values of the states follow the true states well. Hence, the system (7) works as an observer for the system (3).

V. CONCLUSION

We have studied the dynamical Model of the Operation of the HPT Axis in Au-toimmune Thyroiditis. The state TSH has been considered as only output state. Based on a LMI tool for the Lyapunov stability, an observer has been proposed to estimate all other states after rewriting the given system into a descriptor form. Simulations results have verified the effectiveness and validity of this approach.

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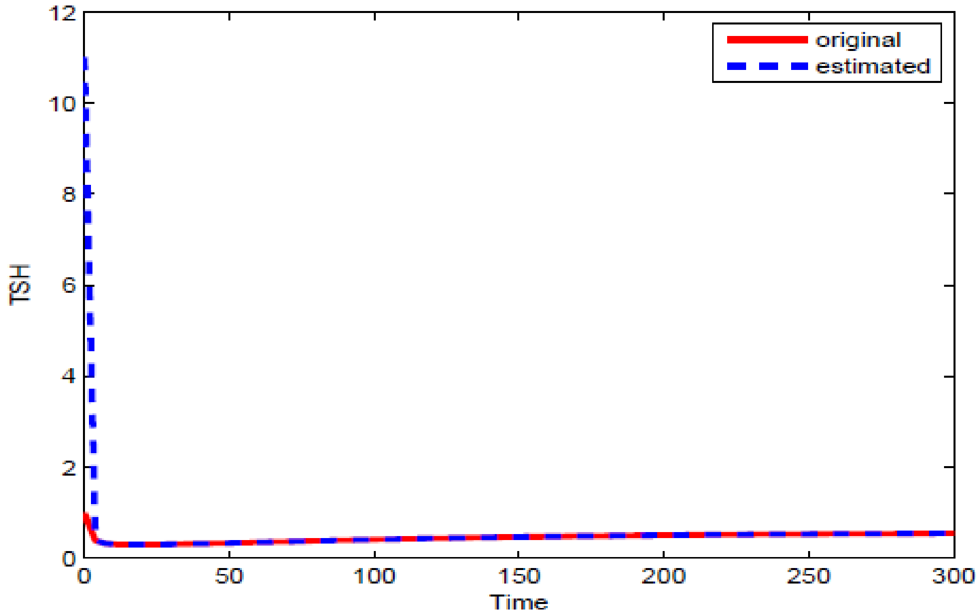

Figure 1: Time response of the original state TSH and estimated state TSH.

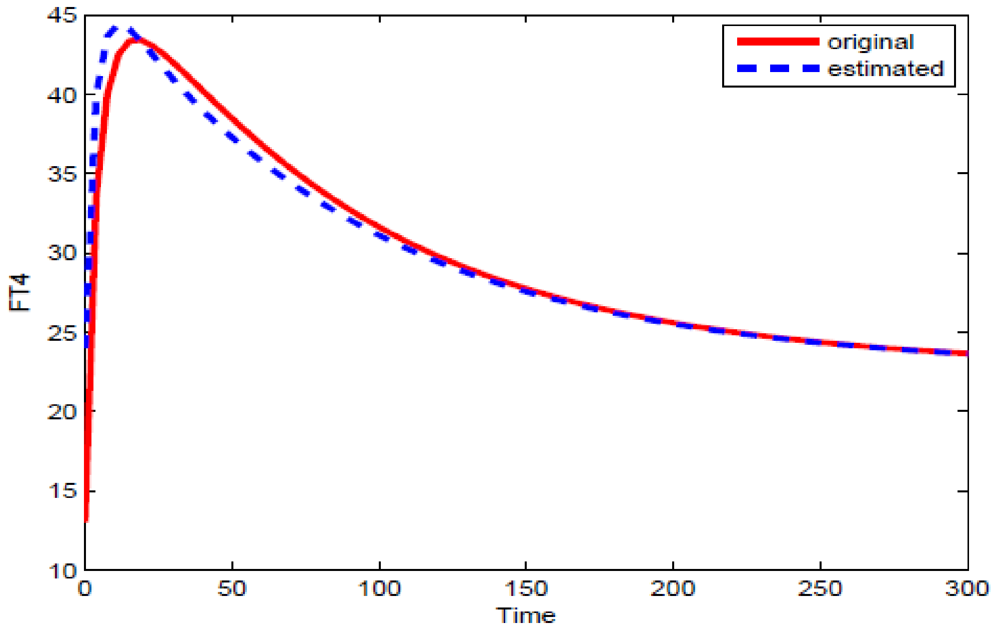

Figure 2: Time response of the original state FT4 and estimated state FT4.

