Managing infectious diseases over connected populations: a non-convex optimal control

Ceddia, M Graziano

Department of Agricultural and Food Economics, University of Reading

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M.G. Ceddia

Department of Agricultural and Food Economics

University of Reading

Email: m.ceddia@reading.ac.uk

Abstract

The paper develops an optimal control model to analyse various management options for infectious diseases that occur in metapopulations, under both Nash and cooperative behaviour. As pathogens are renewable resources with negative value, the problem may be non-convex. Since the disease can be transmitted across various connected populations, externalities are involved. Both aspects deserve attention as two issues arise: a) is eradication of the disease in finite time preferable to indefinite treatment? b) are cooperative solutions well-behaved? The problem is solved numerically and the results indicate that while eradication is likely to be an optimal strategy when initial levels of infections are relatively low, the internalisation of between-population externalities (as indicated by the first order necessary conditions of the cooperative optimal control problem) might not always be possible. Also, ignoring these two aspects can lead to inadequate policy design.

Keywords: infectious diseases; metapopulation; non-convexities; optimal control.

1 Introduction

The emergence of new infectious diseases has gained significant attention on the policy agenda as recent initiatives both in the USA and in the UK call for interdisciplinary research to better understand the spread and to better manage infectious agents[1]. Traditionally, the study of disease dynamics has been the realm of mathematical epidemiology (e.g., Bailey 1975; Anderson and May 1991), whose initial remit has been to understand the properties of a system invaded by a pathogen.

One prominent concept in epidemiology is the basic reproductive ratio of an infection (or other metrics related to it, e.g., Roberts and Heesterbeek 2003), also known as R_0, which indicates the number of secondary cases of infections generated by one primary case. As in an uninvaded system the infection will spread if and only if $R_0>1$, the epidemiological literature focuses on control measure that can bring $R_0<1$ so as to achieve eradication in finite time. As it is not clear how control should be distributed over time, it is commonly assumed that the effort should be constant over time (e.g., Anderson and May 1991).

More recently bioeconomic approaches to disease management have been advocated (e.g., Fenichel et al. 2010; Fenichel and Horan 2007, a, b; Barrett and Hoel 2007), since infectious diseases can be modelled as a renewable resource with negative value whose control through the use of limited means involves trade-offs. It is normal to frame the disease management question into an optimal control (OC) problem requiring the maximisation of some objective function depending on the fraction of healthy and susceptible individuals and control costs, given some initial conditions and the equations describing the dynamics of the infection. The main contrasts between the bioeconomic approaches and those based solely on mathematical epidemiology concern the desirability of eradication (compared to other possible outcomes, like steady-state solutions) and the resulting optimal allocation of control effort over time (as

opposed to a constant control). Gersovitz (2003) asks *"whether settling for an internal steady-state with positive infection is dominated by a push for eradication in finite time"* (as reported in Barrett and Hoel 2007 p. 629). The question of whether it is optimal to exhaust a renewable resource (like a disease) in finite time or to maintain the system indefinitively in steady-state is not new in economics and relates to the existence of non-convexities. Lewis and Schmalensee (1977), for example, look at the optimal management of a renewable resource (a fishery) when non-convexities (due to the presence of fixed costs) exist. In particular they compare two sets of policies: a) driving the system towards a steady-state in an infinitely long horizon (the 'continuous harvesting solution') and b) exhausting the resource in finite time (the 'abandonment solution'). Because of the fixed costs, convergence to the steady-state might not be optimal. In fact the authors claim that *"…the presence of non-convexities can radically alter the nature of the optimal resource management strategy. Without numerically evaluating alternative payoffs, one cannot be sure in general that continuous harvesting will be superior to abandonment"* (p. 348). In the case of infectious diseases non-convexities could arise because the resource under consideration has a negative value (Rondeau 2001). Barrett and Hoel (2007) develop a theoretical model and derive an intuitive cost-benefit rule for eradication (i.e., when the marginal costs of vaccination are relatively low compared to the 'discounted' marginal damages of the infection). This paper also extends their analysis to the case of multiple connected populations.

