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Optimal vaccine distribution in a spatiotemporal epidemic model with an application to rabies and raccoons

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ABSTRACT

We formulate an S–I–R (Susceptible, Infected, Immune) spatiotemporal epidemic model as a system of coupled parabolic partial differential equations with no-flux boundary conditions. Immunity is gained through vaccination with the vaccine distribution considered a control variable. The objective is to characterize an optimal control, a vaccine program which minimizes the number of infected individuals and the costs associated with vaccination over a finite space and time domain. We prove existence of solutions to the state system and existence of an optimal control, as well as derive corresponding sensitivity and adjoint equations. Techniques of optimal control theory are then employed to obtain the optimal control characterization in terms of state and adjoint functions. To illustrate solutions, parameter values are chosen to model the spread of rabies in raccoons. Optimal distributions of oral rabies vaccine baits for homogeneous and heterogeneous spatial domains are compared. Numerical results reveal that natural land features affecting raccoon movement and the relocation of raccoons by humans can considerably alter the design of a cost-effective vaccination regime. We show that the use of optimal control theory in mathematical models can yield immediate insight as to when, where, and what degree control measures should be implemented.

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1. Introduction

Diffusive partial differential equation (PDE) models are frequently used to study the continuous spatiotemporal spread of disease among a population of susceptible (S), infected (I), and recovered or immune (R) individuals [1,2]. An underlying assumption throughout PDE S–I–R models is that infected individuals transmit the disease only to susceptibles at their current location. In 1981, Webb [3] analyzed a one-dimensional S–I–R model which included constant diffusive movement of all individuals as well as no-flux boundary conditions. For classical solutions, Webb showed that as $t \to \infty$, the function S converges to a constant function while the function I converges to 0. Thus, the infection dies out as $t \to \infty$, but not for lack of susceptible individuals, some of whom never contract the disease. In 1987, Fitzgibbon and Morgan [4] extended this model to bounded domains of arbitrary dimension and proved similar asymptotic results.

Our goal is to use optimal control techniques to characterize optimal spatial and temporal vaccine distributions which slow the spread of an infection. Previous analysis of non-spatial S–I–R models has shown that vaccination applied above a specific threshold value leads to successful elimination of the disease [5,6]. In this paper, we investigate vaccination effects in a spatial-temporal epidemic model with reaction–diffusion PDEs that include transport effects and no-flux boundary conditions, using a weak solution formulation [7]. In 2002, Bendahmane et al. [8] proved the existence of at least one

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weak solution for a non-linear reaction–diffusion PDE system with L^1 data and no-flux boundary conditions. We formulate an S–I–R model similar to that of Bendahmane et al. [8,9] with L^∞ data and we include vaccination as a control variable. Alternative control variables used in non-spatial S–I–R models include isolation, antiviral treatment, and increased sanitation [10–12], and these features in space and time could be investigated using techniques illustrated in this paper. For our problem formulation, an objective functional is constructed under the assumption that an optimal control minimizes the infected population and costs associated with control while balancing the maximization of the susceptible population over some finite space and time domain.

In Section 2, we present the model in a general framework and the associated optimal control problem. Principles of optimal control theory are used in Section 3 to characterize the optimal strategy of vaccination. The existence and uniqueness of the optimality system are stated informally and the proofs are outlined in Appendix A. As an illustrative application, Section 4 provides numerical approximations of optimal spatiotemporal vaccination strategies with parameter values chosen specifically for rabies and raccoons. Lastly, concluding remarks are provided in Section 5.

2. Model formulation and optimal control problem

Let $S = S(x,t)$, $I = I(x,t)$, and $R = R(x,t)$ represent the density (or size) of the susceptible, infected, and immune classes of a population at a given location x and time t. Let Ω be an open and bounded subset of $\mathbf{R}^n$. Set $Q = \Omega \times (0,T)$ for some fixed time $T > 0$. Given a control $v(x,t)$ representing the density (or quantity, respectively) of vaccine at location x and time t, the corresponding state variables $(S,I,R) = (S,I,R)(v)$ satisfy the system

$$\begin{aligned} L_1 S &= b(x,t)(S+R) - \mu_1(x,t)S - \beta(x,t)SI - av(x,t)S, \\ L_2 I &= \beta(x,t)SI - \mu_2(x,t)I, \\ L_3 R &= -\mu_1(x,t)R + av(x,t)S \end{aligned} \tag{1}$$

for $(x,t) \in Q$ and the operators L_k, $k = 1,2,3$, are defined as

$$L_k u \equiv \frac{\partial u}{\partial t} - \sum_{i,j=1}^{n} \left(a_{ij}^k(x,t)u_{x_i}\right)_{x_j} + \sum_{i=1}^{n} \left(b_i^k(x,t)u\right)_{x_i}.$$

Initial conditions and no-flux boundary conditions are given by

$$S(x,0) = S_0(x), \qquad I(x,0) = I_0(x), \qquad R(x,0) = R_0(x) \quad \text{for } x \in \Omega, \tag{2}$$

$$\frac{\partial S}{\partial \nu} = 0, \qquad \frac{\partial I}{\partial \nu} = 0, \qquad \frac{\partial R}{\partial \nu} = 0 \quad \text{on } \partial\Omega \times (0,T). \tag{3}$$

Our formulation is such that only individuals in the S and R classes give birth. The parameter b is a birth rate, μ_1 is a natural death rate, and μ_2 is an increased death rate due to disease. The horizontal incidence term βIS assumes the infection rate of susceptibles is proportional to the number of infected and susceptible individuals at the current time with β being the mass action coefficient. The rate at which susceptibles at location x at time t are effectively vaccinated depends on the quantity of vaccine available, $v(x,t)$, and the vaccine uptake parameter, $a > 0$. The boundary conditions imply that the population does not diffuse across the boundary. The conormal outward vector, ν, has components $\nu_i = \sum_{j=1}^{n} a_{ij}\eta_j$ with the outward normal vector on $\partial\Omega$ denoted by η.

The following are assumed to hold:

1. $S_0(x), I_0(x), R_0(x) \in L^\infty(\Omega)$ and $S_0(x) > 0$, $I_0(x) > 0$, $R_0(x) \geqslant 0$,
2. $b, \mu_1, \mu_2, \beta \in L^\infty(Q)$ and $b \geqslant 0$, $\mu_1 \geqslant 0$, $\mu_2 \geqslant 0$, $\beta \geqslant 0$,
3. $a_{ij}^k, b_i^k \in C^1(\bar{Q})$ and $a_{ij}^k = a_{ji}^k$ for $k = 1,2,3$,
4. $\sum_{i,j=1}^{n} a_{ij}^k \xi_i \xi_j \geqslant \theta \sum_{i=1}^{n} \xi_i^2$, $k = 1,2,3$, where $\theta > 0$.

Define the space $Z = L^2(0,T;H^1(\Omega))$ and the bilinear form

$$B^k[t,u,\phi] = \int_\Omega \sum_{i,j=1}^{n} a_{ij}^k(x,t)u_{x_i}\phi_{x_j}\,dx\,dt + \int_\Omega \sum_{i=1}^{n} \left(b_i^k(x,t)u\right)_{x_i}\phi\,dx\,dt$$

for $u, \phi \in Z$ and $k = 1,2,3$.

Definition. For the system (1)–(3), a weak solution $(S,I,R) \in Z^3$ with $S_t, I_t, R_t \in L^2(0,T;H^1(\Omega)^*)$ must be non-negative and satisfy (2), (3) and the variational formulation of (1) given by

$$\int_0^T \langle S_t, \phi_1\rangle\, dt + \int_0^T B^1[t, S, \phi_1]\, dt = \int_Q b(S+R)\phi_1\, dx\, dt - \int_Q \beta SI\phi_1\, dx\, dt - \int_Q (\mu_1 - av)S\phi_1\, dx\, dt,$$

$$\int_0^T \langle I_t, \phi_2\rangle\, dt + \int_0^T B^2[t, I, \phi_2]\, dt = \int_Q \beta SI\phi_2\, dx\, dt - \int_Q \mu_2 I\phi_2\, dx\, dt,$$

$$\int_0^T \langle R_t, \phi_3\rangle\, dt + \int_0^T B^3[t, R, \phi_3]\, dt = \int_Q av S\phi_3\, dx\, dt - \int_Q \mu_1 R\phi_3\, dx\, dt \tag{4}$$

for all $\phi_1, \phi_2, \phi_3 \in Z$ where $\langle , \rangle$ inner product is the duality between $H^1(\Omega)^*$ and $H^1(\Omega)$.

Admissible controls are contained in the set

$$V = \left\{ v \in L^\infty(Q) \mid v : Q \to [0, v_{\max}] \right\}$$

for some positive constant $v_{\max}$. The best strategy for controlling an epidemic outbreak during a time period of length T can be one which minimizes the number of individuals who become infected and the cost of vaccination during the time period. It can also be important to sustain a sizable susceptible population. Therefore, we seek to minimize the objective functional

$$J(v) = \int_Q \left(AI - BS + \Phi(v) \right) dx\, dt$$

where A, B are constant weights and $\Phi(\cdot)$ is a lower semi-continuous convex function representing the cost of vaccination. Costs can be expressed in various forms within the objective functional and the function choice may impact the optimal control [16].

Theorem A.1 states that for T sufficiently small, if given a control $v \in V$, then there exists a unique weak solution $(S, I, R)(v)$. In the existence proof, we use the Banach fixed point theorem on space X^3 where

$$X = C\left([0, T]; L^2(\Omega)\right) \cap \left\{ u \in L^\infty(Q) \mid 0 \leqslant u \leqslant M \text{ a.e. } (x, t) \in Q \right\} \tag{5}$$

for fixed M. This space choice provides biologically justified $L^\infty(Q)$ bounds on S, I, and R.

