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OPTIMAL STRATEGIES FOR PREVENTION OF ECSTASY USE

SUNHWA CHOI[1], JONGGUL LEE[1], AND EUNOK JUNG[1†]

[1]DEPARTMENT OF MATHEMATICS, KONKUK UNIVERSITY, SEOUL 143-701, SOUTH KOREA
E-mail address: ssunhwa.choi@gmail.com, jg4lee@gmail.com, junge@konkuk.ac.kr

ABSTRACT. We have investigated optimal control strategies for prevention of ecstasy use. Ecstasy use has continued at raves and nightclubs in recent years and the reduction of ecstasy use has become one of the important issues in society. We apply optimal control theory to a model of the peer-driven dynamics of ecstasy use. Our goal is to minimize the ecstasy use class and the intervention cost. Optimal control is characterized in terms of the solution of optimality system, which is the state system coupled with the adjoint system and the optimality equations. The numerical simulations show the optimal prevention policies of ecstasy use in various scenarios.

1. INTRODUCTION

Ecstasy, scientifically termed Methylenedioxy-methamphetamine (MDMA), is a chemical drug that is mainly taken orally as a capsule or tablet [11]. Ecstasy has an effect of enhanced sensations, heightened feelings of empathy, self-acceptance, better emotional awareness and feeling of relaxed euphoria [9]. However, taking ecstasy distorts the perception of time and the sense of touch. It also causes chemical changes in the brain [22]. In addition, the stimulant effects of the drug cause severe dehydration and hyperthermia that may possibly lead to muscle breakdown and kidney, liver and cardiovascular failure [12].

During the late 70s and early 80s, ecstasy was used by psychologists and therapists as a tool to treat patients with traumas, phobias and other relevant disorders [22]. However, there is no legitimate medical use for MDMA in the United States. In addition, a growing number of recreational use of ecstasy was reported and evidently showed a wide spread of abuse as a recreational drug at raves and night clubs. Most abusers are adolescent and young adults [13, 17, 19]. MDMA became a schedule I controlled substance under the Federal Controlled Substances Act. However the use of ecstasy has continued in recent years and the reduction of ecstasy use has become one of the important social issues.

Song et al. developed a mathematical model of transmission for ecstasy use that concerns the influence of peer pressure as a major factor of taking ecstasy [1]. In their results, peer pressure can drive a sudden increase in ecstasy use although threshold conditions seem to

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† Corresponding author.

predict against this growth and the most important factor is the parameter ϵ, the peer pressure rate of recruitment into the susceptible class, in determining the extent of ecstasy use.

In this paper, we have applied optimal control theory to Song's model. The optimal strategies for preventing ecstasy use have been proposed for various scenarios. Optimal control theory has been applied to problems in the areas of economics [16, 18, 23], biology [2, 3, 8, 10, 14, 20], physiology [5, 6, 7, 21], and engineering [4], however to the best of our knowledge, it has not been applied to the prevention of ecstasy use. We have considered two different strategies: in Strategy 1, the controls associated with ϕ and α, which have influence on the ecstasy use class I, have been introduced. In Strategy 2, the controls associated with ϵ and δ_s, which have impact on the susceptible class S, have been considered. The detailed description of parameters are given in the following mathematical model subsection. Strategy 1 is a direct way to minimize I, while Strategy 2 is an indirect way to minimize I by reducing S population. Our objective functional balances the effect of minimizing the ecstasy use class and the cost implementing the control programs.

The paper is organized as follows: Section 2 describes a mathematical model with controls of ecstasy use transmission. The reproductive number and objective functional of this model is also introduced in this section. Section 3 presents the results and discussion on numerical studies of optimal controls. Summary and conclusions are given in the final section.

2. Epidemic model and materials

2.1. **Mathematical model.** In this work, optimal control theory is applied to a model developed by Song et al.: *'Raves, clubs and ecstasy: the impact of peer pressure'* [1]. A population of individuals between the ages of 13 and 25 are divided into the following four classes. The non-core class, $A(t)$, consists of individuals who never use ecstasy and do not frequent raves and nightclubs. The core population is composed of susceptible individuals $S(t)$, ecstasy users $I(t)$ and recovered individuals $V(t)$ who regularly visit nightclubs and raves. The susceptible class, $S(t)$, is a group of individuals who do not use ecstasy but are likely to become ecstasy users because of their immersion in the rave and nightclub culture. The ecstasy class and recovered class consists of individuals who are habitual ecstasy users and no longer using ecstasy, respectively. The total population, $P = A(t) + S(t) + I(t) + V(t)$, is a constant in time.

The mathematical model without controls is given by the following system of differential equations:

$$
\begin{aligned}
\frac{dA}{dt} &= \mu P + \delta_v V \frac{A}{P} + \delta_s S \frac{A}{P} - \varepsilon A \frac{S+I}{P} - \mu A, \\
\frac{dS}{dt} &= \varepsilon A \frac{S+I}{P} - \delta_s S \frac{A}{P} - \phi S \frac{I}{P} - \mu S, \\
\frac{dI}{dt} &= \phi S \frac{I}{P} + \alpha V \frac{I}{P} - \gamma I \frac{A+S+V}{P} - \tau I - \mu I, \\
\frac{dV}{dt} &= \gamma I \frac{A+S+V}{P} + \tau I - \delta_v V \frac{A}{P} - \alpha V \frac{I}{P} - \mu V,
\end{aligned}
\tag{2.1}
$$

Parameter μ is the rate of leaving a class as a result of aging or death. ε is the peer pressure rate of the core population $S+I$ on the noncore population A and ϕ is the peer pressure rate of ecstasy users I on susceptible population S. τ and γ are the recovery rate without peer pressure and from peer pressure, respectively. α is the relapse rate due to peer pressure. δ_v is the rate at which recovered individuals go back to the noncore as a result of peer pressure and δ_s is the rate at which susceptible individuals go back to the noncore due to peer pressure.