Early models of epidemics assumed a single homogenous population (Keeling and Rohani 2008, provide a good introduction), while subsequently this restrictive assumption has been relaxed in order to allow for heterogeneity, as contact rates between different subgroups in the population are likely to vary. Among the many factors which determine the degree of heterogeneity in a given population, the spatial distribution of its various subgroups is

particularly important in explaining the probability of a system being invaded and the persistence of the infection (Park et al. 2001; Keeling 1999; Hagenaars et al. 2004). The recent cases of swine flu pandemics and avian influenza show the importance of spatial connectivity in disease dynamics, as some diseases can be transmitted over long ranges by migrating populations (Waldenström et al. 2007; Stallknecht and Brown 2007) and/or through travel and trade (Kilpatrick et al. 2006).

The management of infectious diseases over a number of separate but connected populations is likely to involve reciprocal externalities, as control of the disease in one particular region will generate some benefits to all regions (e.g., Barrett 2003; Sandler and Arce 2002). It is then natural to model the non-cooperative solution, to identify the corresponding Nash equilibria, and the cooperative solution, to identify the optimal management rule. In fact, by comparing the first order necessary conditions (FONC) of the cooperative solution with those of the non-cooperative one, it should be possible to identify a suitable way (e.g., taxes, subsidies, etc.) to internalise the externalities and ameliorate welfare. However, if the problem is non-convex can the FONC still be relied upon to indicate the appropriate strategy to internalize the externalities? To the best of my knowledge, this aspect has not been formally addressed yet in the context of infectious diseases. Rowthorn et al. (2009), for example, apply an OC framework to the management of an infectious disease over two connected populations, but they only consider the cooperative solution. Similarly, Mbah and Gilligan (2009) consider an analogous problem, where disease transmission between different species is allowed. The purpose of this paper is then to shed light on the implications of non-convexities, for the optimal management of an infectious disease occurring over several connected populations, with respect to: a) the choice between eradication policies and convergence to steady-states and b) the ability to identify a suitable way to internalise the disease spill over.

2 Spatial models of epidemics

Several approaches have been explored in order to deal with the effects of spatial heterogeneity on epidemics (e.g., McCallum 2008). The most common ones fall in the following categories: reaction-diffusion models, network models and metapopulation models. Such a classification is not clear-cut as, for example, network approaches (e.g., lattice and cellular automata) have been used to study the behaviour of a metapopulation. In this section I will focus on network models and metapopulation models, as diffusion-reaction models can be thought of as a special case of the metapopulation approach (Smith et al. 2009).

2.1 Networks and epidemics

In network models each individual is assigned a fixed set of 'contacts' to which it can transmit the infection (see Keeling and Eames 2005, for a review of network models in epidemics). Here I will refer to network models as those in which, each node is the smallest unit of analysis (e.g., infected person or infected premise) and the dynamic processes within the node are not considered. The attention is focused on characterizing the network structure (e.g. small-world, scale-free, random, lattice etc.) for the disease under consideration and, through computer simulations, understanding the implications for the disease dynamics. So for example, it appears that infectious diseases can spread more easily in scale-free and small-world networks than in regular lattices and random networks. Closely related to the network approach is the use of lattice/cellular automata (LCA) models, which allows explicit representation of the spatial distribution of the nodes. LCA models are discrete dynamical system formed by a finite number of cells, where each cell is endowed with a state (e.g. susceptible, infected, recovered etc.) which changes at each step following a transition rule (e.g., White et al. 2007). In LCA models the

spread of the disease occurs through the interaction between each individual/node with its immediate neighbourhood. Su et al. (2009), for example, use a LCA model to investigate the effects of spatial clustering and habitat loss on a parasite-host (prey-predator) system and their results show that both phenomena (i.e., habitat loss and degree of clustering) have important consequences on both the dynamics and equilibrium of the system.

2.2 Metapopulation and epidemics

The metapopulation[2] framework (Levin 1976), on the other hand, provides a useful starting point to address the issue of spatial heterogeneity in epidemiological models in situations where one wants to investigate also the dynamics within each local deme. Indeed the way Rowthorn et al. (2009) and Mbah and Gilligan (2009) deal with spatial heterogeneity in their epidemiological framework closely resembles a metapopulation approach. Metapopulation frameworks have also been used to explore the effect of host mobility (Rodriguez and Torres-Sorando, 2001) on disease dynamics.

