The Design of a Synergetic Controller for Tuberculosis Epidemic System

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***Abstract*—Eradication of the Tuberculosis (TB) epidemic has been studied in various aspects. Like other epidemic diseases, the TB epidemic system can be represented in the form of a compartmental model which provides the feasibility to apply the feedback control approach for defining the control policy. The application of the synergetic control (SC) with the improvement convergence rate to define the treatment programs for infectious and persistent latent subpopulations for the TB epidemic system, hence, became the main focus of this study. In order to increase the convergence rate, the time varying macro variable was selected. The proof of the TB epidemic system stability under the time varying synergetic control (TVSC) was presented. Then, the demonstration of feasibility and improvement of the convergence rate of the TVSC method ensued. The simulation of the TB epidemic system as manipulated by the TVSC method was carried out. The simulation results were compared to those of the conventional synergetic control (SC) method. Based on the numerical simulation, the control policy corresponding to the TVSC method could track the reference signals satisfying the control objective to minimize the target subpopulations and could improve the convergence rate of the control TB epidemic system. Thus, the TVSC method is an applicable and effective approach to determine control policy for the TB epidemic system.**

***Index Terms*—tuberculosis, epidemic system, epidemic control, nonlinear feedback control, synergetic control**

I. Introduction

Referring to World Health Organization (WHO) [1], [2], Tuberculosis (TB) disease is a significant global public health problems caused by *Mycobacterium tuberculosis*. This pathogen normally infects human lungs and can further disseminate to other organs [1]-[3]. TB has caused significant concerns, especially in the HIV–positive population due to its potentially-fatal opportunistic characteristic [1]-[4]. Based on the information presented by [1], [2] in 2018, TB infection in human was 10 million individuals and caused up to 1.5 million deaths. Approximately one-sixth of the deaths were among HIV-positive individuals [1], [2]. The infection can be transmitted through airborne route from various activities such as coughing, sneezing, speaking, singing and splitting [1], [2], [5]. Inhaling a small amount of the germs, the exposed person can be infected by TB [1], [5]. After bacterial infection, a board spectrum can be categorized in three main forms which are active TB disease, latent TB infection (LTBI) and TB self-cure [5], [6]. The active case commonly shows symptoms, for example, fever, chest pain, fatigue, anorexia and weight loss [1], [3], [5]. LTBI individuals are those of infected asymptomatic individuals who have the specific immune activated by the bacterial antigens. Importantly, the LTBI individuals potentially turn to be to the active TB ones [5]-[7]. In accordance with the World Health Organization (WHO), reduction of new TB infections is an important issue. Preventing the reactivation of LTBI from becoming the active TB can reduce the new TB infections [2], [7]. Control of the TB spread focuses on the prevention of new infection in susceptible individuals and reactivation in LTBI individuals. The first prevention can be achieved by vaccination control program, while the later prevention required both drug treatment and vaccination control programs [2], [6]. Vaccination control, BCG, is available to prevent infection of susceptible individuals. However, the efficacy of the vaccine depends on the age of the vaccinated individuals, since efficacy of immunization for children is about 30%, while it fluctuates for the case of adults. Moreover, it cannot provide long-term immunity [6], [8]. Even though a higher efficacy vaccine candidate was found, but it

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remains in the process of vaccine trials [6], [9]. Both active TB and LTBI individuals can be treated by four drugs: isoniazid, rifampicin, pyrazinamide and ethambutol. These two groups of infected individuals can be treated by the same drugs; however, they required different regimens [1], [2], [6], [7].

The dynamics of TB epidemic can be represented through the nonlinear compartmental models. Various compartmental TB epidemic models have been developed to describe the dynamic behavior of the TB epidemic by using the law of mass action [10]-[26]. Differences of the models result from the subpopulations, control strategies and factors contained in each of the models [10]-[26]. Accordingly, dynamical analysis involved with the stability analysis can be conducted base on these compartmental models such as the determination of the reproduction number (R_0), the disease free equilibrium (*DFE*), and the sensitivity analysis [10]-[26]. Along with the dynamical analysis, determination of the control policy containing various controls such as treatment and vaccination controls to eliminate the spread of the TB is another aspect, which has been studied based on these compartmental models through the optimal control approach according to the Pontryagin's maximum principle [18]-[26]. Likewise, feedback control concept is also a feasible approach to determine different control policies for various epidemic systems. The feasibility has been confirmed through several previous works [27]-[36].