2.2. **Reproductive numbers.** The threshold for many epidemiology models is the basic reproductive number R_0, which is defined as the average number of secondary infections produced by one infected individual in a completely susceptible population. For typical epidemiology models, an infection can get started in a fully susceptible population if and only if $R_0 > 1$. Thus the basic reproduction number R_0 is often considered as the threshold quantity that determines whether an infection can invade and persist in a new host population.

The ecstasy model has two thresholds that determine whether ecstasy will become an epidemic. The first one, R_c, describes the average number of individuals pressured into becoming new core members (rave and nightclub frequenters) by a member of the core population; $R_c = \frac{\epsilon}{\mu+\delta_s}$. The second one, R_0, as the basic reproductive number describes the conditions that ecstasy users must overcome to infect more individuals; $R_0 = \frac{\phi(1-\frac{\mu}{\epsilon-\delta_s})}{\gamma+\tau+\mu}$. The derivation of these reproductive numbers is given in [1]. This model behaves differently from the typical models because the thresholds, R_c and R_0, are based on local conditions. That is, they are very sensitive to peer pressure, and the existence of ecstasy endemic in the system depends on both the power of this peer pressure and initial number of members in the classes. This induces that if $R_c > 1$, even if $R_0 < 1$, there might be an endemic equilibrium. The same is still true for a certain case when $R_0 > 1$, even if $R_c < 1$.

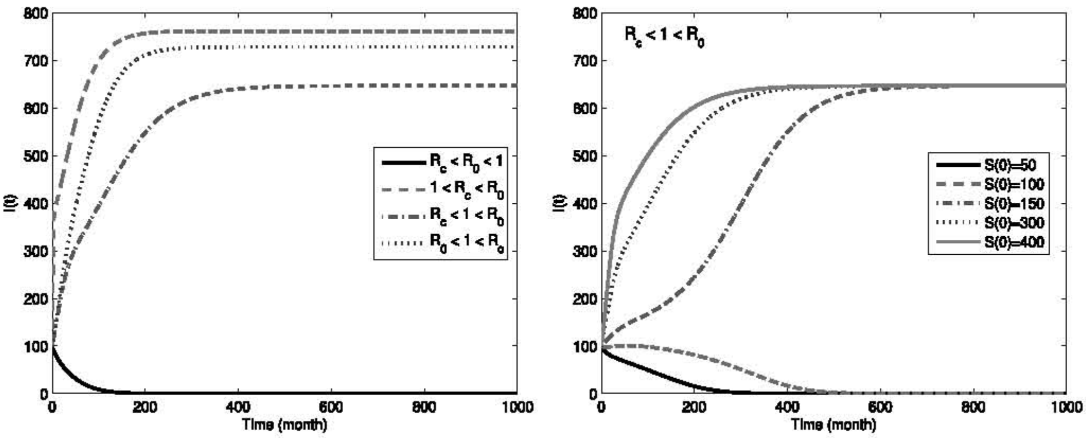

FIGURE 1. The state variable $I(t)$ as a function of time with the different conditions various reproductive numbers and $S(0)$ are considered in the left and right frames, respectively. Note that $I(0) = 100$ is chosen.

Figure 1 illustrates the state variable $I(t)$ as a function of time with the different conditions. The left panel shows that the different conditions of thresholds, R_c and R_0, determine whether ecstasy will become an endemic. The right panel shows that the asymptotical behavior of $I(t)$ depends on initial conditions of $S(t)$ when $R_c < 1 < R_0$. In Figure 1, the left panel indicates that the existence of endemic equilibria is possible even when $R_0 < 1$ and the right panel indicates that when S_0 is small enough, $I(t)$ will go to zero even if $R_0 > 1$. We now choose the three scenarios which have the endemic equilibrium and apply optimal control theory to the system (1) in each scenario. The detailed parameters in each scenario are given in Table 1.

TABLE 1. Parameters

Parameter	**Scenario 1** $1 < R_c < R_0$	**Scenario 2** $R_c < 1 < R_0$	**Scenario 3** $R_0 < 1 < R_c$
ϕ	2.75	0.275	0.275
μ	0.007	0.007	0.007
ε	0.0391	0.03	0.0391
δ_s	0.032	0.032	0.032
δ_v	0.05	0.05	0.05
γ	0.011	0.011	0.011
τ	0.016	0.016	0.016
α	0.5	0.5	0.5
R_c	1.00256	0.76923	1.00256
R_0	1.13919	36.39706	0.11392

2.3. **Control strategies.** We have proposed two strategies to minimize the ecstasy use group, I: one is a direct policy (Strategy 1) to reduce I population. The controls $u_1(t)$ and $u_2(t)$ associated with the distancing factor ϕ and relapse rate α are, respectively, considered in Strategy 1. Another is an indirect policy (Strategy 2) to control I population. The controls $u_3(t)$ and $u_4(t)$ associated with peer pressure factors ϵ and δ_s to become core-susceptible and non-core population are introduced in Strategy 2, in order to reduce the core-susceptible S population.