3. Optimal control characterization

For detailed background and methodology of optimal control theory for systems of PDEs, see books by Lions [13], Li and Yong [14], and Lenhart and Workman [15]. In Theorem A.2, the existence of an optimal control is obtained through a minimizing sequence argument and continuous dependence of the states on the control. To obtain the necessary conditions for the optimal control, the objective functional J is differentiated with respect to the control v. Specifically, for v, $h \in V$, we take the Gateaux derivative of J with respect to v in the direction h,

$$\lim_{\epsilon \to 0} \frac{J(v + \epsilon h) - J(v)}{\epsilon}.$$

Because the objective functional contains the state variables, we also differentiate the map from the control to the states. In Theorem A.3, we show that the control-to-states mapping, $v \in V \to (S, I, R) \in Z^3$, is differentiable in the sense that there exist $\Psi_1, \Psi_2, \Psi_3 \in Z$ such that

$$\frac{S(v + \epsilon h) - S(v)}{\epsilon} \rightharpoonup \Psi_1, \qquad \frac{I(v + \epsilon h) - I(v)}{\epsilon} \rightharpoonup \Psi_2, \qquad \frac{R(v + \epsilon h) - R(v)}{\epsilon} \rightharpoonup \Psi_3$$

in Z as $\epsilon \to 0$ for any $v \in V$ and $h \in L^\infty(Q)$ such that $v + \epsilon h \in V$ for ϵ small. These derivatives, called sensitivities, solve a linearized version of the state equations given by

$$\begin{aligned}
&L_1\Psi_1 - b(\Psi_1 + \Psi_3) + \mu_1\Psi_1 + \beta\Psi_1 I + \beta\Psi_2 S + av\Psi_1 = -ahS,\\
&L_2\Psi_2 - \beta\Psi_1 I - \beta\Psi_2 S + \mu_2\Psi_2 = 0,\\
&L_3\Psi_3 + \mu_1\Psi_3 - av\Psi_1 = ahS
\end{aligned} \tag{6}$$

for $(x, t) \in Q$. For conciseness, the above system can be written as $\mathcal{L}(\Psi_1, \Psi_2, \Psi_3)^\tau = (-ahS, 0, ahS)^\tau$ where $\mathcal{L}$ is the appropriate operator and τ denotes the transpose. The initial conditions satisfied by the sensitivities are

$$\Psi_1(x, 0) = \Psi_2(x, 0) = \Psi_3(x, 0) = 0 \quad \text{for } x \in \Omega \tag{7}$$

and corresponding boundary conditions are

$$\frac{\partial \Psi_1}{\partial \nu} = \frac{\partial \Psi_2}{\partial \nu} = \frac{\partial \Psi_3}{\partial \nu} = 0 \quad \text{on } \partial\Omega \times (0,T). \tag{8}$$

We introduce $\mathcal{L}^*$, the adjoint of the operator of the linearized equations. Theorem A.4 proves the existence of the adjoint variables (p_1, p_2, p_3) satisfying $\mathcal{L}^*(p_1,p_2,p_3)^\tau = (-B, A, 0)^\tau$. Here, the right-hand side of the adjoint system is the derivative of the integrand in the objective functional with respect to each state variable. Suppose v^* is an optimal control and $(S^*, I^*, R^*) = (S, I, R)(v^*)$ are the corresponding state variables. The adjoint system becomes

$$\begin{aligned}
&L_1^* p_1 - b p_1 + \mu_1 p_1 + \beta I^* p_1 + a v^* p_1 - \beta I^* p_2 - a v^* p_3 = -B,\\
&L_2^* p_2 + \beta S^* p_1 - \beta S^* p_2 + \mu_2 p_2 = A,\\
&L_3^* p_3 - b p_1 + \mu_1 p_3 = 0
\end{aligned} \tag{9}$$

where L_k^*, $k = 1, 2, 3$, are defined as

$$L_k^* p_k = -\frac{\partial p_k}{\partial t} - \sum_{i,j=1}^{n} \left(a_{ij}^k(x,t)(p_k)_{x_i}\right)_{x_j} - \sum_{i=1}^{n} b_i^k(x,t)(p_k)_{x_i}.$$

Conditions at the final time T for the adjoint variables are given by

$$p_1(x,T) = 0, \qquad p_2(x,T) = 0, \qquad p_3(x,T) = 0 \quad \text{for } x \in \Omega \tag{10}$$

and the appropriate boundary conditions are

$$\begin{aligned}
&\frac{\partial p_1}{\partial \nu} + \left(\sum_{i=1}^{n} b_i^1 \cdot \eta_i\right) p_1 = 0,\\
&\frac{\partial p_2}{\partial \nu} + \left(\sum_{i=1}^{n} b_i^2 \cdot \eta_i\right) p_2 = 0,\\
&\frac{\partial p_3}{\partial \nu} + \left(\sum_{i=1}^{n} b_i^3 \cdot \eta_i\right) p_3 = 0 \quad \text{on } \partial\Omega \times (0,T).
\end{aligned} \tag{11}$$

Through standard optimality techniques, analyzing the objective functional and utilizing relationships between the state and adjoint equations, a characterization of the control is formulated. The following theorem characterizes the optimal control for the case in which the costs associated with implementing the control are given by $\Phi(v) = cv^2$ for some $c > 0$. Optimal control characterizations for other cost functionals can be derived with similar techniques.

Theorem 1. *Suppose $J(v) = \int_Q (AI - BS + cv^2)\,dx\,dt$ for some $c > 0$. Given an optimal control $v^* \in V$ and corresponding states $(S^*, I^*, R^*) = (S, I, R)(v^*)$, the optimal control is characterized by*

$$v^* = \min\left(\left(\frac{(p_1 - p_3)aS^*}{2c}\right)^+, v_{\max}\right). \tag{12}$$

Proof. Suppose v^* is an optimal control and $(S^*, I^*, R^*) = (S, I, R)(v^*)$ are the corresponding state variables. Consider $v^\epsilon \equiv v^* + \epsilon h \in V$ and corresponding state solution $(S^\epsilon, I^\epsilon, R^\epsilon) = (S, I, R)(v^\epsilon)$. Since the minimum of the objective functional is attained at v^*, we have

$$\begin{aligned}
0 &\leqslant \lim_{\epsilon \to 0^+} \frac{J(v^\epsilon) - J(v^*)}{\epsilon}\\
&= \lim_{\epsilon \to 0^+} \int_Q \left(A\left(\frac{I^\epsilon - I^*}{\epsilon}\right) - B\left(\frac{S^\epsilon - S^*}{\epsilon}\right) + \frac{c(v^\epsilon)^2 - c(v^*)^2}{\epsilon}\right) dx\,dt\\
&= \lim_{\epsilon \to 0^+} \int_Q \left(A\left(\frac{I^\epsilon - I^*}{\epsilon}\right) - B\left(\frac{S^\epsilon - S^*}{\epsilon}\right) + c\left(\frac{v^\epsilon - v^*}{\epsilon}\right)(v^\epsilon + v^*)\right) dx\,dt\\
&= \int_Q \left(A\Psi_2 - B\Psi_1 + 2ch v^*\right) dx\,dt
\end{aligned}$$

$$= \int_Q \left((\Psi_1, \Psi_2, \Psi_3)(-B, A, 0)^\tau + 2ch v^*\right) dx\,dt$$

$$= \int_Q \left((\Psi_1, \Psi_2, \Psi_3)\mathcal{L}^*(p_1, p_2, p_3)^\tau + 2ch v^*\right) dx\,dt.$$

In the appropriate weak sense, the above inequality and equalities imply

$$0 \leqslant \int_Q \left((p_1, p_2, p_3)\mathcal{L}(\Psi_1, \Psi_2, \Psi_3)^\tau + 2ch v^*\right) dx\,dt$$

$$= \int_Q \left((p_1, p_2, p_3)\left(-ahS^*, 0, ahS^*\right)^\tau + 2ch v^*\right) dx\,dt$$

$$= \int_Q \left(-hp_1 aS^* + hp_3 aS^* + 2ch v^*\right) dx\,dt$$

$$= \int_Q h\left(2cv^* - ap_1 S^* + ap_3 S^*\right) dx\,dt.$$

By standard arguments varying h, we obtain

$$v^* = \min\left(\left(\frac{(p_1 - p_3)aS^*}{2c}\right)^+, v_{\max}\right). \qquad \square$$

The optimality system consists of the state system (1)–(3), the adjoint system (9)–(11), and the characterization of the control (12). In Theorem A.5, the solution to the optimality system is shown to be unique for T sufficiently small in the case where $\Phi(v) = cv^2$ for some $c > 0$, which implies the corresponding uniqueness of the optimal control.

4. Application to rabies and raccoons

4.1. Application to rabies and raccoons

In 1986, Murray et al. used partial differential equations to study the spatial spread of rabies in the fox populations of Europe [17,18]. Since then, the spread of rabies in foxes and other wildlife has been extensively studied with various spatial models [19–23], but the application of control or optimal control within these models is limited. Using the model from [18], Evans and Pritchard [24] applied control of initial conditions in culling and quarantine to drive the fox population to a desired profile. Currently, many areas in the eastern US and Canada strategically distribute oral rabies vaccine baits by hand and by aircraft in an effort to mitigate the spread of rabies among raccoons [25,26]. After eating a bait, a healthy raccoon will develop antibodies in two to three weeks that will provide protection if the raccoon is exposed to an infected raccoon. Asano et al. [27] use optimal control theory to characterize optimal vaccination levels for a raccoon metapopulation model with continuous time and discrete space. Additionally, Ding et al. [28] investigate similar results for discrete space and time.