3 The ecological constraints and the ecological approach to infectious diseases policies

I begin with the characterisation of the epidemiological model which underlies the entire analysis. Consider the case of an infectious disease occurring in two[3] spatially distinct populations (regions) and allow for transmission between these populations to occur. The dynamics of the disease in the i-th region are expressed in terms of a classical Susceptible-Infected-Susceptible (SIS) model with total (constant) population N_i, i=1,2. This class of models is appropriate to describe bacterial or parasitic infections for which no permanent immunity exists (see Bailey 1975, for an introduction to the SIS model). The population is partitioned into

susceptible (S_i) and infected/infectious (I_i) individuals. If disease transmission between individuals of different populations is allowed, the equations of motion of the infection[4] can be expressed as follows (e.g., Rowthorn et al. 2009)

$$\dot{I}_i = \beta_i(N_i - I_i)I_i - \alpha_i u_i - \omega_i I_i + p_{ji}(N_i - I_i)I_j, \; i = 1,2 \; and \; j \neq i \quad (1)$$

where u_i represents the level of (public/collective) control (treatment)[5] in the i-th region, α_i is the effectiveness of the control, β_i is the infectiousness of the disease, ω_i is the recovery rate associated with the disease (ω^{-1} is the duration of the disease) and p_{ji} indicates the probability of disease transmission from the j-th to the i-th region. This version of the SIS model is relatively simple as it ignores the fact that some parameter values might change with the progression of the epidemics, for example as a result of individuals' defensive behavior (D'Onofrio and Mandfredi 2009). Such a simplification is introduced in order to focus the attention on public management decisions of epidemics (u_i in this case).

One way to illustrate the dynamics of the system is to draw the zero-isoclines associated with (1). The important thing to notice is that at this stage the controls (u_i) enter the equations of motion as exogenous factors.

[Figure 1 here]

For example, in figure 1, I parameterize (1) and represent the dynamics for three different levels of control. The left panel is drawn for $u_1=u_2=0$. In the un-controlled system there is

only one steady-state (which is a locally asymptotically stable node), other than the origin (which is unstable), and the infection will naturally progress towards the steady-state. The central panel is drawn for intermediate levels of control ($u_1=u_2=0.2$). In this case the system has two steady-state equilibria: a high infection equilibrium (which is a locally asymptotically stable node) and a low infection equilibrium (which is a saddle point). For intermediate levels of control, eradication (i.e., bringing the system to the origin) is possible, depending on initial conditions. The right panel is drawn for high levels of control ($u_1=u_2=0.3$). In this case the system has two equilibria with complex roots but again eradication is possible, depending on the initial conditions.

Figure 1 provides a representation of the epidemiologists' approach to the management of an infectious disease. Given the prevalence of the disease at a given point in time (the initial conditions of the system), a constant level of control can be determined so as to achieve complete eradication. However, when framing the problem in a bioeconomic fashion the level of control is endogenously determined (e.g., Fenichel et al. 2010) and the phase-space becomes four-dimensional. For this reason the representation in Figure 1 can give only an incomplete picture.

4 Bioeconomic approaches to infectious disease management: the general model

As the ecological constraints have been illustrated, the purpose of this section is to provide a general characterisation of the economic problem at hand. The main objective of the paper is to investigate some of the implications of non-convexities in an OC problem of epidemics management in a metapopulation. As a more detailed discussion on the second order sufficient conditions (SOSC) is presented in subsequent sections and in the Appendix, at this stage it is

important to correctly frame the problem so that admits solution. If an existence theorem applies, then at least one can be sure that the FONC identify the set of candidates for an optimal solution even when the SOSC do not hold (Seierstad and Sydsaeter 1987, p. 11).