We assume all controls are regarded as effort over [0,1]. The extreme values, 0 and 1, represent as no-effort and full-effort, respectively. The term, $1 - u_1(t)$, is the effort to reduce the movement of individuals from S class to I class. For instance, making strong policies to enter club may keep away ecstasy users from clubs. The first control $u_1(t)$ is called distancing control. The term, $1 - u_2(t)$, is the effort to prevent a recurrence of taking ecstasy. One of these strategies is to set restricted areas of clubs and bars for V individuals during the full length of time recommended as after care. The second control $u_2(t)$ is relapse control. The third and fourth controls, $u_3(t)$ and $u_4(t)$, are behavior changing controls. The term $1 - u_3(t)$ is the effort to protect noncore individuals from the peer pressure of core population. To do so, the changing culture is one of important issues. Creating a sound culture atmosphere, such that sports activities or family gatherings, changes the individuals' curiosity about the rave and nightclub culture. Moreover, education in childhood for harm effects of taking drugs or going nightclubs is one of the important strategies. The control $u_4(t)$ is the effort to increase the movement from the susceptible class S to noncore class A with the maximum rate, δ_s (see Table 1). For instance, holding a local sports events or festivals that teenagers can also participate, so people can join these events instead of going to clubs.

Our goal is to minimize ecstasy users (I) while keeping the intervention cost low. We consider Strategy 1 and Strategy 2 as follows:

Direct strategy (Strategy 1): distancing control ($\mathbf{u_1(t)}$), relapse control ($\mathbf{u_2(t)}$)
Objective functional is J_1, and our goal is to find an optimal control pair (u_1^*, u_2^*).

$$\min_{\Omega_1} J_1(u_1, u_2) = \int_0^T [I(t) + \frac{1}{2}B_1 u_1^2(t) + \frac{1}{2}B_2 u_2^2(t)]dt, \tag{2.2}$$

where $\Omega_1 = \{(u_1, u_2) \in L^1(0,T) | 0 \le u_i \le 1, i = 1, 2\}$, subject to

$$\begin{aligned}
\frac{dA}{dt} &= \mu P + \delta_v A\frac{V}{P} + \delta_s A\frac{S}{P} - \varepsilon A\frac{S+I}{P} - \mu A, \\
\frac{dS}{dt} &= \varepsilon A\frac{S+I}{P} - \delta_s A\frac{S}{P} - (1-u_1(t))\phi S\frac{I}{P} - \mu S, \\
\frac{dI}{dt} &= (1-u_1(t))\phi S\frac{I}{P} + (1-u_2(t))\alpha I\frac{V}{P} - \gamma I\frac{A+S+V}{P} \\
&\quad - \tau I - \mu I, \\
\frac{dV}{dt} &= \gamma I\frac{A+S+V}{P} + \tau I - \delta_v A\frac{V}{P} - (1-u_2(t))\alpha I\frac{V}{P} - \mu V.
\end{aligned} \tag{2.3}$$

Indirect strategy (Strategy 2): behavior changing controls ($\mathbf{u_3(t)}, \mathbf{u_4(t)}$)
Objective functional is J_2, and our goal is to find an optimal control pair (u_3^*, u_4^*).

$$\min_{\Omega_2} J_2(u_3, u_4) = \int_0^T [I(t) + \frac{1}{2}B_3 u_3^2(t) + \frac{1}{2}B_4 u_4^2(t)]dt, \tag{2.4}$$

where $\Omega_2 = \{(u_3, u_4) \in L^1(0,T) | 0 \le u_i \le 1, i = 3, 4\}$, subject to

$$\begin{aligned}
\frac{dA}{dt} &= \mu P + \delta_v A\frac{V}{P} + u_4(t)\delta_s A\frac{S}{P} - (1-u_3(t))\varepsilon A\frac{S+I}{P} - \mu A, \\
\frac{dS}{dt} &= (1-u_3(t))\varepsilon A\frac{S+I}{P} - u_4(t)\delta_s A\frac{S}{P} - \phi S\frac{I}{P} - \mu S, \\
\frac{dI}{dt} &= \phi S\frac{I}{P} + \alpha I\frac{V}{P} - \gamma I\frac{A+S+V}{P} - \tau I - \mu I, \\
\frac{dV}{dt} &= \gamma I\frac{A+S+V}{P} + \tau I - \delta_v A\frac{V}{P} - \alpha I\frac{V}{P} - \mu V.
\end{aligned} \tag{2.5}$$

We assume that the costs are nonlinear in the quadratic forms. The weight coefficients B_i for $i = 1, \cdots, 4$ are balancing cost factors because of size and importance of other parts in the objective functional.

3. RESULTS AND DISCUSSION

In this section, we investigate numerically optimal strategies to reduce the ecstasy use class. Optimal solutions are obtained by solving an optimality system which is composed of the state system, the adjoint system and the optimality equations. We use an iterative method to obtain the optimal solutions as follows: first the state system is solved with guessed controls over the simulated time using a forward scheme. The adjoint system with the transversality conditions is solved by the backward scheme using the updated state variables and the guessed controls. Then the controls are updated by using a convex combination of the previous controls and the characterized control values. This process is repeated and finally the iteration is stopped when the unknown variables between the previous iteration and the current iteration are close enough.

We shall now investigate optimal strategies under three different scenarios in Table 1. In each scenario, two different strategies (Strategy 1 and Strategy 2) are considered. The parameters for each scenario are given in Table 1 and the initial values of state variables are considered as $A(0) = 600$, $S(0) = 300$, $I(0) = 100$, $V(0) = 0$. In all simulations the simulated duration, 240 months, and the time step, $dt = 0.1$, are chosen. The cost coefficients ($B_1 = 1, B_2 = 1, B_3 = 1, B_4 = 1$) are used as the default values in our simulations. In each scenario, we calculate the relative cost using the control. The relative cost associated with $u_i(t)$, Cu_i during the simulated time is defined as follows:

$$Cu_i = \sum_{j=1}^{N} \frac{1}{2} B_i u_{i,j}^2 dt \quad \text{for } i = 1,\ 2,\ 3,\ 4. \tag{3.1}$$

The relative total cost (TC) for Strategy 1 and Strategy 2 are, respectively, $\sum_{j=1}^{N} \frac{1}{2}(B_1 u_{1,j}^2 + B_2 u_{2,j}^2)dt$ and $\sum_{j=1}^{N} \frac{1}{2}(B_3 u_{3,j}^2 + B_4 u_{4,j}^2)dt$, where N is the total number of timestep and $u_j = u((j-1)dt)$.