In this section, we extend this survey of optimal raccoon vaccination regimes to a continuous time and space domain and explore the influence of realistic heterogeneous spatial domains on vaccine distribution. Landscape features, such as rivers and heavy forest cover, and long-distance translocation (LDT) of raccoons are known to perpetuate irregular dynamics in the rabies wave front. We compare optimal strategies of vaccine bait placement on a homogeneous spatial domain with those on a heterogeneous domain incorporating a river, forest cover, and LDT.

For this application, let $\Omega \subset \mathbf{R}^2$ represent a rectangular grid of size 30 km $\times$ 20 km. We simplify our original model to include only diffusive movement in the x and y directions. Given a control $v = v(x, y, t)$ representing the density of vaccine baits at location $(x, y) \in \Omega$ on week t, the corresponding susceptible ($S = S(x, y, t)$), infected ($I = I(x, y, t)$), and immune ($R = R(x, y, t)$) raccoon population densities satisfy

$$\frac{\partial S}{\partial t} = a_{11}(x, y)S_{xx} + a_{22}(x, y)S_{yy} + b(t)(S + R) - \mu_1 S - \beta SI - avS, \tag{13}$$

$$\frac{\partial I}{\partial t} = a_{11}(x, y)I_{xx} + a_{22}(x, y)I_{yy} + \beta SI - \mu_2 I, \tag{14}$$

$$\frac{\partial R}{\partial t} = a_{11}(x, y)R_{xx} + a_{22}(x, y)R_{yy} - \mu_1 R + avS \tag{15}$$

for all $(x, y, t) \in \Omega \times [0, T]$. Initial conditions are specified by

$$S(x, y, 0) = S_0(x, y), \qquad I(x, y, 0) = I_0(x, y), \qquad R(x, y, 0) = R_0(x, y) \tag{16}$$

for $(x, y) \in \Omega$ and no-flux boundary conditions are given by

$$\frac{\partial S}{\partial x} = 0, \qquad \frac{\partial I}{\partial x} = 0, \qquad \frac{\partial R}{\partial x} = 0 \quad \text{on } \big(\{x = 0\} \cup \{x = 30\}\big) \times (0, T), \tag{17}$$

$$\frac{\partial S}{\partial y} = 0, \qquad \frac{\partial I}{\partial y} = 0, \qquad \frac{\partial R}{\partial y} = 0 \quad \text{on } \big(\{y = 0\} \cup \{y = 20\}\big) \times (0, T). \tag{18}$$

Several rabies models include additional classes to track the exposed (infectious but not infected) raccoons as well as the quantity of baits on the ground [23,28,29]. For simplicity, we classify a raccoon to be susceptible if not previously exposed to rabies, infected if able to transmit rabies, or immune if vaccinated. Data and model predictions indicate low levels of natural immunity (1–5%) within raccoon populations, suggesting that raccoons develop little or no natural immunity to rabies [30]. Thus, we ignore natural immunity in our model and assume all rabies immunity is gained through vaccination.

Raccoons give birth during the spring of each year, March 20–June 21, an approximate 14 week period. See Clayton et al. [29] for the effect of the raccoon birth pulse in an ODE rabies model. Assuming a 50/50 sex rate within the population and that half the population are mature females, a reproductive rate of 1.34 year^{-1} is estimated [23,29]. Dividing this yearly rate by the 14 week period, we find $b(t) = 0.096$ week^{-1} for t within the birthing period. When t is not within the birthing period, we let $b(t) = 0$. For the simulations, we assume the birthing period to be weeks 13 through 27. The constant year-long natural death rate, $\mu_1 = 0.026$ week^{-1}, is calculated so that in absence of any disease or spatial spread, the susceptible population at $t = 0$ weeks and $t = 52$ weeks are approximately equal [29]. Rabies-related death rate is estimated to be $\mu_2 = 0.490$ week^{-1} [23,29]. The rate of infection βI is taken to be $0.03I$ [20,21,29]. The vaccine uptake rate a, a parameter with units (vaccine $\cdot$ week)$^{-1}$, is an indication of how successful the grounded baits are in vaccinating a raccoon. That is, to successfully vaccinate a raccoon, a bait must be first found and then eaten by a susceptible raccoon. This process can be inhibited by deterioration of the bait, human removal of the bait, or consumption of the bait by an animal other than a susceptible raccoon. Determining the value of a is not straightforward. We present results here for $a = 0.01$ (vaccine $\cdot$ week)$^{-1}$ and discuss how the parameter value influences the optimal control.

Infection starting in one corner of our domain can spread, possibly irregularly, to the opposite corner within a 52-week period. Irregularity in the rabies wave front can be attributed to the presence of rivers and forested land. Using a network model based on the adjacency of Connecticut townships, Smith, Waller, Russell, Childs, and Real [22] found that forestation slows the spread of rabies by nearly three times and that rivers reduce the local transmission by five-fold. In the model which best fit the Connecticut data, rabies did not cross rivers separating heavily forested townships. It is also known that the long distance translocation (LDT) of an infected raccoon can give rise to irregularity in the rabies wavefront. Smith et al. identified two putative LDT events which were shown to have effects on the spread of rabies within neighboring Connecticut townships. Our goal in this application is to identify how the optimal vaccination changes given the presence of spatial barriers and the relocation of an infected raccoon ahead of the rabies wavefront.

In the following subsection, we numerically approximate optimal vaccination strategies for (1) a homogeneous spatial domain with constant diffusion coefficients and a uniform initial susceptible population and (2) a heterogeneous spatial domain with spatially dependent diffusion coefficients and a heterogeneous initial susceptible population. In heterogeneous case, movement within the forested area and across the river is inhibited and the initial susceptible population is assumed to be the largest in non-forested (urban) areas and absent on the river [31]. See Table 1 for a list of all parameter values used in the homogeneous and heterogeneous examples. The boundary conditions imply that raccoons neither enter nor exit our domain.

The set of admissible controls, denoted by V, will consist of all measurable functions satisfying $0 \leqslant v(x, y, t) \leqslant v_{\max}$ a.e. $(x, y, t) \in \Omega \times [0, T]$. Here, $v_{\max}$ is a large positive constant representing an upper bound on the density of baits placed at each location. For this application, we state the optimal control problem as follows. Find $v^*(x, y, t) \in V$ which minimizes the objective functional

$$\int_{\Omega \times [0,T]} \big(I(x, y, t) + cv^2(x, y, t)\big)\, dx\, dy\, dt$$

subject to system (13)–(18). Above, T is the number of weeks over which we apply control and observe population dynamics. Note that we have simplified the original formulation of the objective functional so that $B = 0$ and, without loss of generality, $A = 1$. The cost of vaccination is expected to be a non-linear function of v. Here, we choose a quadratic function indicating additional costs associated with high levels of vaccination. The parameter c, with units $\frac{\text{raccoon/km}^2}{\text{vaccine}^2}$, balances the squared cost of vaccine with the cost associated with the infected population. An optimal control will be one which minimizes a combination of the cost of vaccination and the infectious population over the spatial domain Ω and a time period of length T weeks.

4.2. Numerical results

An iterative numerical scheme is employed to approximate solutions to the optimality system, which contains initial conditions for the state variables and final time conditions for the adjoints variables. The iterative process begins with

Table 1
Parameters values.

Description (units)	Notation	Homogeneous	Heterogeneous
Spatial domain	Ω	30 km × 20 km	[a]
Spatial subdomain	Ω_I	3 km × 2 km	[a]
Initial susceptible population raccoons/km^2	$S_0(x, y)$	30 for $(x, y) \in \Omega$	0 for (x, y) on river 10 for (x, y) in forest 30 for (x, y) elsewhere
Initial infected population raccoons/km^2	$I_0(x, y)$	2 for $(x, y) \in \Omega_I$ 0 for (x, y) elsewhere	[a]
Initial immune population raccoons/km^2	$R_0(x, y)$	0 for $(x, y) \in \Omega$	[a]
Diffusion coefficient km^2/week	$a_{11}(x, y)$	0.50 for $(x, y) \in \Omega$	0.01 (x, y) in river 0.20 for (x, y) in forest 0.50 for (x, y) elsewhere
Diffusion coefficient km^2/week	$a_{22}(x, y)$	0.50 for $(x, y) \in \Omega$	0.20 for (x, y) in forest 0.50 for (x, y) elsewhere
Birth rate week^{-1}	$b(t)$	0.096 for $13 \leqslant t < 28$ 0 otherwise	[a]
Natural death rate week^{-1}	μ_1	0.026	[a]
Death rate of infected week^{-1}	μ_2	0.490	[a]
Transmission rate $\frac{1}{\text{raccoon/km}^2\cdot\text{week}}$	β	0.03	[a]
Vaccine uptake rate $\frac{1}{\text{raccoon/km}^2\cdot\text{week}}$	a	0.01	[a]
Balancing coefficient (raccoon/km)^2/vaccine^2	c	0.10	[a]
Vaccine time period (weeks)	T	20	[a]

[a] Same as homogeneous value.

an initial guess for the control variable. Using an explicit finite difference method, we approximate solutions to the state equations given the initial conditions and the control variable. Using the state solutions and the control variable, a finite difference method is again used to solve the adjoint equations with final time conditions. Lastly, we update the control value with the current state and adjoint solutions. This process is repeated until successive values of the control variable, the states variables, and the adjoint variables are sufficiently close.