Synergetic control approach based on analytical design of aggregated regulators (ADAR) is among the promising approaches for defining the eradicating control policies for epidemic systems, which typically involve multiple subpopulations and multiple control strategies as seen in previous works [18], [20]-[22], [24], [26], [30]-[33], [35]-[36]. The concept of the synergetic control (SC) method was introduced by Kolesnikov et al. [37]-[39]. In the synergetic controller design, the selection of macro variables is an essential part. Under the appropriate selection, the problem from noise and parameter sensitivity can be eliminated. The global stability of the control system is achievable [40], [41]. The chattering free characteristic of the control system is one advantage of the SC approach [40]-[43]. The SC method has been employed to synthesis the feedback control law of high-order nonlinear systems such as power systems [40], [41], [44], robotic systems [43], [45], and biological and epidemic systems [34]-[36], [46].

Increasing the convergence rate of the control system is worth consideration. Like terminal or finite time sliding mode control (SMC), terminal synergetic control is a typical approach to enhance the convergence rate of the synergetic controllers [43], [46]. However, the designer may involve singularity caused by fractional integer exponent terms in the dynamic evolution [47], [48]. Furthermore, it is beneficial in terms of the controller parameter tuning, if ranges of the parameters are continuous [49]. Time varying sliding surface in SMC can be employed to increase the convergence rate of the control system with continuous controller parameters [50]-[54]. In the synergetic control, various choices of macro variables are available depending on control objectives and the structure of the dynamic system [37], [40]-[46]. Specifically, the concept of the time varying surface in SMC method can be a promising approach for improving the performances of the control system based on the synergetic control method as proposed by Kanchanaharuthai and Mujjalinvimut [44].

Motivated by the utilization of the time varying surfaces in the design of synergetic control in [44] and the capability of the SC method in [37], [40]-[46], the authors adopted the concept of the time varying sliding surface in the SMC method and utilized these sliding surfaces as macro variables in the synergetic controller design procedure to determine the control policy for the TB epidemic system. According to the effectiveness of the drug treatment and variation of the vaccine efficacy, the authors focused only on the TB epidemic system under the policy corresponding to the treatment control.

This paper is organized as follows. The compartmental model representing the TB epidemic system is described in Section II. Then, the synergetic controller design with time varying macro variables is presented in Section III. Section IV presents simulation of the control TB epidemic system. The conclusion is presented in Section V.

II. Tuberculosis Epidemic System

Since determination of the control policy for TB epidemic system based on the treatment control was considered in this work, the TB epidemic model with control inputs presented by Silva et al. [21] and conducted a further study by Denysiuk et al. in [22] was an interested model. This model was developed from the TB model, including both reinfection and post-exposure interventions presented by Gomes et al. [15]. According to the control and the interventions contained in the model, the TB epidemic model in [21], [22] was used for determining the control policy for the TB epidemic system according to the feedback controller design in this work.

The TB model involves following subpopulations: susceptible ($S(t)$), early latent ($L_1(t)$), infected ($I(t)$), persistent latent ($L_2(t)$) and recovered ($R(t)$) subpopulations. According to [21], [22] infected subpopulation refers to active TB infectious individuals. The corresponding TB epidemic model is presented in (1) [21], [22]:

$$\left.\begin{aligned}
\dot{S} &= \mu N - \frac{\beta}{N} IS - \mu S \\
\dot{L}_1 &= \frac{\beta}{N} I(S + \sigma L_2 + \sigma_R R) - (\delta + \tau_1 + \mu) L_1 \\
\dot{I} &= \phi\delta L_1 + \omega L_2 + \omega_R R - (\tau_0 + \varepsilon_1 u_1 + \mu) I \\
\dot{L}_2 &= (1-\phi)\delta L_1 - \sigma \frac{\beta}{N} I L_2 - (\omega + \varepsilon_2 u_2 + \tau_2 + \mu) L_2 \\
\dot{R} &= (\tau_0 + \varepsilon_1 u_1) I + \tau_1 L_1 + (\varepsilon_2 u_2 + \tau_2) L_2 - \sigma_R \frac{\beta}{N} IR \\
&\quad - (\omega_R + \mu) R.
\end{aligned}\right\} \quad (1)$$

