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Investigation of nonlinear epidemiological models for analyzing and controlling the MERS outbreak in Korea



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ABSTRACT

Much concern has arisen regarding serious epidemics due to the Middle East Respiratory Syndrome (MERS) coronavirus. The first MERS case of Korea was reported on 20 May 2015, and since then, the MERS outbreak in Korea has resulted in hundreds of confirmed cases and tens of deaths. Deadly infectious diseases such as MERS have significant direct and indirect social impacts, which include disease-induced mortality and economic losses. Also, a delayed response to the outbreak and underestimating its danger can further aggravate the situation. Hence, an analysis and establishing efficient strategies for preventing the propagation of MERS is a very important and urgent issue. In this paper, we propose a class of nonlinear susceptible-infectious-quarantined (SIQ) models for analyzing and controlling the MERS outbreak in Korea. For the SIQ based ordinary differential equation (ODE) model, we perform the task of parameter estimation, and apply optimal control theory to the controlled SIQ model, with the goal of minimizing the infectious compartment population and the cost of implementing the quarantine and isolation strategies. Simulation results show that the proposed SIQ model can explain the observed data for the confirmed cases and the quarantined cases in the MERS outbreak very well, and the number of the MERS cases can be controlled reasonably well via the optimal control approach.

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1. Introduction

First confirmed on 20 May 2015, the latest outbreak of Middle East Respiratory Syndrome coronavirus (MERS-CoV) infections in Korea accounted for 186 laboratory-confirmed cases, including 36 deaths, 138 recovered individuals discharged from hospitals, and 12 remaining in hospitals up to 28 July 2015, a de facto end date of the outbreak (Ministry of Health and Welfare, MoH). It spread remarkably fast in hospitals, which has caused the largest MERS outbreak outside the Middle East. The case fatality rate of 19.4% is, however, much lower than the reported rate of 37.7% prior to the outbreak in Korea, according to the World Health Organization (WHO). The MERS-CoV is a novel betacoronavirus which was first identified from the sputum of a 60-year-old man in fall 2012 (Zaki et al., 2012). Clinical features of MERS range from mild illness to fatal conditions such as acute respiratory distress syndrome

and multi-organ failure resulting in death, especially in patients with underlying comorbidities (Zumla et al., 2015). Although it is initially known as a zoonotic disease, human-to-human transmission occurs in health care settings and now is linked with significant morbidity (Oboho et al., 2015). This outbreak of the MERS-CoV infection, including the index cases roommates, their caregiver, and even the healthcare workers, in what is called as a super-spreading event (Kupferschmidt, 2015), raised several important issues for global public health surveillance and raised several issues regarding infection control policies, including the control of nosocomial transmission to avoid a repeated outbreak (Keeling and Rohani, 2008).

In this study, we carry out an epidemiological assessment of the MERS-CoV outbreak in Korea in order to provide a mathematical framework for understanding the complex dynamics of the pathogen spread and establishing efficient guidelines for implementing quarantine and isolation strategies. More specifically, we propose a class of nonlinear susceptible-infectious-quarantined (SIQ) models for analyzing and controlling the MERS outbreak in Korea. The proposed SIQ model is innovative, in that the MERS

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transmission probability is time-dependent, monotone decreasing, and squashing-type. More specifically, it is initially almost flat, then decreasing rapidly, and finally gradually reaching a saturation point, which is reasonable because this can reflect the change in individuals' hygienic behaviour with time. Recently, there has been much interest in investigating some aspects of the time-dependent nature of the disease transmission probability. In particular, several methods have been considered to model the time-dependence due to the impact of media coverage (Cui et al., 2008; Liu et al., 2007; Sun et al., 2011; Xiao et al., 2015). However, these studies have mostly focused on only a single factor under consideration. In this paper, we consider all relevant factors that can affect the MERS transmission probability (e.g., media coverage, increased awareness, etc.) collectively, and try to model the resultant time-dependent transmission probability using a sigmoidal function. Note that the sigmoidal functions are quite popular in the field of machine learning when one needs to address monotone and squashing-type phenomena. For the proposed SIQ model, we perform the task of parameter estimation, and apply optimal control theory to the controlled SIQ model, with the goal of minimizing the infectious compartment population and the cost of implementing the quarantine and isolation strategies. Simulation results show that the proposed SIQ model can explain the observed data for the confirmed cases and the quarantined cases in the MERS outbreak very well, and the number of the MERS cases can be controlled reasonably well via the optimal control approach. Finally in the last two sections of this paper, discussion and concluding remarks are given along with brief descriptions of data treatment.

2. Methods and results

2.1. The SIQ model for the MERS analysis

In this section, we will propose a nonlinear susceptible-infectious-quarantined (SIQ) model for analyzing the MERS outbreak in Korea. The SIQ model is a generalization of an epidemiological population model involving susceptible, infectious, and quarantined compartments (Hethcote et al., 2002; Keeling and Rohani, 2008; Lenhart and Workman, 2007; Xiao et al., 2015). In the SIQ model, the four compartment populations are used as the model's state variables: $S(t)$, the number of individuals that are susceptible to the MERS disease at time t ; $I(t)$, the number of individuals that are actively infectious at time t ; $S_q(t)$, the number of quarantined susceptible individuals at time t ; and $C_q(t)$, the number of confirmed cases at time t . Note that in the SIQ model, Q stands for the super-compartment comprising S_q and C_q (see Fig. 1). Also, note that $C_q(t)$ is a collective sink-type compartment, which includes the number of the MERS patients under treatment, the recovered cases, and the dead cases altogether at time t . As shown in Fig. 1, the SIQ model considers two kinds of non-pharmaceutical interventions: quarantine of the susceptible and infected individuals, and isolation of the infectious individuals following contact tracing. As a result of a contact tracing, a proportion, q , of individuals who are contacted in connection with a MERS patient is quarantined. The quarantined individuals can move to compartments C_q or S_q , depending on whether they are exposed to the MERS coronavirus or not. Hence, the quarantined individuals, if uninfected, move to the compartment S_q at a rate of $c(1 - \beta(t))q$, where c is the contact rate, i.e., the average number of contacts of the whole population per unit time, and $\beta(t)$ is the probability of the MERS transmission per contact at time t . Note that in the SIQ model, the MERS transmission probability, $\beta(t)$, is time-dependent, monotone decreasing, and squashing-type. Obviously, using time-dependent transmission probability is more reasonable than using the constant one, because it can reflect the change of individuals' hygienic behavior with time. As shown in Fig. 1, if infected, the

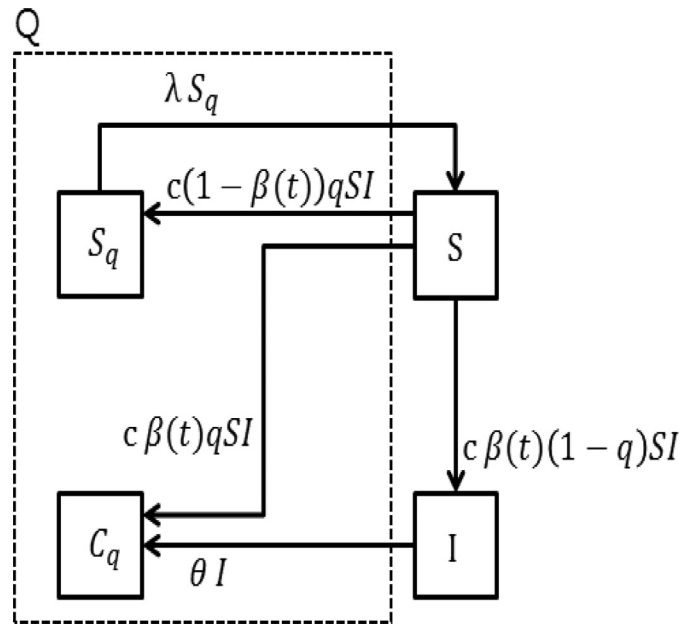


Fig. 1. The SIQ model.

quarantined individuals move to the compartment C_q at a rate of $c\beta(t)q$. Also, the remaining proportion (i.e., the proportion missed from the contact tracing), $1 - q$, can move to compartment I or stay in compartment S , depending on whether they are exposed to the MERS coronavirus or not. The transmission dynamics of the SIQ model is illustrated in Fig. 1, and its state equations are as follows:

$$\begin{aligned}
 \dot{S}(t) &= -c(1 - \beta(t))qS(t)I(t) - c\beta(t)qS(t)I(t) - c\beta(t)(1 - q)S(t)I(t) + \lambda S_q(t) \\
 \dot{I}(t) &= c\beta(t)(1 - q)S(t)I(t) - \theta I(t) \\
 \dot{S}_q(t) &= c(1 - \beta(t))qS(t)I(t) - \lambda S_q(t) \\
 \dot{C}_q(t) &= c\beta(t)qS(t)I(t) + \theta I(t)
 \end{aligned}
 \tag{1}$$