The infection is assumed to originate in the subdomain Ω_I at week $t = 0$ as reflected by the initial conditions in Table 1. For the homogeneous and heterogeneous spatial domains, respectively, Figs. 1 and 2 display the spread of infection over a period of 52 weeks in the absence of vaccination. For the homogeneous spatial domain, the constant diffusion coefficients, in combination with the homogeneous initial susceptible population, yield a uniform wavefront, propagating from one corner of the spatial grid to the opposite corner within the 52-week time period. For the heterogeneous spatial domain, infection spreads irregularly due to the varying diffusion coefficients and heterogeneous initial susceptible population. Rabies spreads predominantly up and around the river and does not appear to greatly impact the heavily forested area within the domain.

In our numerical tests, we first consider the optimal vaccination starting at week $t = 0$, the time at which rabies is first detected within our domain. Although the results for this case are not displayed, the optimal distribution of vaccine is identical in both spatial domains. For both the homogeneous and the heterogeneous domain, the optimal strategy is one which immediately vaccinates the site of infection and allocates a reduced amount of vaccine in adjacent areas. The density of baits is highest at time $t = 0$ and declines to zero within a few weeks. The optimal control successfully contains rabies to the bottom, left-hand corner of the domain. Specifically, the density of the infected class after 20 weeks is reduced below 1 raccoon/km^2 on Ω, a threshold criteria that we will hereon use as a sign of successful rabies elimination.

For a more realistic scenario, we assume that the initial infection spreads for twenty-one weeks without intervention. Given the progression of the infection on week $t = 21$ (Figs. 1 and 2), we compute the optimal 20-week vaccination starting on week $t = 21$. Figs. 3 and 4 display the results for the homogeneous and heterogeneous domains, respectively. Both schemes show control being applied at heaviest amounts initially and continuing with tapering amounts. Although, we allow control to be applied for twenty weeks ($T = 20$), the simulations suggests very little or no vaccine is needed after ten weeks. Both vaccine strategies successfully eliminate rabies in the domain by week $t = 41$.

For the homogeneous case, the strategy is to immediately place an arc of vaccine bait in front of the infectious wave. The arc extends from the top to the bottom of the domain and it's exact placement is determined by the vaccine uptake parameter, a. In Fig. 3, we assume $a = 0.01$ and the arc is placed well in advance of the infectious wave. This placement allots ample time for susceptible raccoons to eat the baits and become immune. This immunity is sufficient to prevent

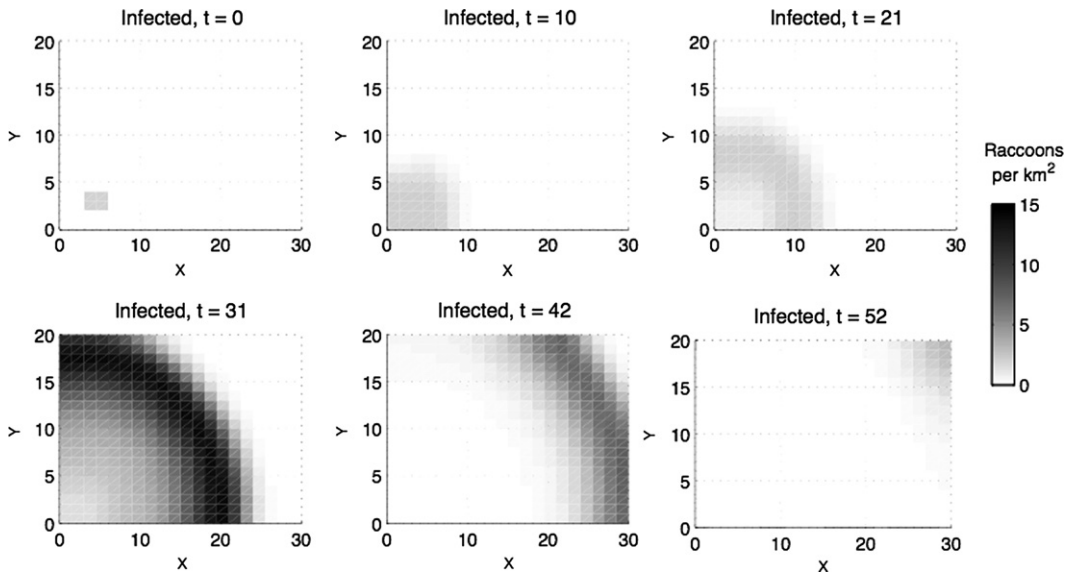

Fig. 1. In the absence of vaccination, infection starting in Ω_I spreads as an expanding wave throughout the homogeneous spatial domain.

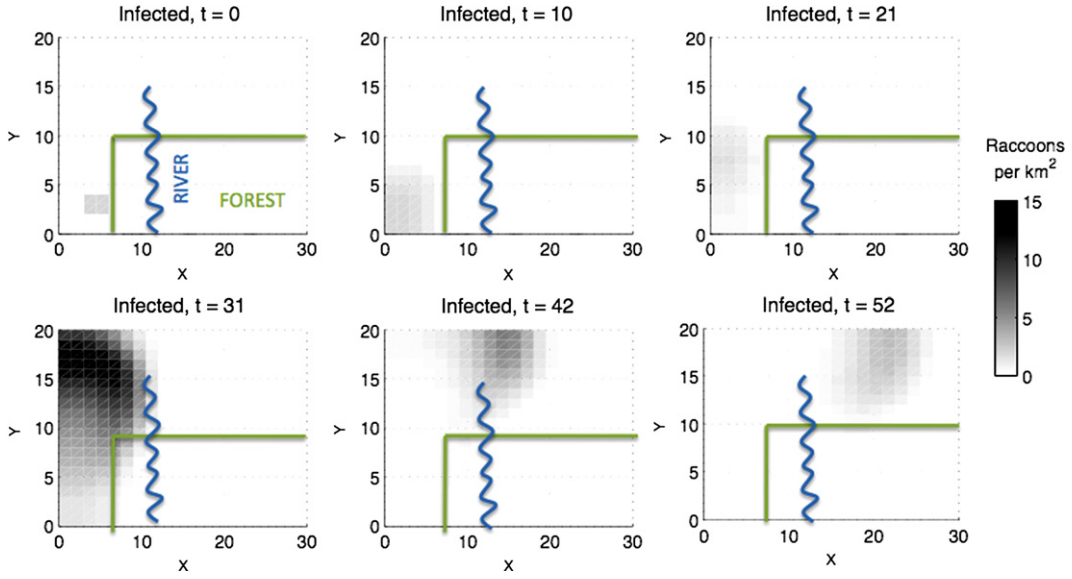

Fig. 2. In the absence of vaccination, infection starting in Ω_I spreads irregularly throughout the heterogeneous spatial domain.

rabies from spreading past the vaccine barrier. In additional simulations, we found that by increasing the value of a, the optimal vaccine distribution remains in the shape of an arc but is placed closer to the infectious wave.

In the corresponding heterogeneous case, we find that the optimal vaccination is considerably curtailed, only forming a partial arc in front of the infectious wave and allowing the natural barriers to act in place of vaccination. Initially, the edges of forested areas and areas containing the river are fortified with a relatively small quantity of vaccine. With the partial vaccine arc and natural land features acting as a *cordon sanitaire*, the resulting population dynamics indicate that rabies does not cross to the right side of the river.

Lastly, we assess the influence of long distance translocation (LDT) on the optimal vaccination on a heterogeneous domain. We again assume that the infection originating in Ω_I at $t = 0$ weeks progresses without intervention until $t = 21$ weeks as in Fig. 2. At $t = 21$ weeks, one additional infected raccoon appears in the upper right-hand corner of Ω. Even though the LDT is minor in comparison to the existing infection, it is an immediate concern. The optimal strategy starting at $t = 21$ weeks, seen in Fig. 5, immediately applies the largest concentration of vaccine on the site of the LDT. For our objective functional and cost coefficients, it is cost-effective to prevent the new focus from becoming a widespread epidemic while also vaccinating near the existing infectious wave. Even with the intense local vaccination, the LDT event does produce several secondary infections. However, with the two-part vaccination regime, the infectious wave produced by the

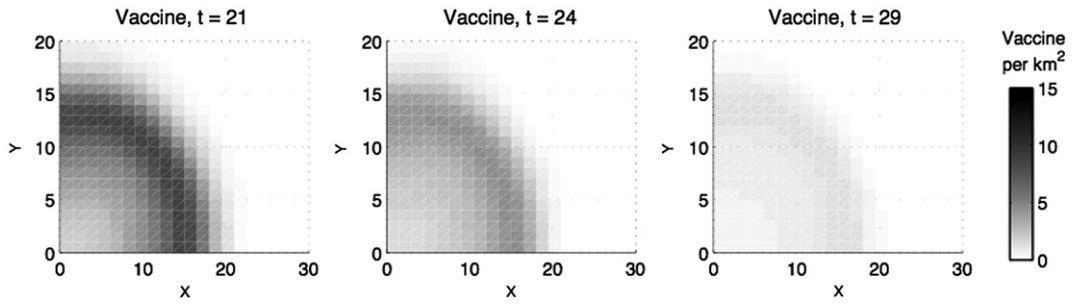

Fig. 3. For the homogeneous spatial domain, the optimal vaccination starting at week 21 is shown at weeks 21, 24 and 29.

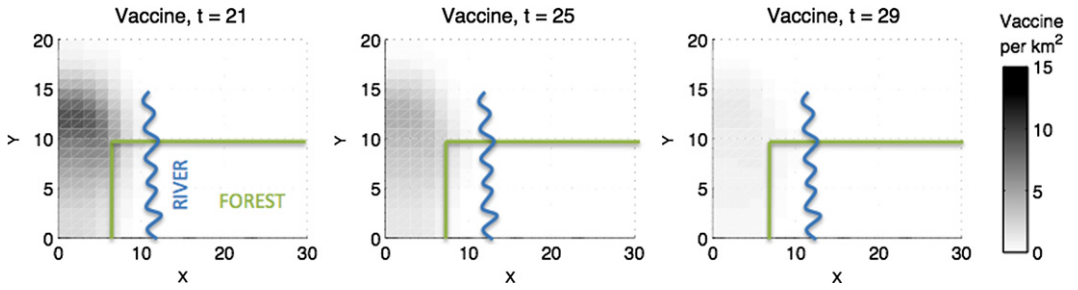

Fig. 4. For the heterogeneous spatial domain, the optimal vaccination starting at week 21 is shown at weeks 21, 25 and 29.