We have investigated the direct (Strategy 1) and indirect (Strategy 2) control strategies to reduce the ecstasy user group for three scenarios. In Figures 2- 4, the optimal controls and the corresponding state variables as functions of time are, respectively, displayed in the top two frames and bottom two frames. The blue dashed, red dash-dotted and black solid curves represent, respectively, Strategy 1, Strategy 2 and the case without controls, respectively. Before the detailed analysis of strategies for each scenario, we would like to emphasize that "Strategy 1 (direct strategy) is more efficient than Strategy 2 (indirect strategy) for all scenarios".

Scenario 1 ($1 < R_c < R_0$) is considered in Figure 2. Note that $R_c = 1.00256$ and $R_0 = 1.13919$ are considered in Scenario 1. The left top two frames represent optimal controls $u_1(t)$ and $u_2(t)$ in Strategy 1. The controls $u_1(t)$ is fully used during almost simulated time, while $u_2(t)$ is fully applied to the first 90 months and then it is rapidly decreased to almost zero.

TABLE 2. Relative costs for Strategy 1 and Strategy 2 in three scenarios. Note that, $A(0) = 600,\ S(0) = 300,\ I(0) = 100$ and $V(0) = 0$.

		Scenario 1	Scenario 2	Scenario 3
Strategy 1	u1	116.805	79.359	97.600
	u2	45.643	44.478	45.950
	total	162.488	123.838	143.550
Strategy 2	u3	104.016	80.783	83.707
	u4	3.887	40.807	40.803
	total	107.903	121.590	124.510

The corresponding optimal solution, ecstasy users $I(t)$, is decreased to zero near 70 months. This implies that the effort to reduce, ϕ, the peer pressure rate of ecstasy users on susceptible populations, $u_1(t)$, plays the most effective control to minimize the ecstasy use class in Strategy 1. The right top two frames represent optimal controls $u_3(t)$ and $u_4(t)$ in Strategy 2. At a glance, we observe that the control associated with the peer pressure factor ϵ to become core-susceptible population, $u_3(t)$, is more dominated than one associated with the peer pressure factor δ_s to become non-core population, $u_4(t)$. As we expected, the S population rapidly become a zero state, and the I population has a peak and then it is reduced smoothly to zero near 200 months. The relative total amount (TC) for Strategy 1 and Strategy 2 are around 162.5 and 107.9, respectively. Although the TC for Strategy 2 is cheaper than one for Strategy 1, it takes much longer period to reduce the ecstasy users $I(t)$. Strategy 1 might be the better choice if the intervention is focused on controlling the ecstasy users.

Now we consider Scenario 2 ($R_c < 1 < R_0$; $R_c = 0.76923,\ R_0 = 36.39706$) and Scenario 3 ($R_0 < 1 < R_c$; $R_c = 1.00256,\ R_0 = 0.11392$) together. All parameters are the same in two scenarios except recruitment into the core-susceptible class, ϵ, (see Table 1). Although one threshold condition seems to predict against the grow of ecstasy users, a sudden increase in ecstasy user class can be driven if we do not consider control strategies (see the black solid I in Figure 3 and Figure 4). Figure 3 and Figure 4 depict the results of Scenario 2 and Scenario 3, respectively. The optimal solutions of these scenarios are qualitatively similar. In Strategy 1 the distancing control, ϕ, plays an important factor and the ecstasy users are decayed to zero without peak. On the other hand, in Strategy 2 the peer pressure of recruitment into the core-susceptible class, ϵ, has a dominated role to reduce the ecstasy users. Note that the ecstasy user class I has a peak and then it is smoothly reduced to zero after the long period. The relative total costs of Strategy 1 and Strategy 2 are, respectively around 124 and 122 in Scenario 2. And the relative total costs of Strategy 1 and Strategy 2 are, respectively, around 144 and 125 in Scenario 3. Since the relative total costs of Strategy 1 and Strategy 2 are in the similar order, Strategy 1 might be the better one to control fast reduction of ecstasy users as if Scenario 1.

Remind that $I(0) = 100$ is chosen as a default initial value for the ecstasy user class. We now consider ten initial values of I, $I(0) = 10, 20, \cdots, 100$. The initial values of A, $S+I$, and

V are fixed as 600, 400, and 0, respectively. Figure 5 displays each Cu_i for $i = 1, \cdots, 4$ and TC of Strategy 1 and Strategy 2 in three scenarios. If we compare only cost, then the relative total costs associated with Strategy 1 are more expensive than one with Strategy 2 in all three scenarios. However, the fast reduction of ecstasy users can be observed in Strategy 1. Let's consider Strategy 1 in three scenarios (see the left three column frames in Figure 5). If $I(0)$ is small enough, $u_1(t)$ associated with ϕ plays a dominated role; the relapse control associated with α can be ignored. Another observation for the case with small $I(0)$ is that Strategy 1 is cheaper and more effective control strategy than Strategy 2 in Scenario 2 and Scenario 3. If the strategy is focused on the indirect method (Strategy 2), then the control $u_3(t)$ associated with peer pressure of recruitment into the core-susceptible, ϵ, is the most important control factor to reduce the ecstasy user class. Especially it is happened in Scenario 1 (see the right top frame in Figure 5).