The fact that the two populations are connected implies that there is a finite probability p that the infected individuals in one region can transmit the disease to susceptible individuals in the other region, reflecting the existence of an externality. Here I assume that the probability of between-regions disease transmission is exogenously given. Although it is possible to envisage situations in which this hypothesis is not appropriate, there are a number of cases in which it will hold. For example, the connectiveness of two relatively small regions as a result of similarity in climatic conditions is likely to be exogenous, as it is unlikely that the policies followed in such regions could alter the pattern of climate therefore changing the value of p. Similarly the existence of migrating species (e.g., birds) provides a connection path between locations that can be distant even hundreds or thousands of miles and although in principle such migration routes could be altered, in many cases such course of action will be politically or economically unfeasible (e.g., endangered migratory species that nest in natural reserves and carry pathogens that can be transmitted to domesticated species and/or to humans). In these cases adaptation policies are likely to be more important.

Assuming that the infection generates a cost (e.g., people not turning in for work etc.) and that control is costly, the framework is naturally one of cost minimization over time. The objective of the managers will somehow involve choosing the appropriate level of public control/treatment over time to minimize the discounted flow of damages associated with the disease $D_i(I_i)$, with $dD_i/dI_i = D_i' > 0$, $d^2D_i/dI_i^2 = D_i'' \geq 0$, and the costs of its control $C_i(u_i)$, with $dC_i/du_i = C_i' > 0$, $d^2C_i/du_i^2 = C_i'' \geq 0, i = 1,2$. Two possible situations are

considered, namely the case in which each manager (in each region) acts non-cooperatively (i.e., Nash behaviour) and the case in which a single 'meta-regional' manager exists (i.e., cooperative solution).

4.1 The non-cooperative case

Formally, in this case I am interested in finding the Open Loop Nash Equilibrium (OLNE) of a differential game (Basar and Losder 1999). Notice that OLNE solutions need not to be thought of as equilibria emerging in the complete absence of negotiation, but rather they can be thought of as results of negotiations on agreements that are self-enforcing (Dockner and Long 1993). The general problem for the i-th region can be expressed as follows (the problem for region 2 is analogous)

$$Min_{u_i,T} \int_0^T [D_i(I_i) + C_i(u_i)] e^{-\delta t} dt + F_i\big(I_i(T)\big) \quad (2.a)$$

Subject to (1) and

$$I_i(0) = \hat{I}_i \quad (2.b)$$

$$0 \leq I_i(t) \leq 1, 0 \leq u_i \leq \bar{u}_i, I_i(T) \geq 0 \quad (2.c)$$

The term $F_i\big(I_i(T)\big)$ in (2.a) represents the *scrap value* associated with the free terminal stock $I_i(T)$ and I assume $\frac{dF_i}{dI_i(T)} > 0$ and $F_i(0) = 0$. Problem (2.a, 2.b, 2.c) is framed in the most general way, with free terminal state and free terminal horizon (as T is a choice variable in 2.a)

and it encompasses as special cases both eradication in finite time and convergence to steady-state in infinite time. In fact, drawing on Barrett and Hoel (2007) eradication in finite time can be represented by adapting (2.a, 2.c) as follows

$$Min_{u_i,T} \int_0^T [D_i(I_i) + C_i(u_i)] e^{-\delta t} dt \quad (2.d)$$

Subject to (1, 2.b) and

$$0 \leq I_i(t) \leq 1, \; 0 \leq u_i \leq \bar{u}_i, \; I_i(T) = 0 \quad (2.e)$$

As the terminal condition in (2.e) requires eradication by the terminal time T, the scrap value function F_i is omitted from (2.d).

As in Lewis and Schmalensee (1977), convergence to steady-state in infinite time is obtained by modifying (2.a, 2.c) as follows

$$Min_{u_i} \int_0^{\infty} [D_i(I_i) + C_i(u_i)] e^{-\delta t} dt \quad (2.f)$$

Subject to (1, 2.b, 2.c)

Given the infinite horizon, the scrap value function is omitted again.

It is possible to show that problem (2) admits a solution (see Appendix A.1), therefore one can be sure that even if the problem turns out to be non-convex the FONC will identify possible candidates for a solution.