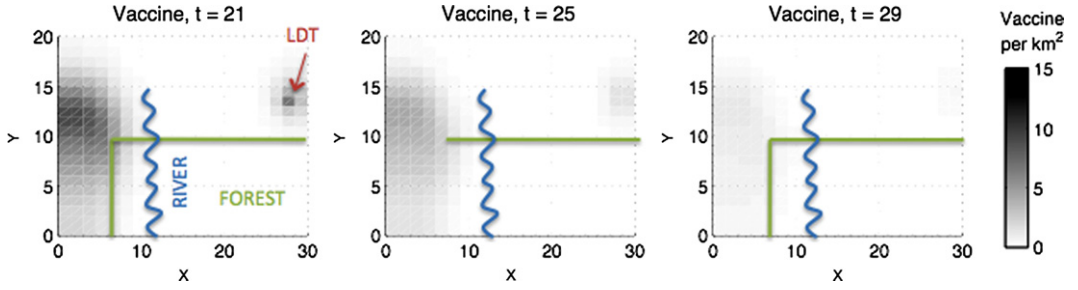

Fig. 5. For the heterogeneous spatial domain with LDT, the optimal vaccination starting at week 21 is shown at weeks 21, 25 and 29.

LDT is limited. Further, the existing outbreak is mitigated by the barrier created by the vaccine in combination with the river and forest cover. By $t = 41$ weeks, successful elimination of the infected class is achieved while maintaining a viable susceptible and immune population.

In Fig. 5, we assume the balancing coefficient to be $c = 0.10$. When a higher cost is associated with vaccination the optimal allocation of vaccine bait will decrease in quantity. In a numerical example with $c = 0.25$, we found that the increased cost of vaccination significantly constrains the optimal amount of vaccine used. Interestingly, the spatial pattern of distribution remains similar to that in Fig. 5. That is, the optimal distribution places vaccine in front of the existing wave front (curtailed by the forest cover and river) while also placing vaccine atop the LDT. With the reduced quantity of vaccine, the optimal strategy for $c = 0.25$ does not contain disease spread and is unsuccessful in eliminating the infected population over a 20-week period. These results suggest that there exists a threshold level of population immunity necessary to contain rabies spread [31].

5. Conclusions

In this article, we present a novel application of optimal control theory to spatiotemporal epidemic models described by a system of partial differential equations. The control variable is the spatial and temporal distribution of vaccine. We prove the existence and uniqueness of the solutions to our parabolic state system as well as prove the existence of an optimal control, sensitivity system, and adjoint system. For a given objective functional, an optimal control is characterized in terms of the corresponding state and adjoint variables. Lastly, uniqueness of the optimality system is shown for sufficiently small time.

As an illustrative application, we solve the optimality system numerically with parameters chosen to model the spread of rabies within a raccoon population. Although partial differential equations have previously been used to model rabies spread among raccoons, optimal control theory was not applied to these models. Our results reveal that the optimal timing and placement of rabies vaccine baits can vary with the spatial structure of a domain. Natural land features which deter raccoon movement (such as a river or forest cover) act as a barrier against the spread of rabies. In our simulations, these barriers aid the optimal vaccination strategies considerably. During the course of an outbreak, long distance translocation of raccoons has been known to occur. Our optimal vaccination strategies suggest that a new epidemic focus resulting from translocation should be addressed immediately and with ample vaccine.

All of the optimal vaccination regimes displayed are considered successful control regimes. For the time period in which optimal control was applied, the spread of rabies was contained to a fraction of our domain and the infected class reached below a specified threshold value ($I(x, y, T) < 1$ for all $(x, y) \in \Omega$). However, for scenarios in which increased costs are associated with control implementation, optimal control schemes are not always successful. An optimal control scheme with a decreased quantity of baits may hinder the rate at which disease spreads, but not contain the spread entirely. Thus, policy makers should consider optimal control theory and mathematical models not only as tools for design control schemes but also as methods for predetermining the scheme's consequences and possible success.

Our work provides a new and useful tool in addressing the control of disease spreading continuously in both space and time. Our model assumes the movement of individuals can be explained by diffusive and/or advective terms. Further, we assume the traditional mass action disease incidence term applies. Small modifications to these assumptions can easily be handled but would alter an optimal control. Discrete and distributed time delays may be considered in the incidence term, but these modifications would require some different estimates and control analysis [5,32]. The control of alternative disease dynamics, such as vector-host relationships which may be represented by parabolic PDE systems, can be studied with the techniques outlined here.

Acknowledgments

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Appendix A

Theorem A.1. *For T sufficiently small, given $v(x,t) \in V$, there exists a unique non-negative solution $(S, I, R) \in Z^3$ satisfying* (2), (3), *and* (4). *Furthermore, S, I, and R are bounded uniformly in $L^\infty(Q)$.*

Proof. To obtain $L^\infty(Q)$ bounds on S, I, and R, we apply Banach's fixed point theorem in the space X^3 where X is defined in (5) and has the norm $\|u_1, u_2, u_3\|_{X^3} = (\|u_1\|_X + \|u_2\|_X + \|u_3\|_X)$ where $\|u\|_X = \sup_{0\leqslant t\leqslant T} \|u(t)\|_{L^2(\Omega)}$.

Assume $v \in V$. For some $\lambda > 0$ to be chosen later, we let $w = e^{-\lambda t}S$, $y = e^{-\lambda t}I$, and $z = e^{-\lambda t}R$. The transformed state variables satisfy

$$\begin{aligned}
&\hat{L}_1 w = b(w+z) - \mu_1 w - e^{\lambda t}\beta w y - a v w,\\
&\hat{L}_2 y = e^{\lambda t}\beta w y - \mu_2 y,\\
&\hat{L}_3 z = -\mu_1 z + a v w \quad \text{a.e. } (x,t) \in Q, \qquad (19)\\
&w(x,0) = S_0(x), \qquad y(x,0) = I_0(x), \qquad z(x,0) = R_0(x) \quad \text{for } x \in \Omega, \qquad (20)
\end{aligned}$$

and

$$\frac{\partial w}{\partial \nu}(x,t) = 0, \qquad \frac{\partial y}{\partial \nu}(x,t) = 0, \qquad \frac{\partial z}{\partial \nu}(x,t) = 0 \quad \text{for all } x \in \partial\Omega,\ t \in (0,T) \qquad (21)$$

where

$$\hat{L}_k u \equiv \frac{\partial u}{\partial t} - \sum_{i,j=1}^{n} \left(a_{ij}^k u_{x_i}\right)_{x_j} + \sum_{i=1}^{n} b_i^k u_{x_i} + \left(\sum_{i=1}^{n} \left(b_i^k\right)_{x_i} + \lambda\right) u \quad \text{for } k = 1, 2, 3.$$

Given $(h_1, h_2, h_3) \in X^3$, the system of linear parabolic PDEs described by

$$\begin{aligned}
&\hat{L}_1 w = b(w+h_3) - \mu_1 w - e^{\lambda t}\beta w h_2 - a v w,\\
&\hat{L}_2 y = e^{\lambda t}\beta h_1 y - \mu_2 y,\\
&\hat{L}_3 z = -\mu_1 z + a v h_1 \quad \text{a.e. } (x,t) \in Q, \qquad (22)
\end{aligned}$$

along with (20) and (21), has a unique weak solution $(w, y, z) \in Z^3$ and, furthermore, $w, y, z \in C([0,T]; L^2(\Omega))$ [7]. To ensure $(w, y, z) \in X^3$, we now show that $0 \leqslant w(x,t), y(x,t), z(x,t) \leqslant M$ a.e. $(x,t) \in Q$ for some $M \geqslant 0$.

By first choosing λ sufficiently large and then choosing T sufficiently small, the extension of the Parabolic Maximum Principle to weak solutions [33] gives us $0 \leqslant w$ a.e. $(x,t) \in Q$. Using the function $w(x,t) - Wt$ for some positive constant W, we may conclude $w(x,t) \leqslant \|S_0(x)\|_{L^\infty(\Omega)} + Wt$ a.e. $(x,t) \in Q$. For $T \leqslant \frac{M}{2W}$, we have

$$w(x,t) \leqslant \big\|S_0(x)\big\|_{L^\infty(\Omega)} + \frac{M}{2} \leqslant M \quad \text{a.e. } (x,t) \in Q.$$

Similarly, $y(x,t) \leqslant M$ and $z(x,t) \leqslant M$ a.e. $(x,t) \in Q$. Thus, we have shown that for $(h_1,h_2,h_3) \in X^3$, there exists a unique solution $(w,y,z) \in Z^3 \cap X^3$ to system (20)–(22).