4. Summary and conclusions

We have applied the control mechanism to a mathematical model of ecstasy developed by Song et al. [1] and proposed optimal strategies for prevention of ecstasy users. In their model, the endemic equilibriums exist although the repreductive number is less than one. This result is induced by the peer pressure in the model.

We have considered three scenarios based on their observation and two strategies have been investigated in each scenario. In Strategy 1, the distancing and relapse controls are introduced. This control strategy is a direct way to reduce the ecstasy users. In Strategy 2, two behavior changing controls are considered. This strategy is an indirect way to minimize the ecstasy users by reducing the susceptible individuals who do not use ecstasy but are likely to become ecstasy users.

In this study, we have observed the important features of intervention strategy for prevention ecstasy users. The distancing control $u_1(t)$ associated with peer pressure of ecstasy users on core-susceptible, ϕ, is the most significant control factor to get fast reduction of ecstasy users. We could also get the reduction of ecstasy users by focusing on behavior controls (Strategy 2: indirect strategy). In this case, the behavior control $u_3(t)$ associated with peer pressure of the core population on the non-core population, ϵ, plays a major role to control the ecstasy users.

Overall, these optimal strategies can solve the serious problem of ecstasy use in our society. Not only the distancing control of ecstasy user but also the education efforts of keeping young adults from seeking the excitement of raves and nightclubs should be focused on control strategy of peer-driven ecstasy users.

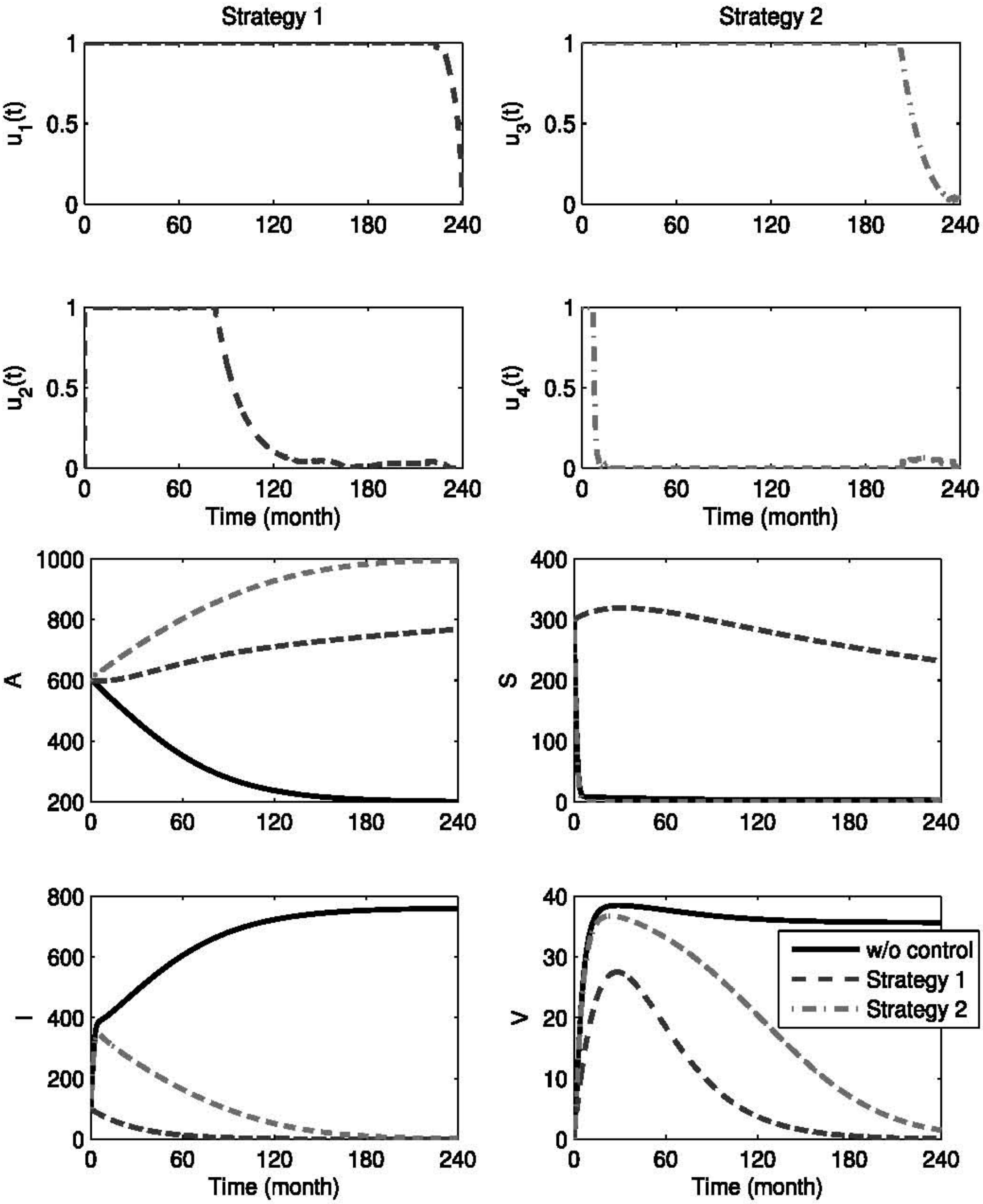

FIGURE 2. The optimal controls and state variables of Strategy 1 and Strategy 2 for Scenario 1 are displayed as functions of time.