The first equation of (1) describes the rate of change of the susceptible compartment population, with four terms on its right-hand side. Its first term concerns the transition from S to S_q due to quarantine of susceptible individuals. This term can be explained in terms of a bilinear incidence law having a contact rate c together with $\beta(t)$, the probability of the MERS transmission per contact at time t , and q , the probability of quarantine per contact. The second and third terms model the transition from S to C_q and the transition from S to I , respectively. The fourth term represents the transition from S_q to S , and this transition means the release from quarantine into the wider community. In the second equation of (1), the rate of change of the infectious compartment population is described by two terms. The first represents the transition from the susceptible state to the infectious state, and the second term denotes the transition from I to C_q due to detection and isolation of the infectious patients. The remaining equations of (1) describe the rates of change of S_q and C_q in the super-compartment Q , respectively, and the exact meaning of their terms can be explained similarly. The natural birth and death rates are not considered in the SIQ model, and this omission allows us to focus on the core theme of the paper. Note that consideration of these additional aspects is relatively straightforward, and would lead us to some further related observations. For example, if the natural birth rate of a susceptible population, Λ , and the natural death rate, d , are consid-

Table 1
Parameters for the SIQ model.

Notation	Meaning
S_0	Initial value of $S(t)$, the number of individuals in the susceptible compartment
c	Contact rate
$\beta(t)$	Probability of MERS transmission per contact (see Fig. 2)
q	Probability of quarantine per contact
λ	Rate at which the quarantined susceptible individuals are released into the wider community
θ	Isolation rate for infectious individuals
t_β	Inflection point of $\beta(t)$
s_β	Parameter determining the slope of $\beta(t)$ at t_β

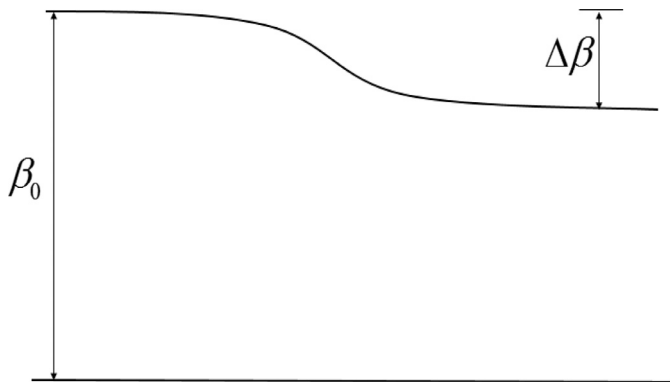


Fig. 2. Squashing-type function, $\beta(t)$, used in the SIQ model.

ered, the resultant reduced SIQ system¹ with a constant transmission probability, β_0 , would have the disease-free equilibrium point $E_0 = (\Lambda/d, 0, 0)$, which is locally asymptotically stable if the basic reproduction number $R_0 < 1$, where $R_0 = \Lambda c \beta_0 (1 - q) / (d(d + \theta))$.

As previously mentioned, the MERS transmission probability, $\beta(t)$, of our SIQ model, is time-dependent, monotone decreasing, and squashing-type. Since many factors (e.g., media coverage, increased awareness, etc.) can alter individuals' hygienic behavior, we employ the squashing-type function of Fig. 2 for $\beta(t)$.² More specifically, we utilize

$$\beta(t) = \beta_0 - \Delta\beta\sigma(s_\beta(t - t_\beta)), \quad (2)$$

where $\sigma(\cdot)$ is the logistic sigmoidal function (Bishop, 2006) defined as $\sigma(x) = 1 / (1 + \exp(-x))$; t_β is the inflection point of $\beta(t)$; s_β is the parameter determining the slope of $\beta(t)$ at its inflection point. Note that the use of logistic sigmoidal functions is quite popular in the field of machine learning (Bishop, 2006) when one needs to represent monotone and squashing-type phenomena. Also, note that using the logistic sigmoidal function of (2) lead to the following simplification when we compute its derivative:

$$\dot{\beta}(t) = -\Delta\beta s_\beta \sigma(s_\beta(t - t_\beta))(1 - \sigma(s_\beta(t - t_\beta))). \quad (3)$$

This property can be utilized effectively in further studies on the qualitative properties of the SIQ model (e.g., study of the global stability of the disease-free and endemic equilibrium points of the SIQ model). An explanation of the SIQ parameters is given in Table 1.

By fitting the SIQ model to the reported data for the confirmed cases and the quarantined cases, we obtain the following

¹ Because the state variable C_q does not appear in the first three equations of system (1), we can further simplify system (1). In the stability analysis, considering the resultant reduced system is sufficient.

² Note that our paper addresses the time-dependent aspect for β . An important approach that can be addressed along these lines is the event-dependent approach, where the transmission probability could be dependent on the number of the newly-added or accumulated MERS cases.

parameters:³

$$\begin{aligned} S_0 &= 1.6 \times 10^{+04}, \quad c = 7.2 \times 10^{-03}, \\ \beta_0 &= 6.5 \times 10^{-03}, \quad \Delta\beta = 3.3 \times 10^{-03}, \\ s_\beta &= 0.78, \quad t_\beta = 2.18 \times 10^{+01}, \quad q = 2.3 \times 10^{-01}, \\ \lambda &= 5.46 \times 10^{-02}, \quad \theta = 3.8 \times 10^{-01}. \end{aligned} \quad (4)$$

We performed simulations based on the estimated parameters. Simulation results (Fig. 4) show that the proposed SIQ model can explain the observed data (Fig. 3) for the confirmed cases and the quarantined cases in the MERS outbreak very well. Our parameter estimation results show that the MERS transmission probability, $\beta(t)$, is initially almost flat, then decreasing rapidly, and finally gradually reaching a saturation point (see the solid line of Fig. 5). This has a natural interpretation, in that as information on the MERS outbreak becomes more widely known with the passage of time, health authorities' and individuals' efforts against the epidemic intensify accordingly, which results in the MERS transmission probability decreasing in the squashing-type fashion, as in Fig. 5. In retrospect, if the initial effort to reduce the MERS transmission probability were more effective, the magnitude of β_0 could be decreased further. In order to investigate this aspect, we additionally performed simulations for a scenario with β_0 reduced to 90% of its estimated value (see the dashed line of Fig. 5). Fig. 6 shows that the infectious population could be reduced significantly if the aforementioned effort were successful. In order to clarify why it is important to consider the incidence rate of the type shown in (2), we also considered the constant beta case, and provided the corresponding simulation results (Fig. 7). Comparing Figs. 4 and 7 shows the superiority of using the time-dependent β .

2.2. The controlled SIQ (C-SIQ) model and optimal control

Since quarantine and isolation strategies are the most important and effective measures against the outbreaks of disease when one does not have valid medicines and vaccine (see e.g., Castillo-Chavez et al., 2003; Day et al., 2006; Yan and Zou, 2009; Yan et al., 2007), one can view the efforts of implementing quarantine and isolation strategies as the actions that control the entire model. In this paper, we utilize optimal control theory (Lenhart and Workman, 2007; Lewis and Syrmos, 1995) for the possibility of improving our control efforts. Note that recent applications of optimal control theory are increasingly used in communities of biological systems (e.g. (Buonomo and Messina, 2012; Joshi et al., 2006; Jung et al., 2002; Kirschner et al., 1997; de Pillis et al., 2007)), and in particular, they have been widely used and discussed in the control

³ Since the proposed model is deterministic, we obtain the model parameters by minimizing the fitting error defined with a weighted sum of the squared error of C_q and the squared error of S_q (For more details, please refer to Section 4.2). Note that our model may be extended to incorporate stochastic terms such as noise arising from variability in the transmission probability, in which case more sophisticated Markov Chain Monte Carlo (MCMC) methods need be used for parameter estimation.