Now we show that the map $A : X^3 \to X^3$ such that $A(h_1,h_2,h_3) = (w,y,z)$ is a strict contraction. Choose (h_1,h_2,h_3), $(\bar{h}_1,\bar{h}_2,\bar{h}_3) \in X^3$. Define $(w,y,z) = A(h_1,h_2,h_3)$ and $(\bar{w},\bar{y},\bar{z}) = A(\bar{h}_1,\bar{h}_2,\bar{h}_3)$. Multiply the PDEs satisfied by differences $(w-\bar{w})$, $(y-\bar{y})$, and $(z-\bar{z})$ by test functions $(w-\bar{w})$, $(y-\bar{y})$, and $(z-\bar{z})$, respectively, and integrate over the domain $Q_s = \Omega \times (0,s)$ for arbitrary $s \in (0,T)$ to obtain

$$\begin{aligned}
&\int_{Q_s} (w-\bar{w})_t (w-\bar{w})\,dx\,dt + \lambda \int_{Q_s} (w-\bar{w})^2\,dx\,dt \\
&\quad + \int_{Q_s} \sum_{i,j=1}^{n} a_{ij}^1 (w-\bar{w})_{x_i} (w-\bar{w})_{x_j}\,dx\,dt + \int_{Q_s} \sum_{i=1}^{n} \big(b_i^1 (w-\bar{w})\big)_{x_i} (w-\bar{w})\,dx\,dt \\
&= \int_{Q_s} b(w-\bar{w})^2\,dx\,dt + \int_{Q_s} b(h_3-\bar{h}_3)(w-\bar{w})\,dx\,dt - \int_{Q_s} \mu_1 (w-\bar{w})^2\,dx\,dt \\
&\quad - \int_{Q_s} e^{\lambda t}\beta(wh_2 - \bar{w}\bar{h}_2)(w-\bar{w})\,dx\,dt - \int_{Q_s} av(w-\bar{w})^2\,dx\,dt, \\
&\int_{Q_s} (y-\bar{y})_t (y-\bar{y})\,dx\,dt + \lambda \int_{Q_s} (y-\bar{y})^2\,dx\,dt \\
&\quad + \int_{Q_s} \sum_{i,j=1}^{n} a_{ij}^2 (y-\bar{y})_{x_i} (y-\bar{y})_{x_j}\,dx\,dt + \int_{Q_s} \sum_{i=1}^{n} \big(b_i^2 (y-\bar{y})\big)_{x_i} (y-\bar{y})\,dx\,dt \\
&= \int_{Q_s} e^{\lambda t}\beta(h_1 y - \bar{h}_1 \bar{y})(y-\bar{y})\,dx\,dt - \int_{Q_s} \mu_2 (y-\bar{y})^2\,dx\,dt, \\
&\int_{Q_s} (z-\bar{z})_t (z-\bar{z})\,dx\,dt + \lambda \int_{Q_s} (z-\bar{z})^2\,dx\,dt \\
&\quad + \int_{Q_s} \sum_{i,j=1}^{n} a_{ij}^3 (z-\bar{z})_{x_i} (z-\bar{z})_{x_j}\,dx\,dt + \int_{Q_s} \sum_{i=1}^{n} \big(b_i^3 (z-\bar{z})\big)_{x_i} (z-\bar{z})\,dx\,dt \\
&= \int_{Q_s} \mu_1 (z-\bar{z})^2\,dx\,dt + \int_{Q_s} av(h_1-\bar{h}_1)(z-\bar{z})\,dx\,dt.
\end{aligned}$$

Utilizing the ellipticity condition (#4 in list of assumptions), we estimate several terms on the left-hand side of the above equations. Summing the inequalities, we obtain

$$\begin{aligned}
&\frac{1}{2}\int_{\Omega} \big((w-\bar{w})^2 + (y-\bar{y})^2 + (z-\bar{z})^2\big)(x,s)\,dx \\
&\quad + \lambda \int_{Q_s} \big((w-\bar{w})^2 + (y-\bar{y})^2 + (z-\bar{z})^2\big)\,dx\,dt \\
&\quad + \frac{\theta}{2}\int_{Q_s} \big(\big|\nabla(w-\bar{w})\big|^2 + \big|\nabla(y-\bar{y})\big|^2 + \big|\nabla(z-\bar{z})\big|^2\big)\,dx\,dt \\
&\leqslant C_0 \int_{Q_s} \big((w-\bar{w})^2 + (y-\bar{y})^2 + (z-\bar{z})^2\big)\,dx\,dt + \int_{Q_s} b(h_3-\bar{h}_3)(w-\bar{w})\,dx\,dt
\end{aligned}$$

$$+\int_{Q_s} e^{\lambda t}\beta(wh_2-\bar{w}\bar{h}_2)(w-\bar{w})\,dx\,dt+\int_{Q_s} e^{\lambda t}\beta(h_1y-\bar{h}_1\bar{y})(y-\bar{y})\,dx\,dt$$
$$+\int_{Q_s} av(h_1-\bar{h}_1)(z-\bar{z})\,dx\,dt \tag{23}$$

where C_0 is a constant depending on θ and the bounds assumed on the model parameters, coefficients b_i^k and $(b_i^k)_{x_i}$, and the control v.

Next we estimate terms on the right-hand side of the above inequality. For example, we estimate

$$\begin{aligned}
&\int_{Q_s} e^{\lambda t}\beta(h_1y-\bar{h}_1\bar{y})(y-\bar{y})\,dx\,dt\\
&\quad=\int_{Q_s} e^{\lambda t}\beta\big(y(h_1-\bar{h}_1)+\bar{h}_1(y-\bar{y})\big)(y-\bar{y})\,dx\,dt\\
&\quad=\int_{Q_s} e^{\lambda t}\beta y(h_1-\bar{h}_1)(y-\bar{y})\,dx\,dt+\int_{Q_s} e^{\lambda t}\beta\bar{h}_1(y-\bar{y})^2\,dx\,dt\\
&\quad\leqslant\frac{1}{2}\int_{Q_s} e^{2\lambda t}y^2\beta^2(y-\bar{y})^2\,dx\,dt+\frac{1}{2}\int_{Q_s}(h_1-\bar{h}_1)^2\,dx\,dt+\int_{Q_s} e^{\lambda t}\beta\bar{h}_1(y-\bar{y})^2\,dx\,dt\\
&\quad\leqslant D_1\big(M+M^2\big)e^{2\lambda T}\int_{Q_s}(y-\bar{y})^2\,dx\,dt+\frac{1}{2}\int_{Q_s}(h_1-\bar{h}_1)^2\,dx\,dt
\end{aligned}$$

where D_1 is a positive constant that depends only on the $L^\infty(Q)$ bounds on β.

By estimating the remaining terms in the right-hand side of (23) in a similar manner and noting the $L^\infty(Q)$ bounds the variables $\bar{w},\bar{y},\bar{z},h_1,h_2,h_3$, we get

$$\begin{aligned}
&\frac{1}{2}\int_{\Omega}\big((w-\bar{w})^2(x,s)+(y-\bar{y})^2(x,s)+(z-\bar{z})^2(x,s)\big)\,dx\\
&\qquad+\big(\lambda-C_1-C_2\big(M+M^2\big)e^{2\lambda T}\big)\int_{Q_s}\big((w-\bar{w})^2+(y-\bar{y})^2+(z-\bar{z})^2\big)\,dx\,dt\\
&\qquad+\frac{\theta}{2}\int_{Q_s}\big(\big|\nabla(w-\bar{w})\big|^2+\big|\nabla(y-\bar{y})\big|^2+\big|\nabla(z-\bar{z})\big|^2\big)\,dx\,dt\\
&\quad\leqslant\int_{Q_s}\big((h_1-\bar{h}_1)^2+(h_2-\bar{h}_2)^2+(h_3-\bar{h}_3)^2\big)\,dx\,dt
\end{aligned}$$

where C_1 and C_2 are constants depending on the $L^\infty(Q)$ bounds of the coefficients and av only. Moreover, for λ first chosen large and then T chosen sufficiently small, we have $\lambda-C_1-C_2(M+M^2)e^{2\lambda T}>0$ and thus

$$\begin{aligned}
&\int_{\Omega}\big((w-\bar{w})^2+(y-\bar{y})^2+(z-\bar{z})^2\big)(x,s)\,dx\\
&\quad\leqslant 2\int_{Q_s}\big((h_1-\bar{h}_1)^2+(h_2-\bar{h}_2)^2+(h_3-\bar{h}_3)^2\big)\,dx\,dt.
\end{aligned}\tag{24}$$

Taking the supremum over $0\leqslant s\leqslant T$ on both sides, we obtain

$$\begin{aligned}
&\|w-\bar{w}\|_X+\|y-\bar{y}\|_X+\|z-\bar{z}\|_X\\
&\quad\leqslant 3(2T)^{1/2}\big(\|h_1-\bar{h}_1\|_X+\|h_2-\bar{h}_2\|_X+\|h_3-\bar{h}_3\|_X\big).
\end{aligned}$$

We must choose T sufficiently small because of previous assumptions, but we can also choose T such that $3(2T)^{1/2}<1$, which ensures that the mapping A is a strict contraction. By Banach's fixed point theorem, there exists a unique solution $(w,y,z)\in Z^3\cap X^3$ to the PDE system (19)–(21).