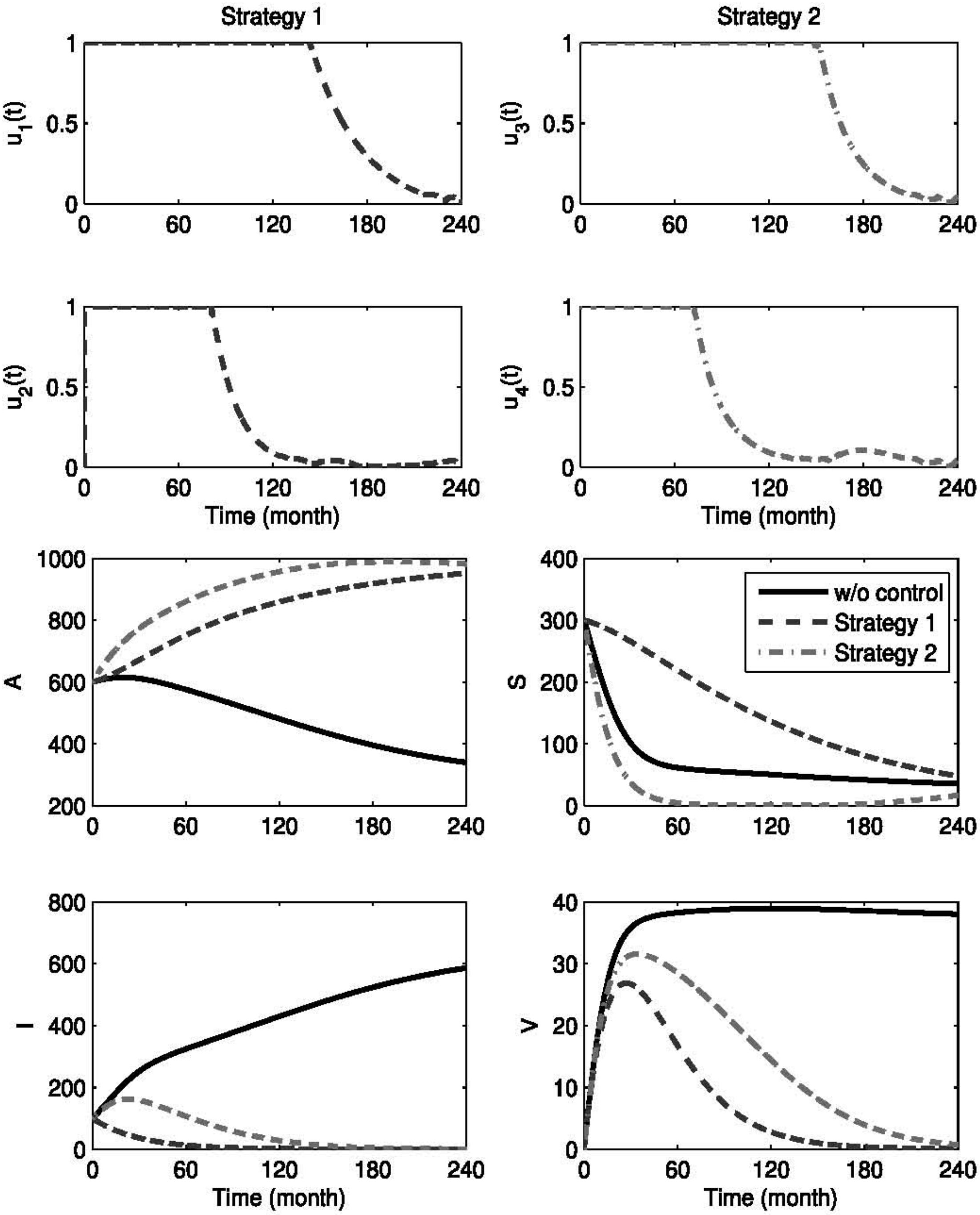

FIGURE 3. The optimal controls and state variables of Strategy 1 and Strategy 2 for Scenario 2 are displayed as functions of time.