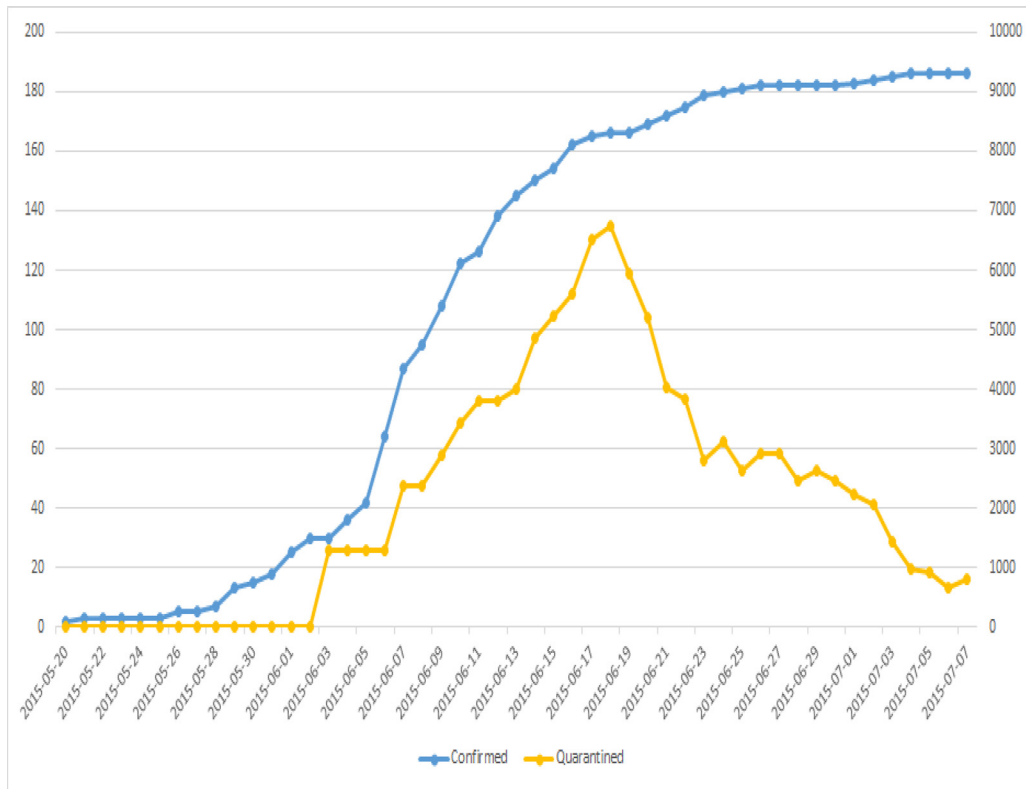


Fig. 3. MERS confirmed cases & quarantine status.

of epidemics (e.g. Caetano and Yoneyama, 2001; Feng et al., 2009; Gupta and Rink, 1973; Joshi et al., 2006; Lenhart and Workman, 2007). By incorporating the control inputs, $q^*(t)$ and $\theta^*(t)$ into our SIQ model (1), one can obtain the following state equations for the controlled model:

$$\begin{aligned} \dot{S}(t) &= -c\{(1 - \beta(t))q^*(t) + \beta(t)\}S(t)I(t) + \lambda S_q(t) \\ \dot{I}(t) &= c\beta(t)(1 - q^*(t))S(t)I(t) - \theta^*(t)I(t) \\ \dot{S}_q(t) &= c(1 - \beta(t))q^*(t)S(t)I(t) - \lambda S_q(t) \\ \dot{I}_q(t) &= c\beta(t)q^*(t)S(t)I(t) + \theta^*(t)I(t) \end{aligned} \tag{5}$$

Note that for the optimal control of (5), it is enough to consider the first three variables only. Hence, we consider the following controlled SIQ (C-SIQ) model:

$$\begin{aligned} \dot{S}(t) &= -c\{(1 - \beta(t))q^*(t) + \beta(t)\}S(t)I(t) + \lambda S_q(t) \\ \dot{I}(t) &= c\beta(t)(1 - q^*(t))S(t)I(t) - \theta^*(t)I(t) \\ \dot{S}_q(t) &= c(1 - \beta(t))q^*(t)S(t)I(t) - \lambda S_q(t) \end{aligned} \tag{6}$$

From the data fitting based on the SIQ model, we have already obtained the estimation results for the quarantine probability, q , and the isolation rate, θ . In retrospect, however, control-theoretic investigation is desirable for the purpose of improving our response to the outbreak. In the following, we consider the problem of improving the quarantine probability and isolation rate further with additional efforts ($\Delta q^*(t)$ and $\Delta \theta^*(t)$) by minimizing an objective function in the form of $J = \int_0^{t_f} g(I(t), \Delta q^*(t), \Delta \theta^*(t))dt$. Note that in this problem, the quarantine probability and isolation rate at time t are represented by

$$\begin{aligned} q^*(t) &= q + \Delta q^*(t) \\ \theta^*(t) &= \theta + \Delta \theta^*(t), \end{aligned} \tag{7}$$

and the control inputs to be determined via optimal control theory are the additional efforts described by $\Delta q^*(t)$ and $\Delta \theta^*(t)$. Here $g(\cdot)$ should be reasonably chosen to reflect the relative importance of the quarantine and isolation efforts over the infection. More precisely, in order to minimize an objective function comprising the

infection cost (i.e., the infectious compartment population) and the cost of implementing quarantine and isolation strategies, we consider the following optimal control problem:

$$\min_{u(\cdot)} \int_0^{t_f} [I(t) + c_q(\Delta q^*(t))^2 + c_\theta(\Delta \theta^*(t))^2]dt \tag{8}$$

subject to the C-SIQ state equations (6).

In the cost rate of this problem, c_q and c_θ are the trade-off constants defining the relative importance of the implementation costs over the infection cost. Note that the cost rate considers quadratic cost terms for the control inputs, which is a commonly used strategy in related control problems dealing with epidemic-model-based systems (e.g., Lenhart and Workman, 2007). Also, note that the existence of an optimal control and corresponding optimal state trajectory comes from the convexity of the integrand of the objective function with respect to the control and the Lipschitz property of the state system with respect to the state variables (see, e.g., Fleming and Rishel, 1975), and based on the existence, we can now rely on the Pontryagin maximum principle (PMP) (Pontryagin et al., 1987) for an optimal solution. As is well known, the necessary conditions for an optimal solution of (8) can be obtained via the Pontryagin maximum principle. For this, the Hamiltonian H of the optimal control problem (8) is defined as

$$\begin{aligned} H(S(t), I(t), S_q(t), p_1(t), p_2(t), p_3(t), \Delta q^*(t), \Delta \theta^*(t)) \\ = I(t) + c_q(\Delta q^*(t))^2 + c_\theta(\Delta \theta^*(t))^2 \\ + p_1(-c\{(1 - \beta(t))(q + \Delta q^*(t)) + \beta(t)\}S(t)I(t) + \lambda S_q(t)) \\ + p_2(c\beta(t)(1 - (q + \Delta q^*(t)))S(t)I(t) - (\theta + \Delta \theta^*(t))I(t)) \\ + p_3(c(1 - \beta(t))(q + \Delta q^*(t))S(t)I(t) - \lambda S_q(t)). \end{aligned} \tag{9}$$

and its costate equations can be obtained via

$$\begin{aligned} \dot{p}_1 &= -\frac{\partial H}{\partial S}, \quad \dot{p}_2 = -\frac{\partial H}{\partial I}, \quad \dot{p}_3 = -\frac{\partial H}{\partial S_q}, \\ p_1(t_f) &= p_2(t_f) = p_3(t_f) = 0. \end{aligned} \tag{10}$$