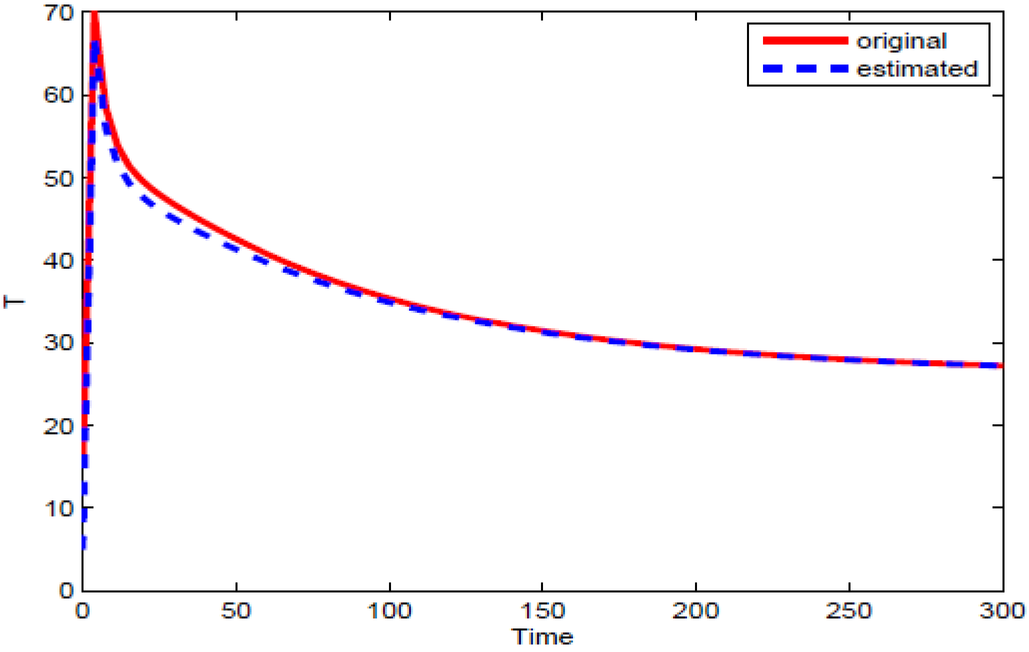

Figure 3: Time response of the original state T and estimated state T.

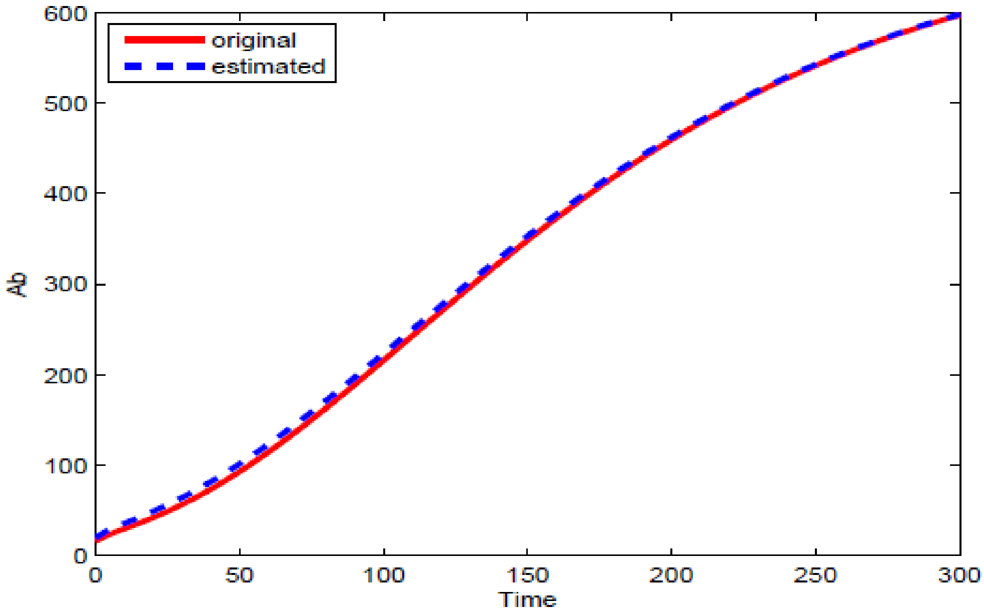

Figure 4: Time response of the original state AB and estimated state Ab.