According to [21], [22], the two control inputs of the model are the prevention measure ($u_1(t)$) and the treatment measure ($u_2(t)$) which are defined as (i) the prevention measure $u_1(t)$ is the effort of the failure prevention of treatment for active TB infectious individuals and (ii) $u_2(t)$ is the fraction of persistent latent individuals being identified and treated. It is worth noting that the control inputs are bounded as $0 \le u_1, u_2 \le 1$ [21], [22]. Parameters of the TB system (1) defined in [15], [21], [22] are presented in the following descriptions. The parameter β is the transmission coefficient. The death and birth rates are denoted by μ. The reduction rate from early latent subpopulation is denoted by δ. The parameter ϕ represents proportional population moving into infected subpopulation. The endogenous reactivation rates of persistent latent infected and treated subpopulations are denoted by ω and ω_R, respectively. The parameters representing the factors corresponding to the reduction of the infection risk caused by the immunity from previous infection for persistent latent and treated individual are defined as σ and σ_R, consecutively. The recovery rate under the treatments of the infected, early latent and persistent latent subpopulations are defined by τ_0, τ_1 and τ_2, respectively. The efficacies of the treatment of the infected and persistent latent subpopulations are denoted by ε_1 and ε_2, respectively. The constant total population is represented by N, $N = S(t) + L_1(t) + I(t) + L_2(t) + R(t)$.

The mathematical model in (1) can be rearranged and written in the affine state space form as (2):

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \\ \dot{x}_5 \end{bmatrix} = \begin{bmatrix} f_1(x) \\ f_2(x) \\ f_3(x) \\ f_4(x) \\ f_5(x) \end{bmatrix} + \begin{bmatrix} 0 & 0 \\ 0 & 0 \\ g_3(x) & 0 \\ 0 & g_4(x) \\ g_{51}(x) & g_{52}(x) \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}, \quad (2)$$

where $x(t) = [x_1\ x_2\ x_3\ x_4\ x_5]^T = [S\ L_1\ I\ L_2\ R]^T$,

$$f_1(x) = \mu N - \frac{\beta}{N} x_3 x_1 - \mu x_1,$$

$$f_2(x) = \frac{\beta}{N} x_3 (x_1 + \sigma x_4 + \sigma_R x_5) - (\delta + \tau_1 + \mu) x_3,$$

$$f_3(x) = \phi\delta x_2 + \omega x_4 + \omega_R x_5 - (\tau_0 + \mu) x_3,$$

$$f_4(x) = (1-\phi)\delta x_2 - \sigma \frac{\beta}{N} x_3 x_4 - (\omega + \tau_2 + \mu) x_4,$$

$$f_5(x) = \tau_0 x_3 + \tau_1 x_2 + \tau_2 x_4 - \sigma_R \frac{\beta}{N} x_3 x_5 - (\omega_R + \mu) x_5,$$

$$g_3(x) = -\varepsilon_1 x_3,\ g_4(x) = -\varepsilon_2 x_4,\ g_{51}(x) = \varepsilon_1 x_3,$$

$$g_{52}(x) = \varepsilon_2 x_4.$$

Further details of the TB model in (1) can be determined from [15], [21], [22].

III. Control Policy-Based Synergetic Controller Design

The control objective and the determination of the control policy for the TB epidemic system based on the design of time varying variable synergetic control (TVSC) are presented. After that, the stability of the control TB epidemic system is examined through the Lyapunov stability approach.