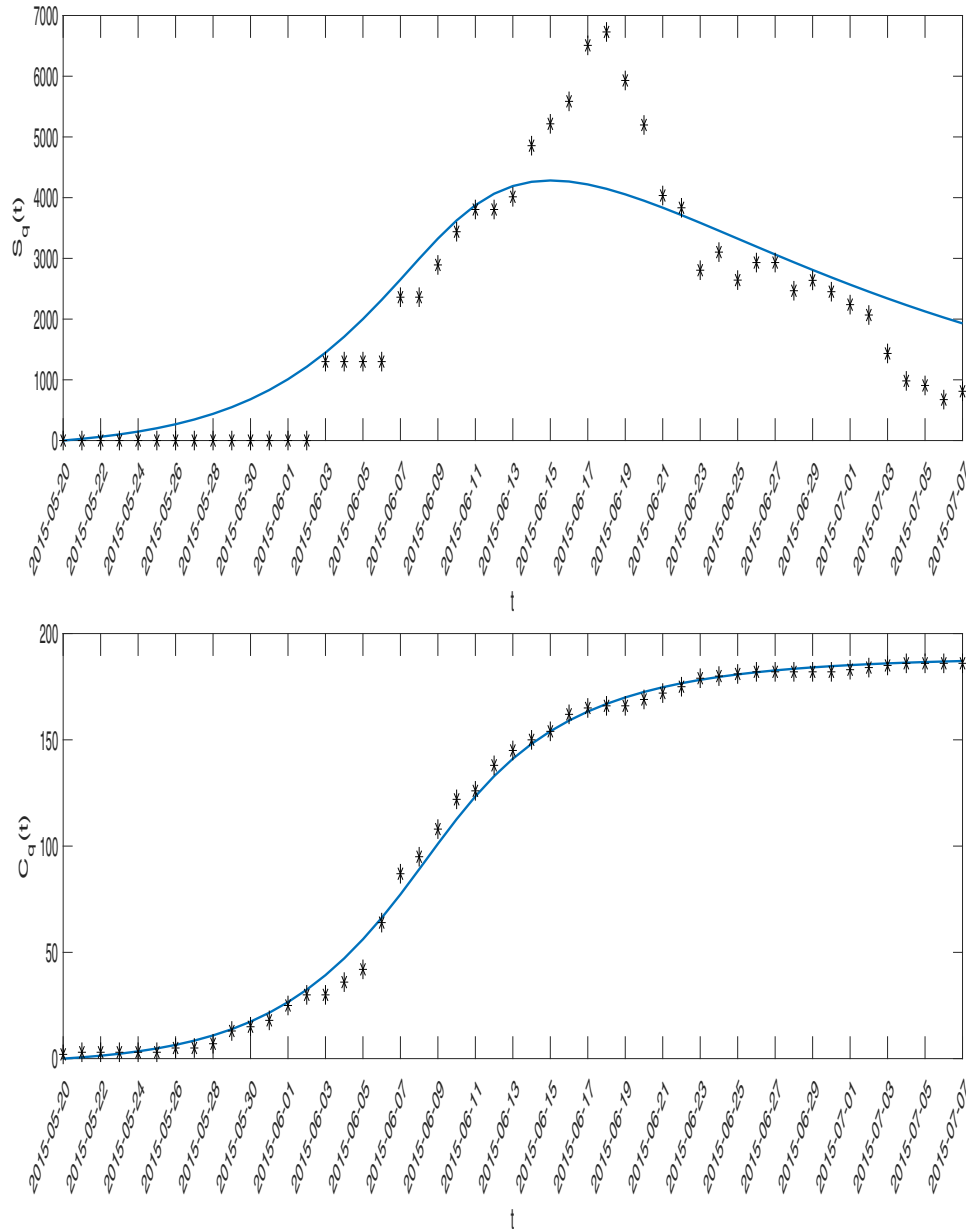


Fig. 4. Simulation results utilizing the SIQ model and the estimated parameters.

From the optimality conditions, $\frac{\partial H}{\partial \Delta q^*} = 0$ and $\frac{\partial H}{\partial \Delta \theta^*} = 0$, we can also obtain the following condition for optimal control:

$$\begin{aligned} \Delta q^*(t) &= \frac{c\{p_1(t)(1-\beta(t))+p_2(t)\beta(t)-p_3(t)(1-\beta(t))\}}{2c_q} S(t)I(t), \\ \Delta \theta^*(t) &= \frac{p_2(t)}{2c_\theta} I(t). \end{aligned} \tag{11}$$

Also, if upper bounds for the nonnegative control inputs are forced, then by confining the control input to be nonnegative and subject to a positive upper bound Δq_{\max} and $\Delta \theta_{\max}$, the optimal control of (8) can be written in the following form:

$$\begin{aligned} \Delta q^*(t) &= \max \left(0, \min \left(\frac{c\{p_1(t)(1-\beta(t))+p_2(t)\beta(t)-p_3(t)(1-\beta(t))\}}{2c_q} S(t)I(t), \right. \right. \\ &\quad \left. \left. \Delta q_{\max} \right) \right), \\ \Delta \theta^*(t) &= \max(0, \min(\frac{p_2(t)}{2c_\theta} I(t), \Delta \theta_{\max})). \end{aligned} \tag{12}$$

From the above steps, we can conclude that any solution to the optimal control problem (8) must satisfy the following:

$$\dot{S}(t) = -c\{(1-\beta(t))(q+\Delta q^*(t))+\beta(t)\}S(t)I(t) + \lambda S_q(t),$$

$$\begin{aligned} \dot{I}(t) &= c\beta(t)(1-(q+\Delta q^*(t)))S(t)I(t) - (\theta+\Delta \theta^*(t))I(t), \\ \dot{S}_q(t) &= c(1-\beta(t))(q+\Delta q^*(t))S(t)I(t) - \lambda S_q(t), \\ \dot{p}_1(t) &= -p_1(t)(-c\{(1-\beta(t))(q+\Delta q^*(t))+\beta(t)\})I(t) \\ &\quad - p_2(t)(c\beta(t)(1-(q+\Delta q^*(t))))I(t) \\ &\quad - p_3(t)(c(1-\beta(t))(q+\Delta q^*(t)))I(t), \\ \dot{p}_2(t) &= -1-p_1(t)(-c\{(1-\beta(t))(q+\Delta q^*(t))+\beta(t)\})S(t) \\ &\quad - p_2(t)(c\beta(t)(1-(q+\Delta q^*(t))))S(t) - (\theta+\Delta \theta^*(t)) \\ &\quad - p_3(t)(c(1-\beta(t))(q+\Delta q^*(t)))S(t), \\ \dot{p}_3(t) &= -p_1(t)\lambda + p_3(t)\lambda, \\ \Delta q^*(t) &= \max \\ &\quad \left(0, \min \left(\frac{c\{p_1(t)(1-\beta(t))+p_2(t)\beta(t)-p_3(t)(1-\beta(t))\}}{2c_q} \right. \right. \\ &\quad \left. \left. S(t)I(t), \Delta q_{\max} \right) \right), \\ \Delta \theta^*(t) &= \max \left(0, \min \left(\frac{p_2(t)}{2c_\theta} I(t), \Delta \theta_{\max} \right) \right), \end{aligned}$$

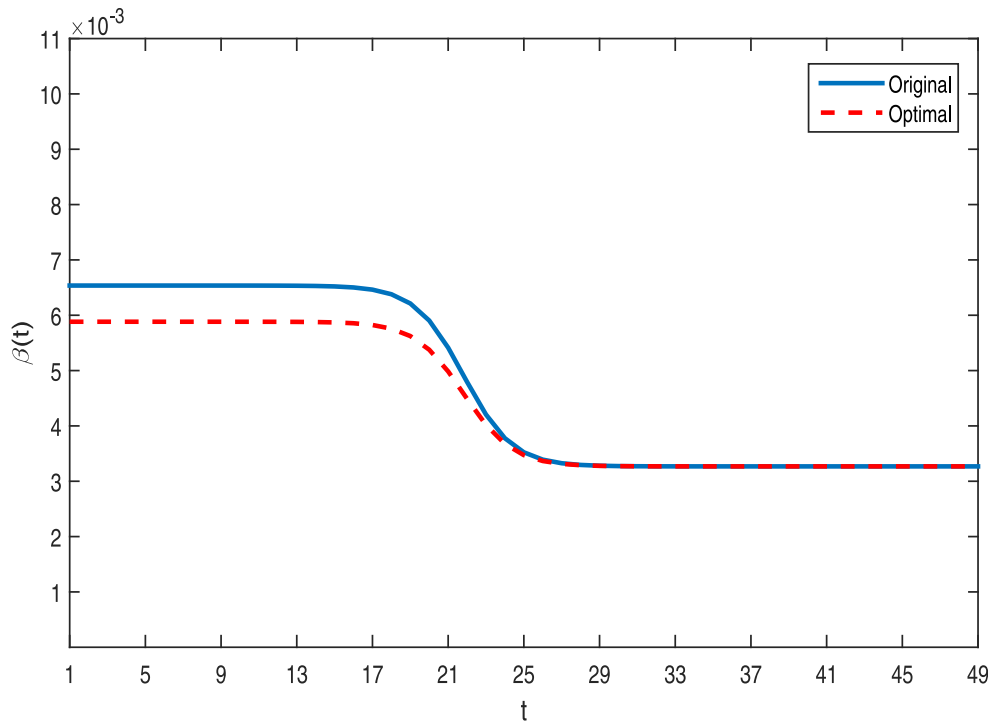


Fig. 5. The MERS transmission probabilities.