4.2 The cooperative case

In the cooperative case, the general problem can be formulated as follows

$$Min_{u_i,T} \int_0^T \sum_{i=1}^2 [D_i(I_i) + C_i(u_i)]\, e^{-\delta t} dt + \sum_{i=1}^2 F_i\big(I_i(T)\big) \quad (3.a)$$

Subject to (1) and $I_i(0) = \hat{I}_i,\ 0 \le I_i(t) \le 1, I_i(T) \ge 0, 0 \le u_i \le \bar{u}_i,\ i = 1,2$ (3.b)

Even in this case, eradication in finite time is obtained by adapting (3.a, 3.b) as follows

$$Min_{u_i,T} \int_0^T \sum_{i=1}^2 [D_i(I_i) + C_i(u_i)]\, e^{-\delta t} dt \quad (3.c)$$

Subject to (1, 2.b), $0 \le I_i(t) \le 1,\ I_i(T) = 0,\ 0 \le u_i \le \bar{u}_i,\ i = 1,2$ (3.d)

Where the scrap value functions F_i are omitted, as eradication by time T is imposed.

Convergence to steady-state in infinite time is given by (omitting the scrap value functions)

$$Min_{u_i,T} \int_0^\infty \sum_{i=1}^2 [D_i(I_i) + C_i(u_i)]\, e^{-\delta t} dt \quad (3.e)$$

Subject to (1, 3.b)

Problem (3) also admits solution, and the same considerations as before apply.

5 A numerical application

This section develops a numerical application to illustrate the implications of non convexities in the management of epidemics in a metapopulation with respect to a) the choice between eradication in finite time and stabilisation and b) the ability of the FONC associated with the cooperative outcome to signal the proper strategy to internalise the between-region spill over.

The purpose of the application is entirely illustrative, as no attempt has been made to represent a specific situation (although most of the parameter values and functional forms have been chosen so as to resemble the analysis developed by Rowthorn et al. 2009). To some extent, the effect of non-convexities in OC problem have been analysed before. So for example Lewis and Schmalensee (1977) compare steady-state versus exhaustion in finite time of a renewable resource when fixed costs are present. Barrett and Hoel (2007) look at the choice between continuous vaccination and eradication of a disease in finite time. Tahvonen and Salo (1996), Rondeau (2001) and Brock and Starrett (2003) show how in non-convex problems multiple steady-states can emerge and the choice of which steady-state to approach may depend on the system's initial conditions. In all the cases above the analysis was greatly served by the use of graphical illustrations. Unfortunately the dimensionality of the problem does not allow me to rely on graphics and therefore I will rely on numerical solutions. As in Gersovitz and Hammer (2003), although quantitative results are reported, my interest is in their qualitative interpretation. All the numerical solutions have been obtained by using the bvp4c solver (Shampine et al. 2000) in Matlab (© Mathworks).

I consider a symmetric case where the infection damage function is parametrised as $D_i(I_i) = kI_i^2, k = 1, i = 1,2,$ while the treatment cost function is $C_i(u_i) = au_i + bu_i^2, a = b = 1$ and the parameters in the epidemiological model (1) are chosen

as $\beta_1 = \beta_2 = 0.2,\ p_{12} = p_{21} = 0.1,\ \alpha_1 = \alpha_2 = 0.2,\ \omega_1 = \omega_2 = 0.05,\ N_1 = N_2 = 1$ and the discount rate is $\delta = 0.05$.

It has already been pointed out that the general problem admits solution both in the OLNE and in the cooperative case, while SOSC are openly tested in both cases. Two kinds of sufficiency theorems are normally reported in the literature: Mangasarian sufficiency theorems and Arrow-type sufficiency theorems (Seierstad and Sydsaeter 1987; Caputo 2005). Mangasarian sufficiency conditions require the Hamiltonian to be jointly convex in the state and control variable. On the other hand, Arrow-type sufficiency conditions are less stringent (normally they are applied when Mangasarian sufficient conditions fail) and require the Maximised Hamiltonian to be convex in the state variable. I use Arrow-type conditions and show that even though necessary Legendre-Clebsch conditions hold, the sign of the second order differential associated with the maximised Hamiltonian is indefinite, suggesting that the problem is neither convex nor concave (see Appendix A.2).