A. Control Objective

According to [21], [22], for the eradication of the TB epidemic, the infected subpopulation (x_3) and the persistent latent subpopulation (x_4) need to be minimized by the control policy, including two control inputs corresponding to the prevention measure (u_1) and the treatment measure (u_2). Referring to Sharifi and Moradi [33], in order to satisfy the control objectives, the monotone decreasing function in the exponential form can be used as a reference signal for the infected and persistent latent subpopulations as (3) [33]:

$$\left.\begin{aligned} x_{3r}(t) &= (x_{3r}(0) - x_{3r}(T))e^{-a_{3r}t} + x_{3r}(T) \\ x_{4r}(t) &= (x_{4r}(0) - x_{4r}(T))e^{-a_{4r}t} + x_{4r}(T). \end{aligned}\right\}, \quad (3)$$

where T is the final time. The convergence rate of each reference signal is defined by a_{3r} and a_{4r}. The values of $x_{3r}(T)$ and $x_{4r}(T)$ are the desired final values of the infected and the persistent latent subpopulations. The differences between the target subpopulations and their reference signals are expressed as (4):

$$\left.\begin{aligned} e_3(t) &= x_3(t) - x_{3r}(t) \\ e_4(t) &= x_4(t) - x_{4r}(t). \end{aligned}\right\} \quad (4)$$

B. Controller Design

Based on the control objectives mentioned above, the goal of the controller design is to synthesize the feedback control law to minimize the dynamic errors in (4).

In accordance with [34]-[37], [40]-[45], [50], the synergetic controller design with time varying macro variables can be conducted as follows:

First, based on the time varying sliding surface presented in [50] and dynamic errors in (4), the macro variables that satisfy the control objective can be selected as (5) [34]-[37], [40]-[46], [50]:

$$\left.\begin{aligned} \psi_3(t) &= e_3(t) + a_3 e^{-b_3 t} \\ \psi_4(t) &= e_4(t) + a_4 e^{-b_4 t}, \end{aligned}\right\} \quad (5)$$

where a_3, a_4, b_3 and b_4 are real constants satisfying $a_3 = -e_3(0)$, $a_4 = -e_4(0)$, $b_3 > 0$ and $b_4 > 0$ [50].

Then, the dynamic evolutions of the selected macro variables in (5) are defined as (6) [34]-[37], [40]-[46]:

$$\left.\begin{aligned} \dot{\psi}_3 + \lambda_3 \psi_3 &= 0 \\ \dot{\psi}_4 + \lambda_4 \psi_4 &= 0, \end{aligned}\right\} \quad (6)$$

where $\lambda_3 > 0$ and $\lambda_4 > 0$.

Finally, the control policy, including the prevention measure (u_1) and the treatment measure (u_2) can be obtained based on the dynamic evolution in (6). Substituting macro variables in (5) into (6), yields that

$$\left.\begin{aligned}[\dot{e}_3 + a_3(-b_3)e^{-b_3 t}] + \lambda_3 \psi_3 = 0\\ [\dot{e}_4 + a_4(-b_4)e^{-b_4 t}] + \lambda_4 \psi_4 = 0.\end{aligned}\right\} \quad (7)$$

According to the dyanmic of TB epidemic system in (2) and dynamic errors in (4), (7) can be written as (8):

$$\left.\begin{aligned}[(f_3(x) + g_3(x)u_1 - \dot{x}_{3r}) + a_3(-b_3)e^{-b_3 t}] + \lambda_3 \psi_3 = 0\\ [(f_4(x) + g_4(x)u_2 - \dot{x}_{4r}) + a_4(-b_4)e^{-b_4 t}] + \lambda_4 \psi_4 = 0.\end{aligned}\right\} \quad (8)$$

After solving (8), the control policy which consists of the prevention measure (u_1) and the treatment measure (u_2) is determined as (9):

$$\left.\begin{aligned}u_1 = g_3(x)^{-1}\{-\lambda_3 \psi_3 - [(f_3(x) - \dot{x}_{3r}) + a_3(-b_3)e^{-b_3 t}]\}\\ u_2 = g_4(x)^{-1}\{-\lambda_4 \psi_4 - [(f_4(x) - \dot{x}_{4r}) + a_4(-b_4)e^{-b_4 t}]\}.\end{aligned}\right\} \quad (9)$$