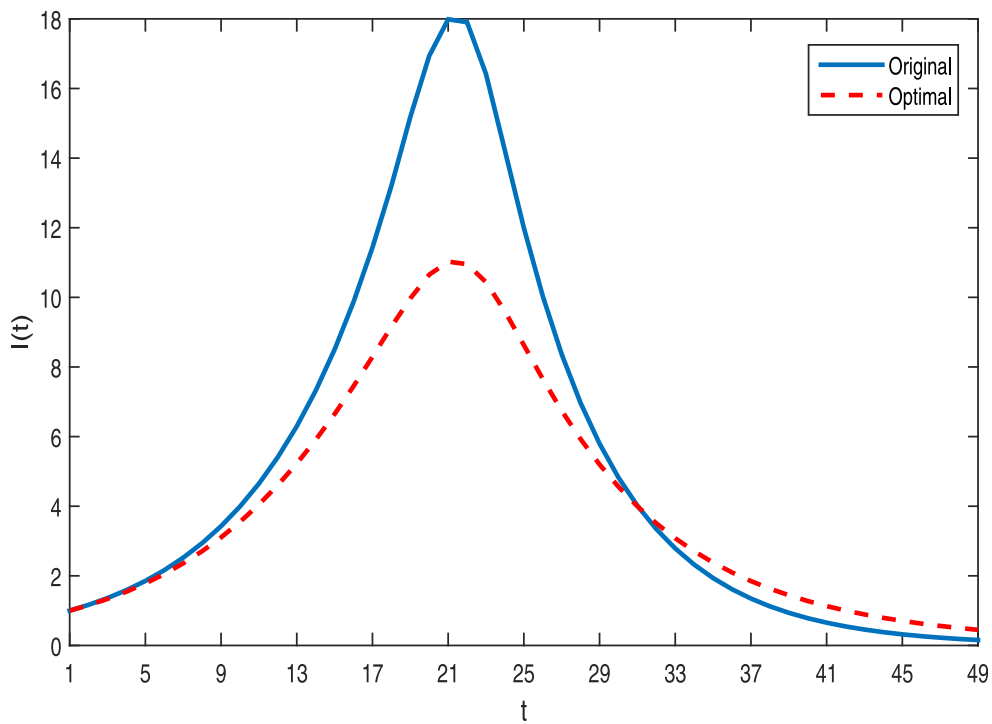


Fig. 6. Simulation results utilizing the SIQ model (Solid line: $I(t)$ when β_0 is the estimated value; dashed line: $I(t)$ when β_0 is reduced to 90% of its original value).

$$\begin{aligned}
 S(0) &= S_0, \\
 I(0) &= I_0, \\
 S_q(0) &= S_{q0}, \\
 p_1(t_f) &= 0, \\
 p_2(t_f) &= 0, \\
 p_3(t_f) &= 0.
 \end{aligned}$$

(13)

By solving this boundary value ordinary differential equation (ODE) problem numerically, we can obtain optimal control inputs for problem (8).

In order to illustrate the optimal control policy, we simulated the optimally controlled C-SIQ system. The parameters considered for the simulations are set to be the same as the estimation results except the control inputs, $\Delta q^*(t)$ and $\Delta \theta^*(t)$. For the trade-

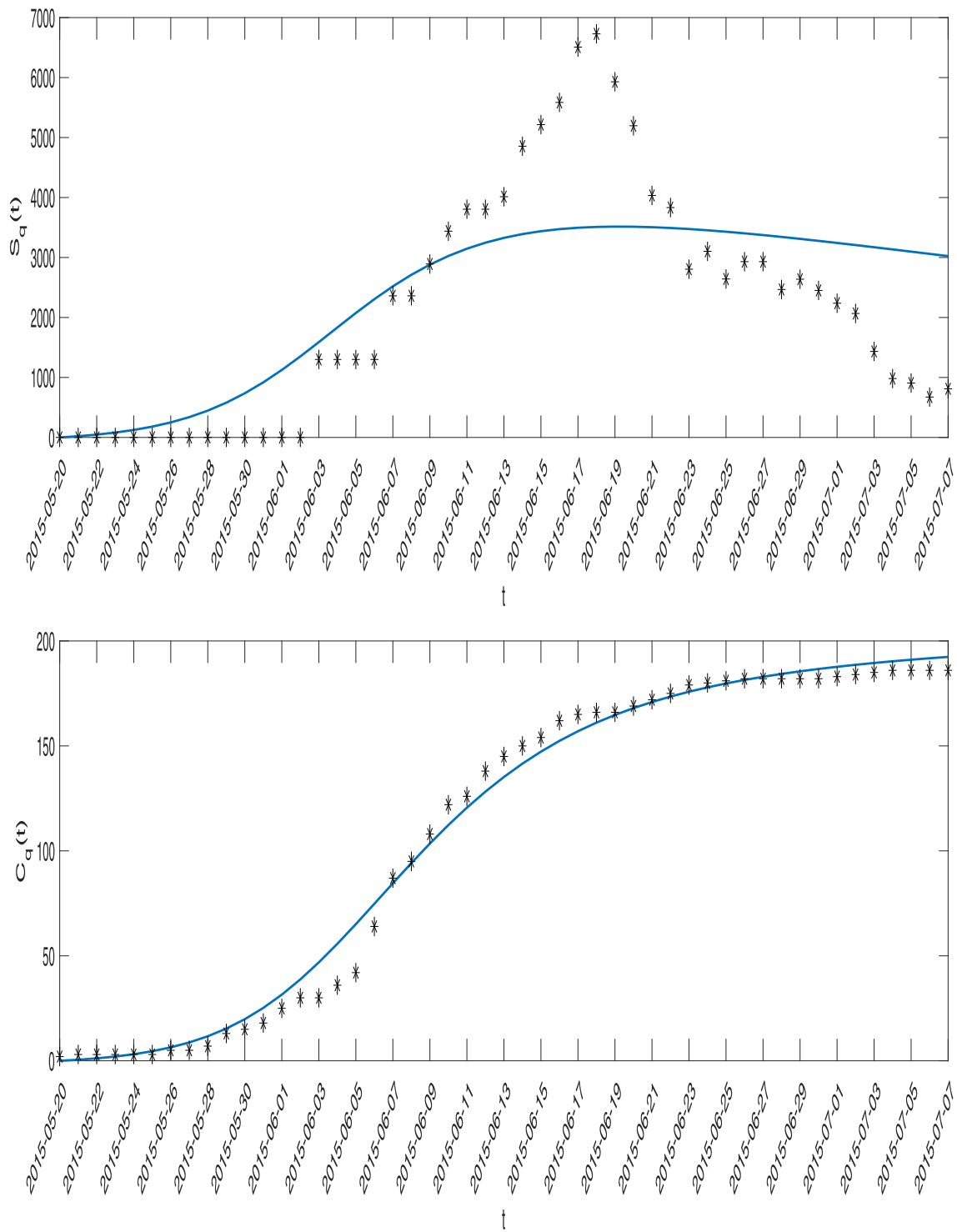


Fig. 7. Simulation results utilizing the simplified SIQ model with constant β , and the estimated parameters.

off constants of (8), we used $c_\theta = 10,000$, $c_q = 1$. The initial conditions for the simulations were also taken from the estimation results, i.e., $S_0 = 16,000$, $I_0 = 1$, and $S_{q0} = 0$. The simulations considered two scenarios. The first scenario does not have bounds on the control inputs, while the second scenario has the bounds of $\Delta q_{\max} = 0.007$ and $\Delta \theta_{\max} = 0.05$. With the goal of keeping the infection level low with reasonable control efforts, we solved the boundary value ODE problem (13) using *bvp4c*, the MATLAB function to solve boundary value problems for ordinary differen-

tial equations). Figs. 8–10 show the simulation results for the first scenario.