It follows that for sufficiently small T, there exists a unique non-negative solution $(S,I,R)\in Z^3$ satisfying (2)–(4). Furthermore, $0\leqslant S(x,t),\ I(x,t),\ R(x,t)\leqslant e^{\lambda T}M$ a.e. $(x,t)\in Q$. □

Theorem A.2. *There exists an optimal control $v^* \in V$ that minimizes the functional $J(v)$.*

Proof. The control variable v is uniformly bounded in Q and S, I, and R are also uniformly bounded in Q by Theorem A.1. Therefore $\inf_{v\in V} J(v) > -\infty$ and there exists a minimizing sequence $v^n \in V$ such that $\lim_{n\to\infty} J(v^n) = \inf_{v\in V} J(v)$. Theorem A.1 allows us to define $(S^n, I^n, R^n) = (S, I, R)(v^n)$ for each n. To obtain uniform bounds on $\|S^n\|_Z$, $\|I^n\|_Z$, and $\|R^n\|_Z$ for all n, we multiply the PDEs satisfied by S^n, I^n, and R^n by the test functions S^n, I^n, and R^n, respectively, and integrate over the domain $Q_s = \Omega \times (0, s)$ for arbitrary $s \in (0, T]$. We then estimate

$$\begin{aligned}
&\frac{1}{2}\int_\Omega \left(\left(S^n\right)^2(x,s) + \left(I^n\right)^2(x,s) + \left(R^n\right)^2(x,s)\right) dx \\
&\quad + \frac{\theta}{2}\int_{Q_s} \left(\left|\nabla S^n\right|^2 + \left|\nabla I^n\right|^2 + \left|\nabla R^n\right|^2\right) dx\,dt \\
&\leqslant \frac{1}{2}\int_\Omega \left((S_0)^2 + (I_0)^2 + (R_0)^2\right) dx + C_3 \int_{Q_s} \left(\left|S^n\right|^2 + \left|I^n\right|^2 + \left|R^n\right|^2\right) dx\,dt \\
&\quad - \int_{Q_s} \beta I^n \left(S^n\right)^2 dx\,dt + \int_{Q_s} \beta S^n \left(I^n\right)^2 dx\,dt - \int_{Q_s} \mu_2 \left(I^n\right)^2 dx\,dt
\end{aligned} \tag{25}$$

where C_3 is a positive constant that depends on θ and the bounds on the b_i^k and $(b_i^k)_{x_i}$ coefficients. Noting that our state variables are uniformly bounded in Q (Theorem A.1), we collect similar squared terms in (25) and obtain

$$\begin{aligned}
&\int_\Omega \left(\left(S^n\right)^2 + \left(I^n\right)^2 + \left(R^n\right)^2\right)(x,s)\,dx \\
&\quad + \theta \int_{Q_s} \left(\left|\nabla S^n\right|^2 + \left|\nabla I^n\right|^2 + \left|\nabla R^n\right|^2\right) dx\,dt \\
&\leqslant \int_\Omega \left((S_0)^2 + (I_0)^2 + (R_0)^2\right) dx + C_4 \int_{Q_s} \left(\left|S^n\right|^2 + \left|I^n\right|^2 + \left|R^n\right|^2\right) dx\,dt
\end{aligned} \tag{26}$$

where C_4 is a new positive constant which depends on θ and the $L^\infty(Q)$ bounds on the coefficients, control variable, and state variables. In particular, we have

$$\begin{aligned}
&\int_\Omega \left(\left(S^n\right)^2 + \left(I^n\right)^2 + \left(R^n\right)^2\right)(x,s)\,dx \\
&\quad \leqslant \int_\Omega \left((S_0)^2 + (I_0)^2 + (R_0)^2\right) dx + C_4 \int_{Q_s} \left(\left|S^n\right|^2 + \left|I^n\right|^2 + \left|R^n\right|^2\right) dx\,dt.
\end{aligned}$$

An application of Gronwall's Inequality yields

$$\int_Q \left(\left|S^n\right|^2 + \left|I^n\right|^2 + \left|R^n\right|^2\right) dx\,dt \leqslant T\left(1 + C_4 T e^{C_4 T}\right) \int_\Omega \left((S_0)^2 + (I_0)^2 + (R_0)^2\right) dx. \tag{27}$$

Thus, (27) together with (26) gives

$$\begin{aligned}
&\sup_{s\in(0,T)} \left(\int_\Omega \left(\left(S^n\right)^2(x,s) + \left(I^n\right)^2(x,s) + \left(R^n\right)^2(x,s)\right) dx\right) \\
&\quad + \theta \int_Q \left(\left|\nabla S^n\right|^2 + \left|\nabla I^n\right|^2 + \left|\nabla R^n\right|^2\right) dx\,dt \\
&\leqslant C_5 \int_\Omega \left((S_0)^2 + (I_0)^2 + (R_0)^2\right) dx
\end{aligned}$$

where the constant C_5 depends on T, θ, and $L^\infty(Q)$ bounds on the states, control and coefficients. From this, we can conclude that $\|S^n\|_Z$, $\|I^n\|_Z$, $\|R^n\|_Z$ are uniformly bounded independent of n. From these bounds and the PDE system, we

can conclude that $\|S_t^n\|$, $\|I_t^n\|$, $\|R_t^n\|$ are uniformly bounded in $L^2(0,T;H^1(\Omega)^*)$ independent of n. In light of these uniform bounds and because $v^n \in L^\infty(Q)$, there exists subsequences S^n, I^n, R^n and v^n such that $S^n \rightharpoonup S^*$, $I^n \rightharpoonup I^*$, $R^n \rightharpoonup R^*$, and $v^n \rightharpoonup v^*$ weakly in Z. Furthermore, $S_t^n \rightharpoonup S_t^*$, $I_t^n \rightharpoonup I_t^*$, and $R_t^n \rightharpoonup R_t^*$ weakly in $L^2(0,T;H^1(\Omega)^*)$.

Because of terms like $\int_Q \beta I^n S^n \phi_1 \, dx\,dt$ in the variational formulation, stronger convergence results are necessary to pass the limit as $n \to \infty$ and conclude that S^*, I^*, R^* are the states associated with the optimal control v^*. Using the compactness result in Corollary 4 of Theorem 5 in [34], we have $S^n \to S^*$, $I^n \to I^*$, and $R^n \to R^*$ strongly in $L^2(Q)$. This is sufficient to conclude $(S^*, I^*, R^*) = (S, I, R)(v^*)$.

To finish the proof, recall $\Phi(\cdot)$ is a lower semi-continuous convex function in the objective functional. Because every lower semi-continuous convex function of a real vector space remains lower semi-continuous when supplied with the weak topology [35], we have

$$\int_Q \Phi\left(v^*\right) dx\,dt \leqslant \liminf_{n\to\infty} \int_Q \Phi\left(v^n\right) dx\,dt.$$

This property gives us

$$\begin{aligned} J\left(v^*\right) &= \int_Q \left(AI^* - BS^* + \Phi\left(v^*\right)\right) dx\,dt \\ &\leqslant \liminf_{n\to\infty} \int_Q \left(AI^n - BS^n + \Phi\left(v^n\right)\right) dx\,dt \\ &= \lim_{n\to\infty} \int_Q \left(AI^n - BS^n + \Phi\left(v^n\right)\right) dx\,dt \\ &= \inf_{v\in V} J(v). \end{aligned}$$

Thus, v^* minimizes the objective functional and is an optimal control. □

Theorem A.3 *(Sensitivities). The mapping $v \in V \to (S, I, R) \in Z^3$ is differentiable in the sense that there exists $\Psi_1, \Psi_2, \Psi_3 \in Z$ such that*

$$\begin{aligned} &\frac{S(v+\epsilon h) - S(v)}{\epsilon} \rightharpoonup \Psi_1, \\ &\frac{I(v+\epsilon h) - I(v)}{\epsilon} \rightharpoonup \Psi_2, \\ &\frac{R(v+\epsilon h) - R(v)}{\epsilon} \rightharpoonup \Psi_3 \end{aligned}$$

in Z as $\epsilon \to 0$ for any $v \in V$ and $h \in L^\infty(Q)$ such that $v + \epsilon h \in V$ for ϵ small. Furthermore, Ψ_1, Ψ_2, Ψ_3 solve system (6)–(8).

Proof. Choose $h \in L^\infty(Q)$, $v \in V$ such that $(v + \epsilon h) \in V$ for ϵ small. Define $(S^\epsilon, I^\epsilon, R^\epsilon) = (S, I, R)(v + \epsilon h)$. The quotients $(\frac{S^\epsilon - S}{\epsilon})$, $(\frac{I^\epsilon - I}{\epsilon})$, and $(\frac{R^\epsilon - R}{\epsilon})$ satisfy system

$$\begin{aligned} &\frac{\partial(\frac{S^\epsilon - S}{\epsilon})}{\partial t} - \sum_{i,j=1}^n \left(a_{ij}^1 \left(\frac{S^\epsilon - S}{\epsilon}\right)_{x_i}\right)_{x_j} + \sum_{i=1}^n \left(b_i^1 \left(\frac{S^\epsilon - S}{\epsilon}\right)\right)_{x_i} \\ &\quad = b\left(\left(\frac{S^\epsilon - S}{\epsilon}\right) + \left(\frac{R^\epsilon - R}{\epsilon}\right)\right) - \mu_1\left(\frac{S^\epsilon - S}{\epsilon}\right) - \beta\left(\frac{S^\epsilon I^\epsilon - SI}{\epsilon}\right) - \left(\frac{a(v+\epsilon h)S^\epsilon - avS}{\epsilon}\right), \\ &\frac{\partial(\frac{I^\epsilon - I}{\epsilon})}{\partial t} - \sum_{i,j=1}^n \left(a_{ij}^2 \left(\frac{I^\epsilon - I}{\epsilon}\right)_{x_i}\right)_{x_j} + \sum_{i=1}^n \left(b_i^2 \left(\frac{I^\epsilon - I}{\epsilon}\right)\right)_{x_i} \\ &\quad = \beta\left(\frac{S^\epsilon I^\epsilon - SI}{\epsilon}\right) - \mu_2\left(\frac{I^\epsilon - I}{\epsilon}\right), \\ &\frac{\partial(\frac{S^\epsilon - S}{\epsilon})}{\partial t} - \sum_{i,j=1}^n \left(a_{ij}^3 \left(\frac{R^\epsilon - R}{\epsilon}\right)_{x_i}\right)_{x_j} + \sum_{i=1}^n \left(b_i^3 \left(\frac{R^\epsilon - R}{\epsilon}\right)\right)_{x_i} \\ &\quad = -\mu_1\left(\frac{R^\epsilon - R}{\epsilon}\right) + \left(\frac{a(v+\epsilon h)S^\epsilon - avS}{\epsilon}\right) \end{aligned} \tag{28}$$

with initial and boundary conditions given by

$$\left(\frac{S^\epsilon - S}{\epsilon}\right)(x,0) = 0, \qquad \left(\frac{I^\epsilon - I}{\epsilon}\right)(x,0) = 0, \qquad \left(\frac{R^\epsilon - R}{\epsilon}\right)(x,0) = 0 \quad \text{for } x \in \Omega,$$

$$\frac{\partial(\frac{S^\epsilon - S}{\epsilon})}{\partial \nu} = 0, \qquad \frac{\partial(\frac{I^\epsilon - I}{\epsilon})}{\partial \nu} = 0, \qquad \frac{\partial(\frac{R^\epsilon - R}{\epsilon})}{\partial \nu} = 0 \quad \text{on } \partial\Omega \times (0,T).$$