C. Control System Stability

In accordance with [34]-[36], [42], [43], [44], [46], the stability of the control system is investigated through the Lyapunov stability approach as follows:

First, the Lyapunov function is defined as (10) [42], [43], [44], [46]:

$$V = 0.5\psi_3^{\,2} + 0.5\psi_4^{\,2}. \quad (10)$$

The derivative of V can be found as (11):

$$\dot{V} = \psi_3 \dot{\psi}_3 + \psi_4 \dot{\psi}_4. \quad (11)$$

Then, substituting (5) into (11), $\dot{V}$ can be obtained as (12):

$$\begin{aligned}\dot{V} &= \psi_3[\dot{e}_3(t) + a_3(-b_3)e^{-b_3 t}] \\ &\quad + \psi_4[\dot{e}_4(t) + a_4(-b_4)e^{-b_4 t}] \\ &= \psi_3[(\dot{x}_3 - \dot{x}_{3r}) + a_3(-b_3)e^{-b_3 t}] \\ &\quad + \psi_4[(\dot{x}_4 - \dot{x}_{4r}) + a_4(-b_4)e^{-b_4 t}].\end{aligned} \quad (12)$$

From the dynamic of TB epidemic system in (2), (12) becomes (13):

$$\begin{aligned}\dot{V} = \psi_3[(f_3(x) + g_3(x)u_1 - \dot{x}_{3r}) + a_3(-b_3)e^{-b_3 t}] \\ + \psi_4[(f_4(x) + g_4(x)u_2 - \dot{x}_{4r}) + a_4(-b_4)e^{-b_4 t}].\end{aligned} \quad (13)$$

Finally, substituting control inputs, u_1 and u_2 , into (13), the result is:

$$\begin{aligned}\dot{V} = \psi_3[(f_3(x) + g_3(x)(g_3(x)^{-1}\{-\lambda_3 \psi_3 - [(f_3(x) - \dot{x}_{3r}) \\ + a_3(-b_3)e^{-b_3 t}]\}) - \dot{x}_{3r}) + a_3(-b_3)e^{-b_3 t}] \\ + \psi_4[(f_4(x) + g_4(x)(g_4(x)^{-1}\{-\lambda_4 \psi_4 - [(f_4(x) - \dot{x}_{4r}) \\ + a_4(-b_4)e^{-b_4 t}]\}) - \dot{x}_{4r}) + a_4(-b_4)e^{-b_4 t}].\end{aligned}$$

$$\dot{V} = -\lambda_3 \psi_3^{\,2} - \lambda_4 \psi_4^{\,2} \le 0. \quad (14)$$

Equation (14) implies that all macro variables converge to zero as the time increases. Consequently, at $\psi_3 = \psi_4 = 0$, it is evident from (5) that the dynamic errors, $e_3(t)$ and $e_4(t)$, converge to zero as the time increases. Thus, the synergetic control with specified macro variables can track the desired reference signals [42], [43], [46], [50].

IV. Simulation of Control TB System

The simulation of the control TB epidemic system under the control policy corresponding to the synergetic control approach is presented in the first subsection. Then, the simulation results are discussed in the later subsection.

A. Simulation Example

The control TB system under the control policy based on the time varying synergetic controller was simulated and compared with the simulation of the control system under the conventional synergetic controller.