Figs. 8 and 9 show that under the optimal control of the first scenario, the best method of fighting the infection is to initially enter large amounts of $\Delta q(t)$ and $\Delta \theta(t)$, and later after 30 days to slowly reduce them to zero. The resultant state trajectory of $I(t)$ (the dashed line of Fig. 10) shows that, with the optimal control strategy, the infectious compartment population can be reduced significantly compared to the original case (the solid line of Fig. 10). To consider the robustness of the quarantine and isola-

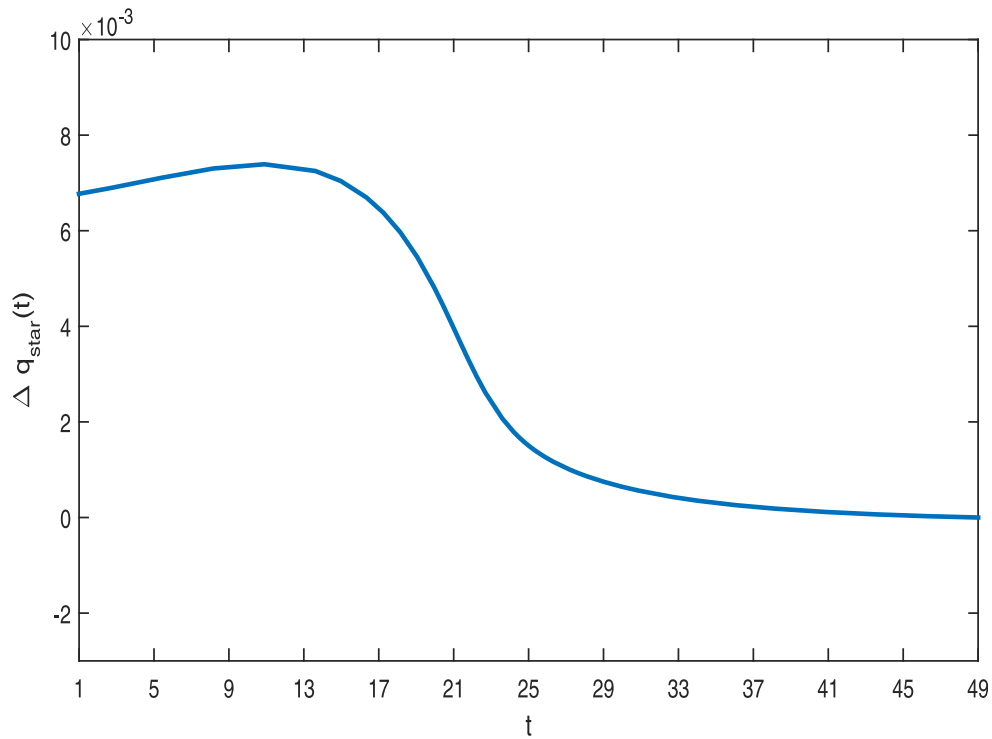


Fig. 8. Optimal control law for $\Delta q(t)$ (the first scenario).

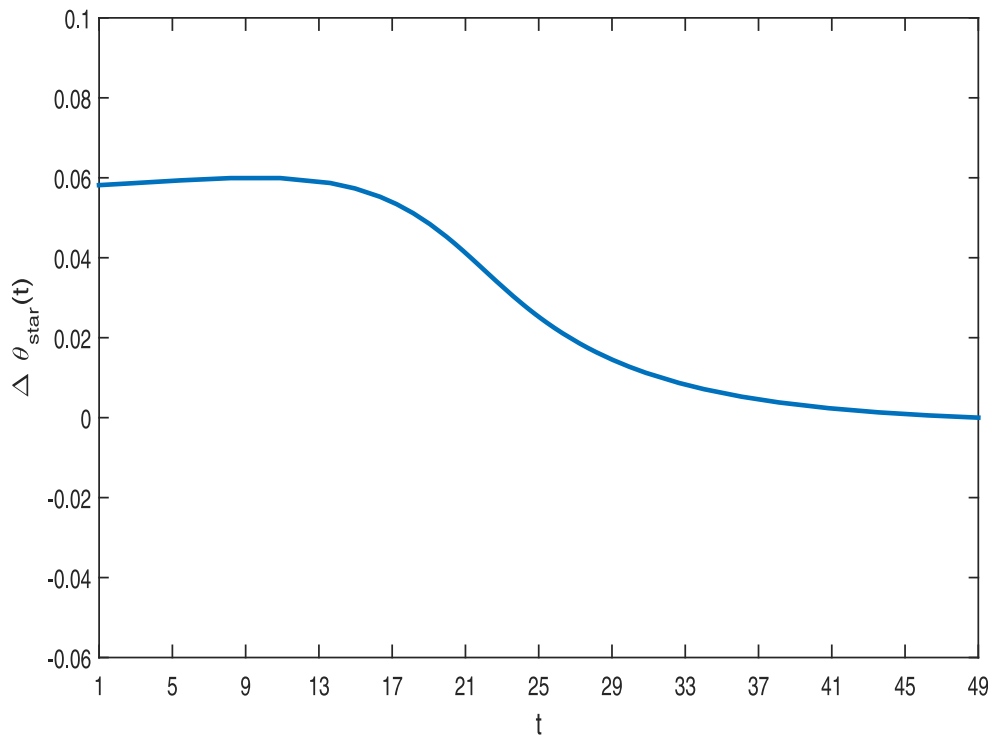


Fig. 9. Optimal control law for $\Delta \theta(t)$ (the first scenario).

tion control, we also conducted sensitivity analysis for the following cases: (1) when c is 10% lower and 10% higher; (2) when λ is 50% lower and 50% higher. For each case we simulated the resultant controlled system, and the results on the number of infectious individuals are shown in Figs. 11 and 12, respectively, for cases (1) and (2). Comparing Figs. 11 and 12 shows that c is more important for the quarantine and isolation control.

Simulation results for the second scenario, which deals with the bounded input case, are shown in Figs. 13–15. Figs. 13 and 14 show that under the optimal control of the second scenario, the best method of fighting the infection is to apply the maximum amounts of the control inputs from the start, and then to slowly reduce them after 30 days to zero. The state trajectory of $I(t)$ resulting from the optimal control is shown in Fig. 15. Note that the

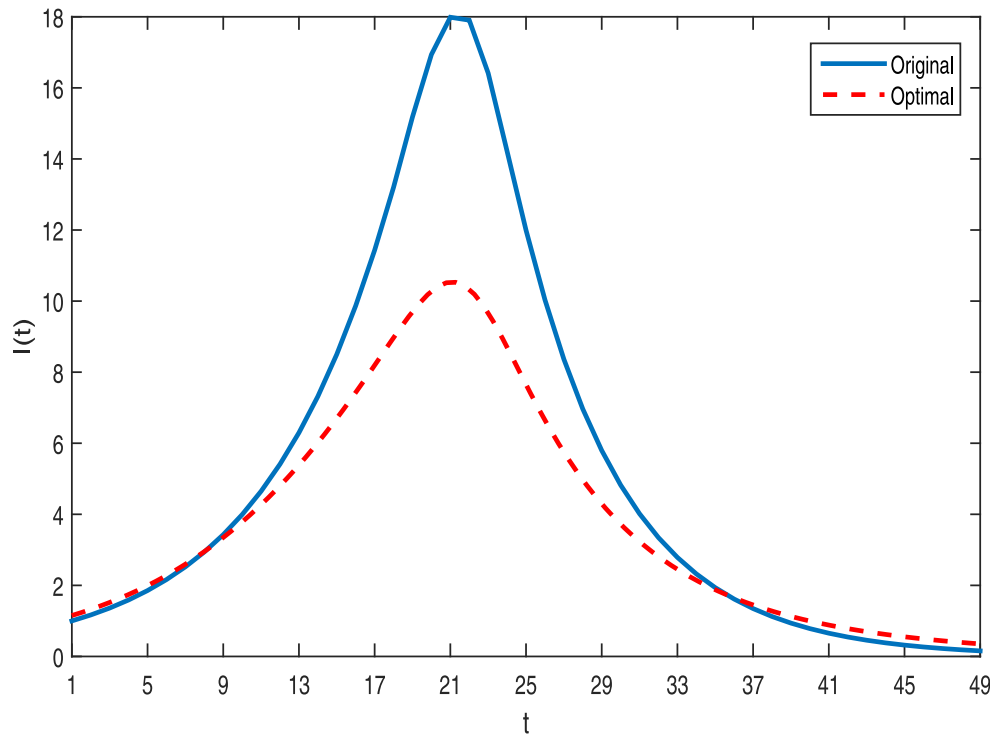


Fig. 10. Number of infectious individuals in the first scenario (Solid line: $I(t)$ of the uncontrolled case; dashed line: $I(t)$ under optimal control).