5.1 The OLNE

In the non-cooperative case I consider a) optimal eradication in finite time and b) convergence to a steady-state in infinite time. The problem is solved numerically by considering three different initial conditions.

5.1.1 Eradication in finite time

Due to the symmetric nature of the differential game eradication will be simultaneous in the two regions. Given the chosen functional forms, problem (2.d, 2.e) becomes

$$Min_{u_i,T} \int_0^T (kI_i^2 + au_i + bu_i^2)e^{-\delta t} dt \quad (4.a)$$

subject to (1), $0 \leq I_i(t) \leq 1, 0 \leq u_i(t) \leq \bar{u}_i$ and $I_i(0) = \hat{I}_i$ (4.b)

and $I_i(T) = 0$ (4.c)

The current value Hamiltonian associated with (4) is

$$\tilde{H}_i = kI_i^2 + au_i + bu_i^2 + \mu_i \dot{I}_i \quad (5)$$

and the FONC for an internal solution include (1) and

$$\frac{\partial \tilde{H}_i}{\partial u_i} = a + 2bu_i - \alpha_i \mu_i = 0 \rightarrow \mu_i = \frac{a+2bu_i}{\alpha_i} > 0 \quad (6.a)$$

$$\dot{\mu}_i - \delta \mu_i = -\frac{\partial \tilde{H}_i}{\partial I_i} = -\left[\mu_i(\beta_i N_i - 2\beta_i I_i - p_{ji} I_j - \omega_i)\right] - 2kI_i \quad (6.b)$$

$$\tilde{H}_i(T) = 0 \quad (6.c)$$

$$\mu_i(T) > 0 \quad (6.d)$$

Through some manipulation (6.a, 6.b) can be used to obtain an equation of motion in the control variable

$$\dot{u}_i = \frac{a+2bu_i}{2b}\left(\delta + \omega_i + 2\beta_i I_i + p_{ji} I_j - \beta_i N_i\right) - \frac{\alpha k I_i}{b} \quad (7)$$

The four-equation system (7, 1) is a boundary value problem (BVP) with initial conditions given by $I_i(0) = \hat{I}_i$ terminal conditions given by $I_i(T) = 0,\ i = 1,2$ and is solved numerically with the bvp4c routine by implementing a shooting method (Judd 1998). As in this problem the terminal time T is free, I use condition (6.c) to identify its optimal value. After substituting (6.a) in (6.c), the latter implies $u_i(T)=0$. The value of T in the BVP problem is then adjusted so as to meet this condition.

When the initial level of infection is relatively low, with $\hat{I}_i = 0.2$, eradication occurs in T=7 and the net present value (NPV) of the programme stands at £ 2.196 (in each region). The corresponding time path of the disease prevalence $I_1(t)$ and control $u_1(t)$ for region 1 are illustrated in figures 2.a and 2.b (cross marker).

[Figures 2.a and 2.b here]

When the initial level of infection is increased, with $\hat{I}_i = 0.5$, eradication takes longer and occurs in T=14 and the NPV of the programme stands at £ 6.588 (in each region). The corresponding infection prevalence and control paths are illustrated in figures 3.a and 3.b (cross marker). Finally, when the initial level of infection is relatively high, $\hat{I}_i = 0.75$, eradication in finite time is not optimal as I am unable to find a value of T which satisfies all the FONC.

[Figures 3.a and 3.b here]

5.1.2 Convergence to steady-state

For the chosen functional forms, problem (2.f) can be rewritten as

$$Min_{u_i} \int_0^{\infty} (kI_i^2 + au_i + bu_i^2)e^{-\delta t} dt \quad (8.a)$$

$$\text{subject to (1)}, 0 \leq I_i(t) \leq 1, 0 \leq u_i(t) \leq \bar{u}_i \text{ and } I_i(0) = \hat{I}_i \quad (8.b)$$

The current value Hamiltonian for this problem is unchanged (see expression 5) and for an interior solution the FONC are given by (6.a, 6.b) and the Arrow-type transversality condition $lim_{t\to\infty} e^{-\delta t}\mu_i(t)I_i(t) = 0$. The FONC can be manipulated to yield four differential equations given by (1) and (7) and the system can be solved for steady-state. In total 9 steady-states are identified, but after ruling out degenerate equilibria (i.e., complex roots and/or negative roots and/or I_i>1) only 2 are left, as indicated in Table 1. An analysis of the Jacobian matrix associated with the dynamic system reveals that both steady-states are saddle points (see Appendix A.3).