The mathematical model of the TB epidemic system with the control inputs presented in [21], [22] was used as a simulation example. The numerical values of system parameters and initial conditions from [15], [21], [22] were also used and defined as follows: $\beta = 75$, $\mu = 1/70\ yr^{-1}$, $\delta = 12\ yr^{-1}$, $\phi = 0.05$, $\omega = 0.0002\ yr^{-1}$, $\omega_R = 0.00002\ yr^{-1}$, $\sigma = 0.25$, $\sigma_R = 0.25$, $\tau_0 = 2\ yr^{-1}$, $\tau_1 = 2yr^{-1}$, $\tau_2 = 1yr^{-1}$, $N = 30000$ individuals , $\varepsilon_1 = 0.25$, $\varepsilon_2 = 0.25$, $x_1(0) = 19000$ individuals, $x_2(0) = 9250$ individuals, $x_3(0) = 1000$ individuals, $x_4(0) = 500$ individuals and $x_5(0) = 250$ individuals. The simulation was carried out from $t = 0$ to $t = 10$ *yrs* , and the incremental time was 0.0001 *yr* . The parameters of the desired reference signals were selected as $a_{3r} = a_{4r} = -1.5$, $x_{3r}(0) = 750$, $x_{4r}(0) = 350$, $x_{3r}(T) = 0$ and $x_{4r}(T) = 0$. The controller parameters were chosen as $\lambda_3 = 0.000010$, $\lambda_4 = 0.000010$, $a_3 = -250$, $a_4 = -150$ and $b_3 = b_4 = 0.3$. For the case of the control policy based on the conventional SC method, the macro variables were selected as $\psi_3 = e_3$ and $\psi_4 = e_4$. Consequently, the control inputs corresponding to the conventional SC method can be obtained as

$$\left.\begin{aligned}u_1 = g_3(x)^{-1}\{-\lambda_3 \psi_3 - [(f_3(x) - \dot{x}_{3r})]\}\\ u_2 = g_4(x)^{-1}\{-\lambda_4 \psi_4 - [(f_4(x) - \dot{x}_{4r})]\}.\end{aligned}\right\} \quad (15)$$

B. Simulation Results and Discussions

The time responses of the infected and the persistent latent subpopulations as manipulated by the time varying macro variable synergetic control (TVSC) and those corresponding to the conventional synergetic control (SC) are plotted and shown in Fig. 1. Then, the control policy, including the effort of the failure prevention of the treatment for active TB infectious individuals (u_1) and the fraction of identified and treated persistent latent

individuals (u_2) for each of TVSC and SC methods are shown in Fig. 2. Considering the time responses of the infected subpopulation (x_3) and persistent latent subpopulation (x_4) in Fig. 1, it was clear that both subpopulations could track the corresponding reference signals which converge to zero asymtotically. Therefore, the control policies corresponding to both TVSC and SC methods could drive the infected and persistent latent subpopulations such that the control objective was satisfied. However, the convergence rate of the control system under the TVSC method was higher compared to that of the conventional SC method. The failure prevention efforts of the treatment for active TB individuals (u_1) of the TVSC and the conventional SC methods are shown in Fig. 2(a). The prevention efforts of both control methods were at the maximum level for a certain period and reduced quickly to zero. After that, the prevention effort of the TVSC increased to the maximum constant level and was maintained in this level until the end of time. Meanwhile, the prevention effort of the SC method stayed at the zero level for the rest of time. The control inputs corresponding to the fraction of identified and treated persistent latent individuals (u_2) of the TVSC and the conventional SC methods are shown in Fig. 2(b). The fractions of identification and treatment of both control methods started at the maximum level and reduced rapidly to zero. Then, they remained at the zero until the end of the simulation time.