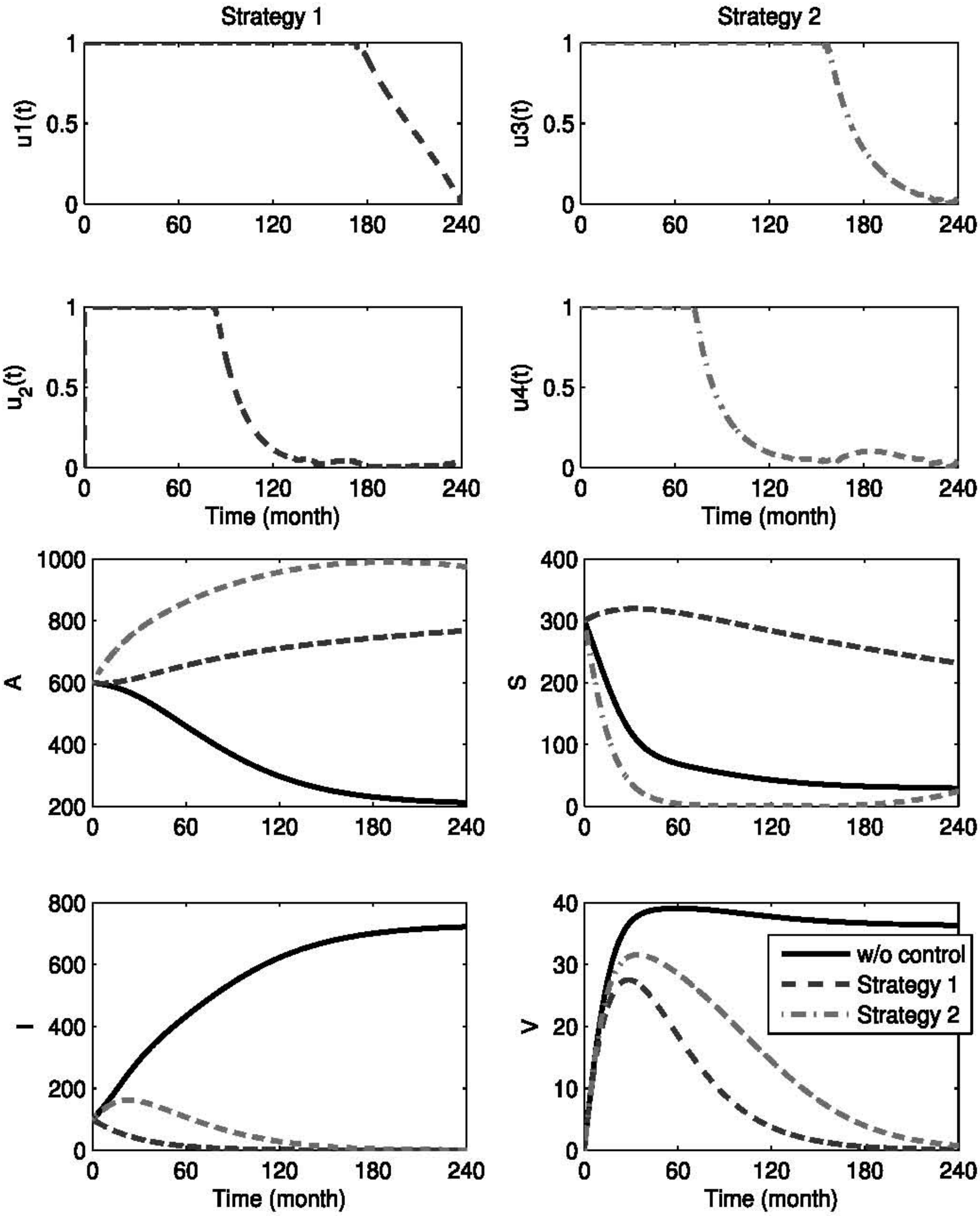

FIGURE 4. The optimal controls and state variables of Strategy 1 and Strategy 2 for Scenario 3 are displayed as functions of time.

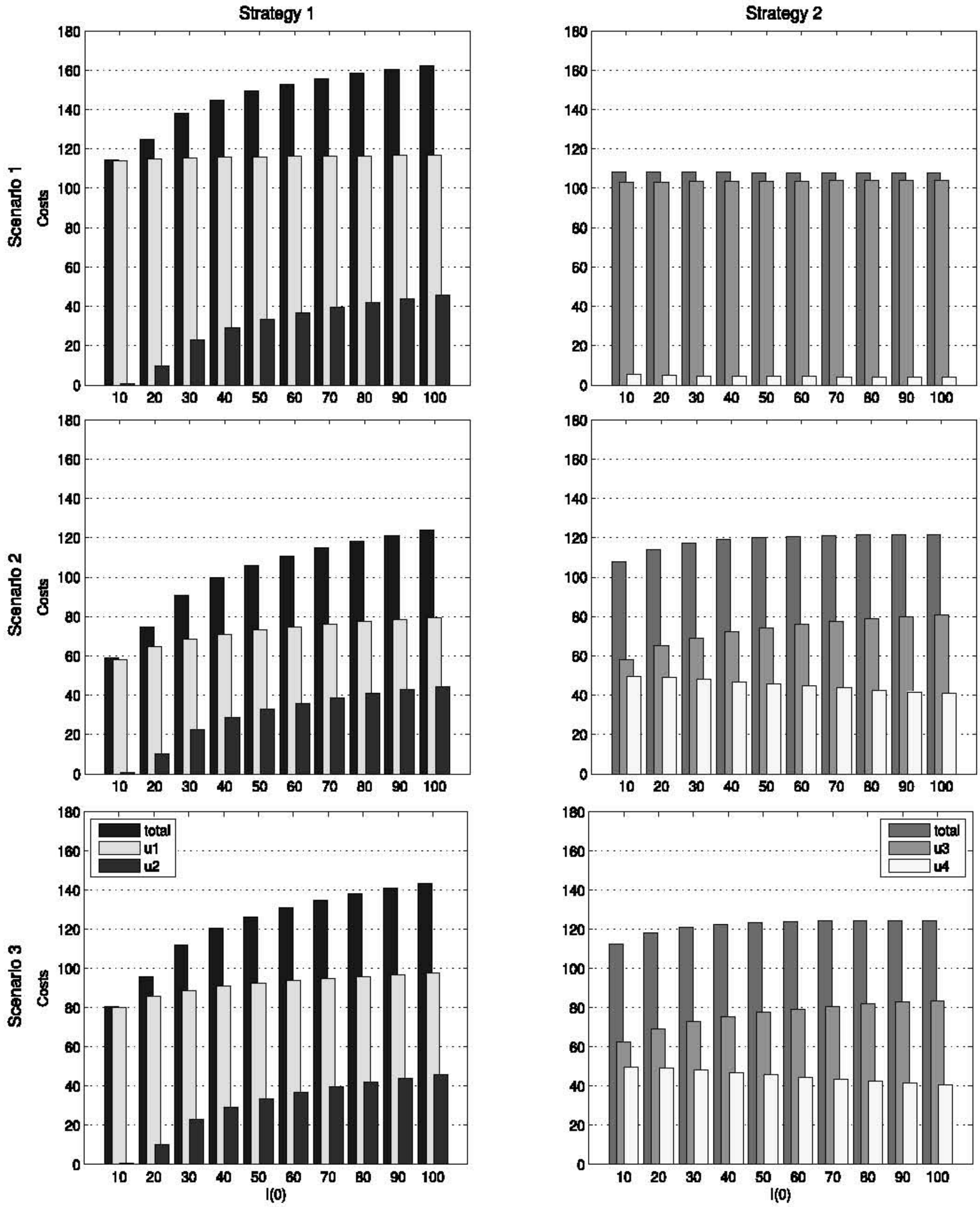

FIGURE 5. Relative costs

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APPENDIX: ANALYSIS OF OPTIMAL CONTROLS