In system (28), we rewrite terms like

$$\frac{a(v+\epsilon h)S^\epsilon - avS}{\epsilon} = ahS^\epsilon + \frac{S^\epsilon - S}{\epsilon}av$$

so that as $\epsilon \to 0$, we may obtain $ahS + av\Psi_1$. Noting that the control and state variables are bounded above by $v_{\max}$ and $M > 0$, respectively, and independent of ϵ, we find that for any $s \in (0,T]$

$$\begin{aligned}
&\int_\Omega \left(\left(\frac{S^\epsilon - S}{\epsilon}\right)^2(x,s) + \left(\frac{I^\epsilon - I}{\epsilon}\right)^2(x,s) + \left(\frac{R^\epsilon - R}{\epsilon}\right)^2(x,s)\right)dx \\
&\quad + \theta \int_{Q_s} \left(\left|\nabla\left(\frac{S^\epsilon - S}{\epsilon}\right)\right|^2 + \left|\nabla\left(\frac{I^\epsilon - I}{\epsilon}\right)\right|^2 + \left|\nabla\left(\frac{R^\epsilon - R}{\epsilon}\right)\right|^2\right)dx\,dt \\
&\quad \leqslant C_6 \int_{Q_s} \left(\left(\frac{S^\epsilon - S}{\epsilon}\right)^2 + \left(\frac{I^\epsilon - I}{\epsilon}\right)^2 + \left(\frac{R^\epsilon - R}{\epsilon}\right)^2\right)dx\,dt + C_7 \int_{Q_s} (ah)^2\,dx\,dt
\end{aligned}$$

where C_6 is a constant which depends on θ and the $L^\infty(Q)$ bounds on the states, control, and coefficients and C_7 depends only on $v_{\max}$ and M. After an application of Gronwall's inequality and simplification, we have

$$\begin{aligned}
&\sup_{s\in(0,T]}\left(\int_\Omega \left(\left(\frac{S^\epsilon - S}{\epsilon}\right)^2(x,s) + \left(\frac{I^\epsilon - I}{\epsilon}\right)^2(x,s) + \left(\frac{R^\epsilon - R}{\epsilon}\right)^2(x,s)\right)dx\right) \\
&\quad + \theta \int_Q \left(\left|\nabla\left(\frac{S^\epsilon - S}{\epsilon}\right)\right|^2 + \left|\nabla\left(\frac{I^\epsilon - I}{\epsilon}\right)\right|^2 + \left|\nabla\left(\frac{R^\epsilon - R}{\epsilon}\right)\right|^2\right)dx\,dt \\
&\quad \leqslant C_7 \int_Q (ah)^2\,dx\,dt. \qquad (29)
\end{aligned}$$

Thus, the right-hand side of (29) is bounded independent of ϵ. We can conclude that $\|(\frac{S^\epsilon - S}{\epsilon})\|_Z$, $\|(\frac{I^\epsilon - I}{\epsilon})\|_Z$, $\|(\frac{R^\epsilon - R}{\epsilon})\|_Z$ are uniformly bounded for ϵ small, which justifies the existence of Ψ_1, Ψ_2 and $\Psi_3 \in Z$ and the convergence of the quotients,

$$\left(\frac{S^\epsilon - S}{\epsilon}\right) \rightharpoonup \Psi_1, \qquad \left(\frac{I^\epsilon - I}{\epsilon}\right) \rightharpoonup \Psi_2, \qquad \left(\frac{R^\epsilon - R}{\epsilon}\right) \rightharpoonup \Psi_3 \quad \text{in } Z.$$

As in the previous proof, we can also conclude

$$\left(\frac{S^\epsilon - S}{\epsilon}\right)_t \rightharpoonup (\Psi_1)_t, \qquad \left(\frac{I^\epsilon - I}{\epsilon}\right)_t \rightharpoonup (\Psi_2)_t, \qquad \left(\frac{R^\epsilon - R}{\epsilon}\right)_t \rightharpoonup (\Psi_3)_t$$

in $L^2(0,T;H^1(\Omega)^*)$ and

$$\left(\frac{S^\epsilon - S}{\epsilon}\right) \to \Psi_1, \qquad \left(\frac{I^\epsilon - I}{\epsilon}\right) \to \Psi_2, \qquad \left(\frac{R^\epsilon - R}{\epsilon}\right) \to \Psi_3$$

in $L^2(Q)$. The strong convergences are used to justify convergence of terms like $\frac{S^\epsilon I^\epsilon - SI}{\epsilon}$, for example. Together, the strong and weak convergence results justify that Ψ_1, Ψ_2, Ψ_3 solve (6)–(8). □

Theorem A.4. *Given an optimal control v^* and corresponding state solution (S^*, I^*, R^*), there exists a weak solution $(p_1, p_2, p_3) \in Z^3$ satisfying the adjoint system* (9)–(11).

Proof. Because the adjoint system is linear in the adjoint variables, there exists a solution (p_1, p_2, p_3) satisfying (9)–(11) [7]. □

Theorem A.5. *When T is sufficiently small, the solution of the optimality system is unique.*

Proof. Suppose (S, I, R), (p_1, p_2, p_3) and $(\bar{S}, \bar{I}, \bar{R})$, $(\bar{p}_1, \bar{p}_2, \bar{p}_3)$ are two solutions of (1)–(3), (9)–(11) with control characterization (12). Assuming $\Phi(v) = cv^2$ for some $c > 0$ in the objective functional, the associated control characterizations are

$$v = \min\left(\left(\frac{(p_1 - p_3)aS}{2c}\right)^+, v_{\max}\right), \qquad \bar{v} = \min\left(\left(\frac{(\bar{p}_1 - \bar{p}_3)a\bar{S}}{2c}\right)^+, v_{\max}\right).$$

For some $\lambda > 0$, let

$$\begin{aligned}
&w = e^{-\lambda t}S, \qquad y = e^{-\lambda t}I, \qquad z = e^{-\lambda t}R,\\
&q_1 = e^{\lambda t}p_1, \qquad q_2 = e^{\lambda t}p_2, \qquad q_3 = e^{\lambda t}p_3,\\
&\bar{w} = e^{-\lambda t}\bar{S}, \qquad \bar{y} = e^{-\lambda t}\bar{I}, \qquad \bar{z} = e^{-\lambda t}\bar{R},\\
&\bar{q}_1 = e^{\lambda t}\bar{p}_1, \qquad \bar{q}_2 = e^{\lambda t}\bar{p}_2, \qquad \bar{q}_3 = e^{\lambda t}\bar{p}_3.
\end{aligned}$$

We consider the differences $w - \bar{w}$, $y - \bar{y}$, $z - \bar{z}$, $q_1 - \bar{q}_1$, $q_2 - \bar{q}_2$, and $q_3 - \bar{q}_3$. Using similar techniques as those in the proof of Theorem A.1, we obtain

$$\begin{aligned}
&\frac{1}{2}\int_\Omega \left((w-\bar{w})^2(x,T) + (y-\bar{y})^2(x,T) + (z-\bar{z})^2(x,T) + (q_1-\bar{q}_1)^2(x,0) + (q_2-\bar{q}_2)^2(x,0) + (q_3-\bar{q}_3)^2(x,0)\right)dx\\
&\quad + \left(\lambda - C_8 - C_9 e^{2\lambda T}\right)\int_Q \left(|w-\bar{w}|^2 + |y-\bar{y}|^2 + |z-\bar{z}|^2 + |q_1-\bar{q}_1|^2 + |q_2-\bar{q}_2|^2 + |q_3-\bar{q}_3|^2\right)dx\,dt\\
&\quad + \frac{\theta}{2}\int_Q \left(\left|\nabla(w-\bar{w})\right|^2 + \left|\nabla(y-\bar{y})\right|^2 + \left|\nabla(z-\bar{z})\right|^2 + \left|\nabla(q_1-\bar{q}_1)\right|^2 + \left|\nabla(q_2-\bar{q}_2)\right|^2 + \left|\nabla(q_3-\bar{q}_3)\right|^2\right)dx\,dt \leqslant 0
\end{aligned}$$

for constants C_8 and C_9, which depend on the L^∞ bounds of the coefficients, states, and controls. If we choose λ sufficiently large and T sufficiently small so that $\lambda - C_8 - C_9 e^{2\lambda T} > 0$, then we must have $w = \bar{w}$, $y = \bar{y}$, $z = \bar{z}$, $q_1 = \bar{q}_1$, $q_2 = \bar{q}_2$, and $q_3 = \bar{q}_3$. Therefore, $S = \bar{S}$, $I = \bar{I}$, $R = \bar{R}$, $p_1 = \bar{p}_1$, $p_2 = \bar{p}_2$, and $p_3 = \bar{p}_3$. Finally, because the optimal control is characterized in terms of the states and the adjoints, we have $v = \bar{v}$. □

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