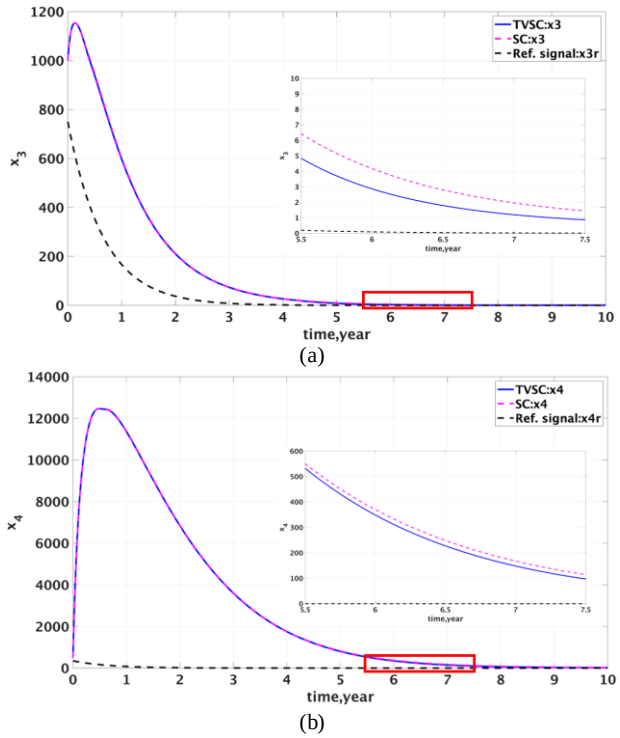

Figure 1. Time responses of the control TB system based on the control policies from the TVSC and SC approaches: (a) Infected subpopulation x_3 and (b) Persistent latent subpopulation x_4.

Overall, the TVSC method required a higher control effort than the SC method did. Still, all control inputs of both methods were free from chattering. This is an important benefit, demonstrating that the determined control policy is implementable in reality. The improvement of the convergence rate of the control TB epidemic system under TVSC method can be achieved by an appropriate selection of controller parameters. Moreover, the singularity can be avoided.

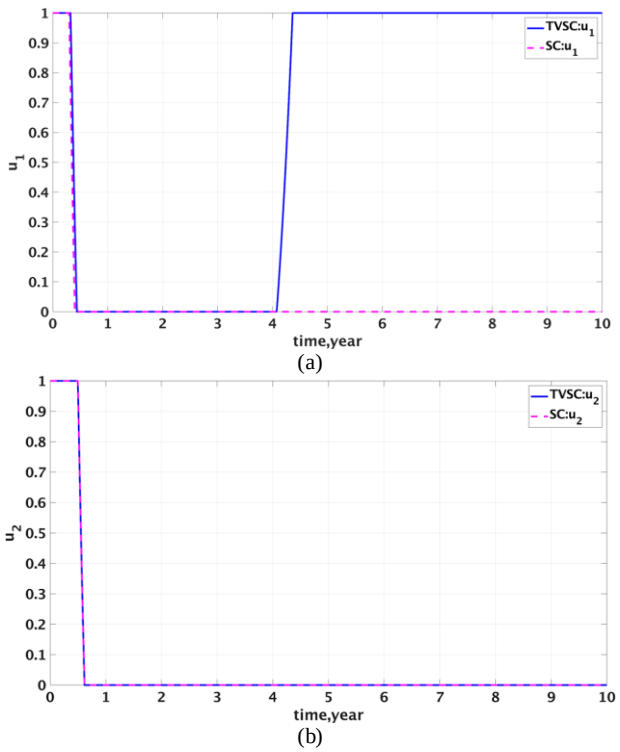

Figure 2. The control policies of the TVSC and SC approaches: (a) Prevention measure u_1 and (b) Treatment measure u_2.

V. Conclusion

In this study, the control policy of the TB epidemic system was synthesized based on the time varying synergetic controller design procedure. Using the synthesized control policy, the control objective to minimize the target subpopulations was satisfied. Furthermore, the improvement of the convergence rate of the control TB epidemic system could be achieved. Thus, it is beneficial to consider the utilization of the synergetic control with time varying macro variables for defining the policy to control the TB epidemic system.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Boonyaprapasorn conducted a literature review, a design and an analysis of the control policy, and the simulation; Choopojcharoen supported the simulation and the literature review of the theoretical background of the feedback control; Pengwang contributed to the manuscript preparation and a literature review.; Sa-Ngiamsunthorn contributed to the literature review of the

theoretical background in dynamical system and reviewed mathematical expressions; Natsupakpong contributed to the manuscript preparation and a literature review; Maneewarn contributed to the literature review in the theoretical background in feedback control and manuscript revision; Thung-od contributed to the manuscript preparation and a literature review. All of the authors had approved the final version of the manuscript.

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