Pontryagin's Maximum Principle [15] states the necessary conditions that optimal solutions must satisfy. By using this principle, a problem of finding optimal control is converted into a problem of minimizing a pointwise Hamiltonian, H, with respect to the controls, u_1, u_2, u_3.

$$H = I + \frac{B_1}{2}{u_1}^2 + \frac{B_2}{2}{u_2}^2 + \sum_{i=1}^{4} \lambda_i g_i, \tag{4.1}$$

where g_i is the right hand side of the ith state equation. An optimal control pair exists because of the convexity of integrand of J with respect to the controls, a priori boundedness of the state solutions, and the Lipschitz property of the state system with respect to the state variables. We obtain the following theorem from Pontryagin's Maximum Principle [15] and the existence of the optimal control pairs [24].

Theorem 4.1. *Suppose optimal controls u_i^* and solutions A^*, S^*, I^*, V^* of the corresponding state System are given, then there are exists adjoint variables $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ satisfying*

$$\begin{aligned}
\dot{\lambda_1} &= -\lambda_1(\delta_v \frac{V^*}{P^*} + \delta_s \frac{S^*}{P^*} - \epsilon \frac{S^*+I^*}{P^*} - \mu) - \lambda_2(\epsilon \frac{S^*+I^*}{P^*} - \delta_s \frac{S^*}{P^*}) \\
&\quad + \lambda_3 \gamma \frac{I^*}{P^*} - \lambda_4(\gamma \frac{I^*}{P^*} - \delta_v \frac{V^*}{P^*}), \\
\dot{\lambda_2} &= -\lambda_1(\delta_s \frac{A^*}{P^*} - \epsilon \frac{A^*}{P^*}) - \lambda_2(\epsilon \frac{A^*}{P^*} - \delta_s \frac{A^*}{P^*} - (1-u_1)\phi \frac{I^*}{P^*} - \mu) \\
&\quad - \lambda_3((1-u_1)\phi \frac{I^*}{P^*} - \gamma \frac{I^*}{P^*}) - \lambda_4 \gamma \frac{I^*}{P^*}, \\
\dot{\lambda_3} &= -1 + \lambda_1 \epsilon \frac{A^*}{P^*} - \lambda_2(\epsilon \frac{A^*}{P^*} - (1-u_1)\phi \frac{S^*}{P^*}) \\
&\quad - \lambda_3((1-u_1)\phi \frac{S^*}{P^*} + (1-u_2)\alpha \frac{V^*}{P^*} - \gamma \frac{A^*+S^*+V^*}{P^*} - \tau \\
&\quad - \mu) - \lambda_4(\gamma \frac{A^*+S^*+V^*}{P^*} + \tau - (1-u_2)\alpha \frac{V^*}{P^*}), \\
\dot{\lambda_4} &= -\lambda_1 \delta_v \frac{A^*}{P^*} - \lambda_3((1-u_2)\alpha \frac{I^*}{P^*} - \gamma \frac{I^*}{P^*}) - \lambda_4(\gamma \frac{I^*}{P^*} - \delta_v \frac{A^*}{P^*} \\
&\quad - (1-u_2)\alpha \frac{I^*}{P^*} - \mu),
\end{aligned} \tag{4.2}$$

and

$$\lambda_1(T) = ... = \lambda_4(T) = 0. \tag{4.3}$$

Furthermore

$$\begin{aligned} u_1^* &= min\Big\{max\Big\{0, \phi S^* \frac{I^*}{P^*} \frac{\lambda_3 - \lambda_2}{B_1}\Big\}, 1\Big\}, \\ u_2^* &= min\Big\{max\Big\{0, \alpha I^* \frac{V^*}{P^*} \frac{\lambda_3 - \lambda_4}{B_2}\Big\}, 1\Big\}. \end{aligned}$$

Proof: Applying Pontryagin's Maximum Principle, we obtain the following adjoint system with the transversality conditions:

$$\frac{d\lambda_1}{dt} = -\frac{dH}{dA}, \ \frac{d\lambda_2}{dt} = -\frac{dH}{dS}, \quad \frac{d\lambda_3}{dt} = -\frac{dH}{dI}, \quad \frac{d\lambda_4}{dt} = -\frac{dH}{dV}$$

and

$$\lambda_1(T) = \cdots = \lambda_4(T) = 0.$$

This adjoint system is evaluated at the optimal control pair and corresponding states, and this gives the system (4.2) and (4.3).

By considering the optimality conditions,

$$\begin{aligned} \frac{dH}{du_1} &= B_1 u_1 + \lambda_2 \phi S \frac{I}{P} - \lambda_3 \phi I \frac{S}{P} = 0, \\ \frac{dH}{du_2} &= B_2 u_2 - \lambda_3 \alpha I \frac{V}{P} + \lambda_4 \alpha V \frac{I}{P} = 0. \end{aligned}$$

at ${u_i}^*$ on the set $\{t|0 < {u_i}^*(t) < 1 \text{ for } i = 1, 2\}$. On this set,

$$\begin{aligned} u_1^* &= \phi S^* \frac{I^*}{P^*} \frac{\lambda_3 - \lambda_2}{B_1}, \\ u_2^* &= \alpha I^* \frac{V^*}{P^*} \frac{\lambda_3 - \lambda_4}{B_2}. \end{aligned}$$

With the bounds on controls, we obtain the characterization of u_1^* and u_2^* in (4.4).

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