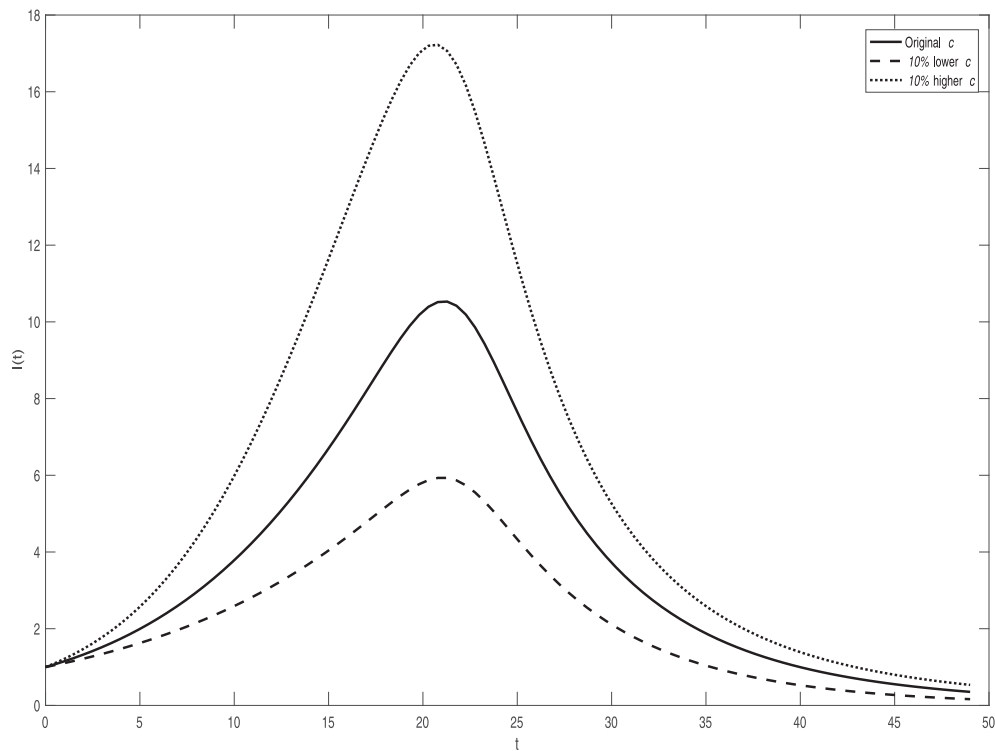


Fig. 11. Number of infectious individuals resulting from the sensitivity analysis for c .

infectious compartment population can be reduced significantly even with the bounds on control inputs. From the simulation results (Figs. 8–15), we can conclude that the MERS disease spread can be properly handled by the optimal control approach, and we can obtain a practical guideline, whereby quarantine and isolation efforts in the early stage are critically important in effectively controlling the MERS outbreak.

3. Discussion and conclusions

In recent years, global pandemic viral infections, including the 2003 severe acute respiratory syndrome, the 2009 H1N1 influenza, and the 2014 Ebola outbreak, have been devastating but provided valuable experience in outbreak responses. For public health control, increased vigilance by health professionals and voluntary

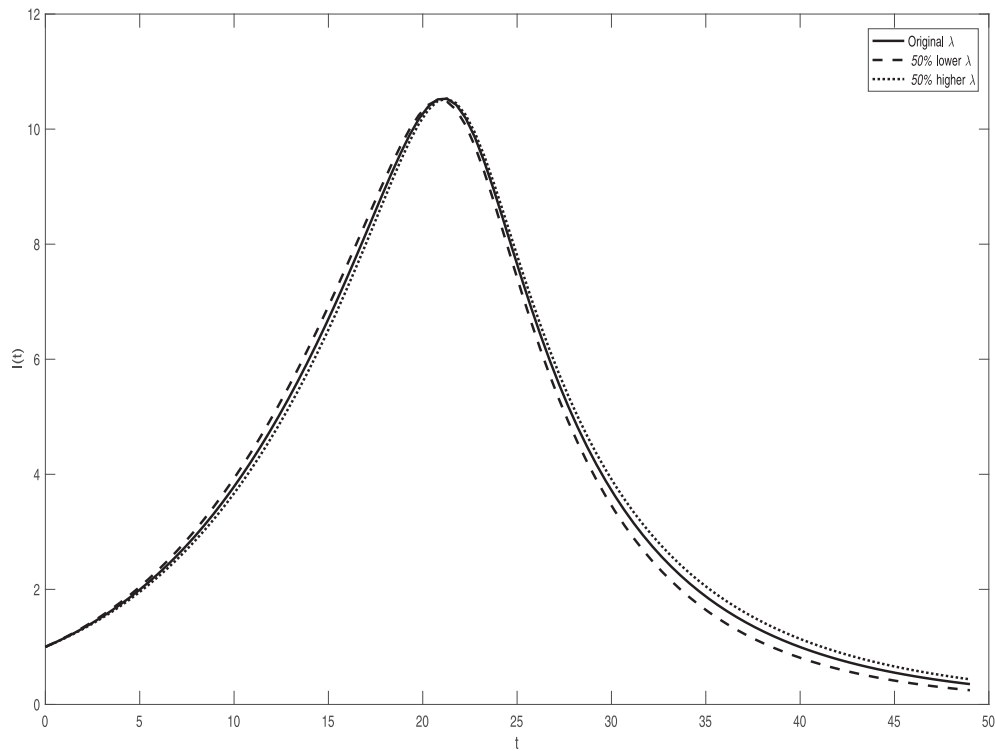


Fig. 12. Number of infectious individuals resulting from the sensitivity analysis for λ .

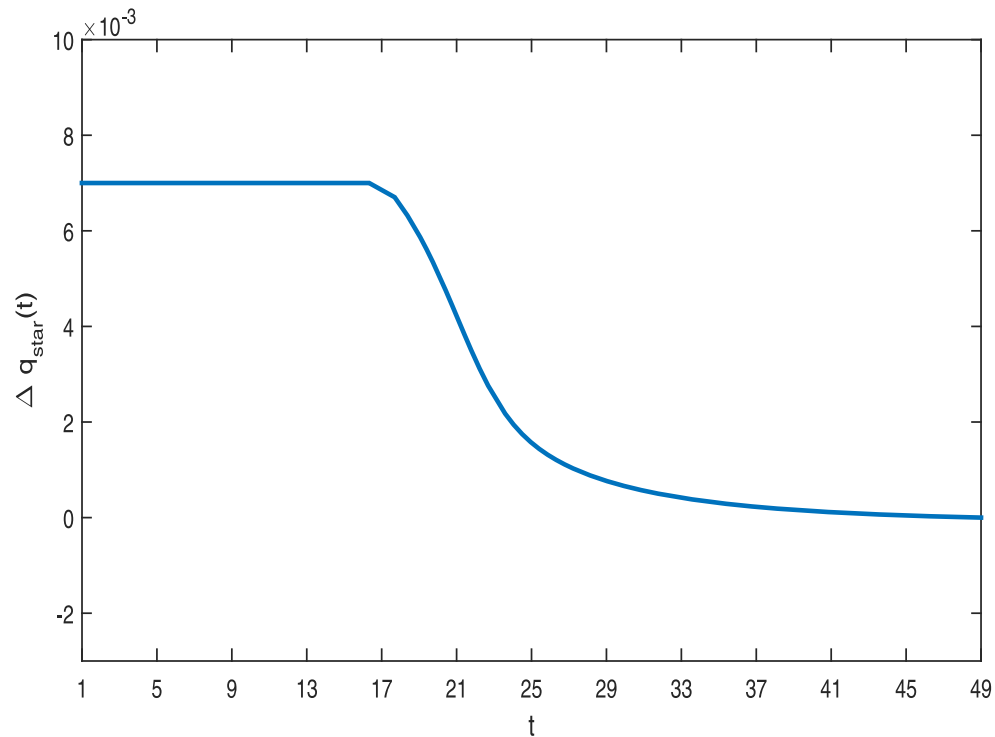


Fig. 13. Optimal control law for $\Delta q(t)$ (the second scenario).

compliance by the public are essential in implementing rapid effective response interventions. In this study, we carried out an epidemiological assessment of the MERS-CoV outbreak in Korea in order to provide a mathematical framework for understanding the complex dynamics of the pathogen spread and establishing efficient guidelines for implementing quarantine and isolation strategies. The following have been observed by the assessment:

- By fitting the SIQ model, which employs a squashing-type function of Fig. 2 for $\beta(t)$, to the real data on the confirmed cases and the quarantined cases, we obtained reasonable performance, as shown in Fig. 4. Also, it turned out that the resultant estimated parameters belonged to plausible ranges. By comparison, the conventional SIQ model utilizing a constant

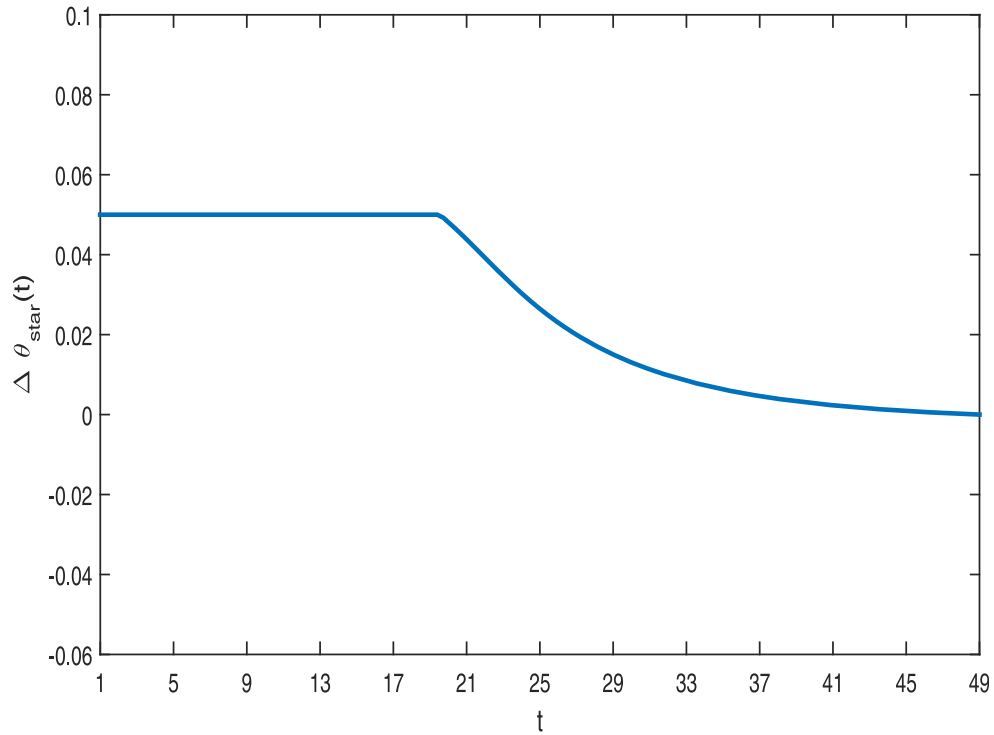


Fig. 14. Optimal control law for $\Delta\theta(t)$ (the second scenario).

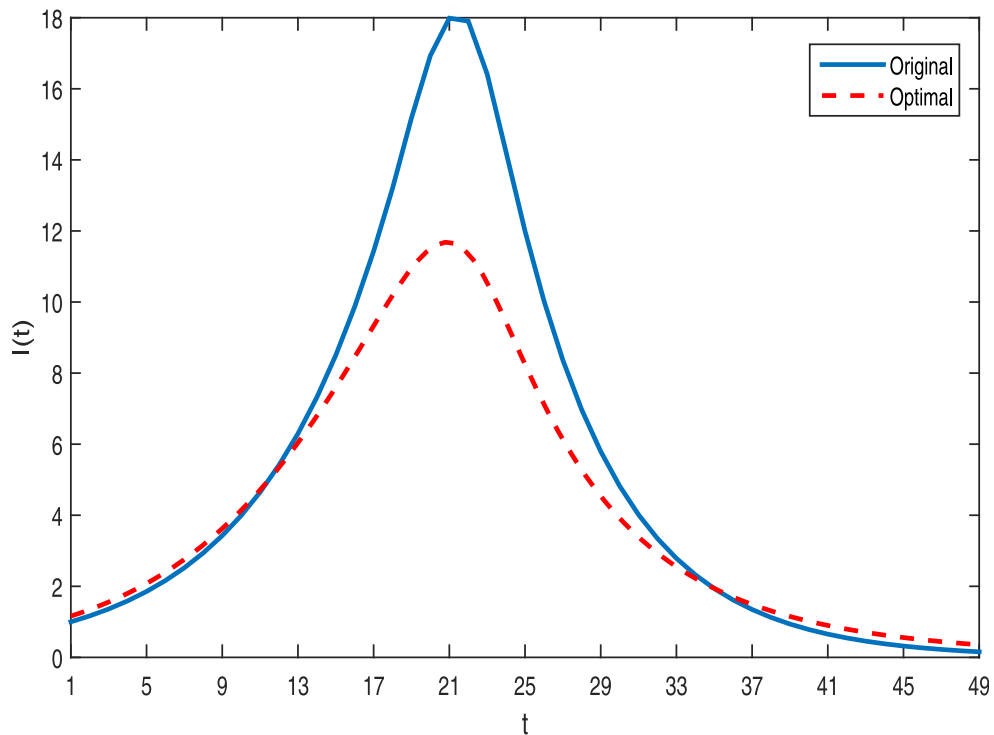


Fig. 15. Number of infectious individuals in the second scenario (Solid line: $I(t)$ of the uncontrolled case; dashed line: $I(t)$ under optimal control).

transmission probability could not explain the observed data well.

- Our nonlinear epidemiological models showed that the MERS transmission probability decreased in the squashing-type fashion and then approached a saturation point in a time-dependent manner. As information on the MERS outbreak be-

came widely known in the nation, efforts against this epidemic, including individuals hygienic behavior, and interventions by health care facilities and by authorities were accordingly strengthened. In our SIQ-based analysis, the inflection point for transmission probability was found to be $t_\beta = 21.8$, corresponding to a couple of days after 7 June 2015. Interest-

ingly, 7 June 2015 was the day when the Korean government revealed the names of 24 MERS-affected hospitals to the public. After releasing the names of affected medical facilities, the rate of increase in new confirmed cases abated. As a practical guideline to avoid another similar unexpected outbreak, we draw the conclusion that combined efforts in the early stage are critically important, and sharing information including the names of affected hospitals or countries, clinical situations, and prevention methods might be important for global public health control.

- We applied optimal control theory to the controlled SIQ model with the goal of minimizing the infectious compartment population and the cost of implementing the quarantine and isolation strategies. Simulation results show that the number of the MERS cases can be controlled reasonably well via the optimal control approach.

In conclusion, this paper proposes a nonlinear epidemiological ODE for the MERS outbreak in Korea, the SIQ model, in which the state variables are defined as the populations of four compartments ($S(t)$, $I(t)$, $S_q(t)$, and $C_q(t)$), and the MERS transmission probability, $\beta(t)$, is modelled by the time-dependent sigmoidal function. We performed the task of parameter estimation for the SIQ model, and the data fitting results explained the observed data for the confirmed cases and the quarantined cases in the MERS outbreak very well. We also applied optimal control theory to the controlled SIQ model with the goal of minimizing the infectious compartment population and the cost of implementing the quarantine and isolation strategies. Our simulation results show that MERS propagation was controlled reasonably well via the optimal control approach. In future work, we will conduct further simulation studies, with the aim of revealing the strengths and weaknesses of the proposed method, and investigate stability and control issues for its various extensions, including a stochastic differential equation (SDE) approach.

4. Data treatment

4.1. Data

We retrieved publicly available data (Ministry of Health and Welfare, MoH) from the Centers for Disease Control and Prevention and the Ministry of Health and Welfare in the Republic of Korea. The data included information on the cumulative number of reported cases. The first MERS case in Korea was confirmed on 20 May 2015, and the numbers of newly confirmed cases and suspected patients who had been quarantined to prevent possible spread of the MERS have reached 186 cases and 16,693 cases, respectively, as of 28 July 2015. The data also included a brief description of each confirmed case with exposure date and onset of symptoms, and they were sufficient to estimate our SIQ model for the MERS outbreak epidemiology. In this model, we assumed MERS is unlikely to spread to another region.

4.2. Parameter estimation

We implemented the parameter estimation procedure as a Matlab program. We used *fminsearch*, a MATLAB function for unconstrained nonlinear optimization, along with some changes of variables in order to carry out the data fitting procedure for the SIQ model (5) with the time-dependent variable $\beta(t)$ specified in (2). The performance index (PI) used in the optimization for parameter estimation was defined as follows:

$$PI = w_1 \times (\text{squared error of } C_q) + w_2 \times (\text{squared error of } S_q). \quad (14)$$

The objective function of (14), PI , was based on the numbers of the confirmed MERS cases and the quarantined cases between 20

May and 07 July. The weight values ($w_1 = 10^4$ and $w_2 = 1$) were obtained empirically via a tuning process based on the training data. Simulation results show that the above set of weight values yielded reasonably good fitting results. Finally, note that a more sophisticated Markov Chain Monte Carlo (MCMC) algorithm (e.g., Rasmussen et al., 2011) could be used for parameter estimation of the SIQ model. However, the use of *fminsearch*, which was simpler and more transparent, was sufficient for the purposes of this paper.

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