[Table 1 here]

Convergence to the steady-state is obtained numerically by implementing a shooting method with the bvp4c routine, where the two boundary values are given by the steady-state

equilibrium and the initial conditions (Judd 1998). After various attempts it turns out that for initial conditions $0 \leq \hat{I}_i \leq 1, i = 1,2$ only steady-state A can be approached. When the initial infection is low, with $\hat{I}_i = 0.2$, the NPV of the programme stands at £ 10.116 (per region) and the associated infection and control paths (for region 1 only) are illustrated in figures 4.a and 4.b (cross marker).

[Figures 4.a and 4.b here]

For higher levels of initial infection, with $\hat{I}_i = 0.5$, the NPV of the programme stands at £ 12.179 and the associated infection and control paths are illustrated in figures 5.a and 5.b (cross marker).

[Figures 5.a and 5.b here]

Finally, for $\hat{I}_i = 0.75$, the NPV of the programme stands at £ 13.977 and the associated infection and control paths are illustrated in figures 6.a and 6.b (cross marker).

[Figures 6.a and 6.b here]

The results up to this point suggest that, under OLNE conditions, eradication is possible only when initial levels of infections are not too high (as already noted by Barrett and Hoel 2007) and the NPV of the corresponding programme is increasing in the initial level of infection. This latter conclusion holds also along the paths converging to the steady-state.

5.2 The cooperative solution

Even in the cooperative case I consider two possibilities, namely a) optimal eradication in finite time and b) convergence to a steady-state in infinite time. Again the problem is solved by considering three different initial conditions.

5.2.1 Eradication in finite time

In this case problem (3.c, 3.d) becomes

$$Min_{u_i,T} \int_0^T \sum_{i=1}^{2} [kI_i^2 + au_i + bu_i^2]\, e^{-\delta t} dt \quad (9.a)$$

$$\text{subject to (1), } 0 \leq I_i(t) \leq 1, 0 \leq u_i(t) \leq \bar{u}_i \text{ and } I_i(0) = \hat{I}_i,\ i = 1,2 \quad (9.b)$$

$$\text{and } I_i(T) = 0,\ i = 1,2 \quad (9.c)$$

The current value Hamiltonian associated with (9) is

$$\tilde{H} = \sum_{i=1}^{2} \left[kI_i^2 + au_i + bu_i^2 + \mu_i \dot{I}_i\right] \quad (10)$$

and the FONC for an internal solution are

$$\frac{\partial \tilde{H}}{\partial u_i} = a + 2bu_i - \alpha_i \mu_i = 0 \rightarrow \mu_i = \frac{a+2bu_i}{\alpha_i} > 0 \quad (11.a)$$

$$\dot{\mu}_i - \delta\mu_i = -\frac{\partial \tilde{H}}{\partial I_i} = -\left[\mu_i\left(\beta_i N_i - 2\beta_i I_i - p_{ji} I_j - \omega_i\right) + \mu_{j\neq i} p_{ij}\left(N_j - I_j\right)\right] - 2kI_i \quad (11.b)$$

$$\tilde{H}(T) = 0 \quad (11.c)$$

$$\mu_i(T) > 0 \quad (11.d)$$

After some manipulation (11.a, 11.b) yield differential equations for the control variables

$$\dot{u}_i = \frac{a+2bu_i}{2b}\left(\delta + \omega_i + 2\beta_i I_i + p_{ji} I_j - \beta_i N_i\right) - \frac{a+2bu_j}{2b} p_{ij}\left(N_j - I_j\right) - \frac{\alpha_i k I_i}{b} \quad (12)$$

whose solution generates the cooperative outcome. Notice the difference between (12) and (7). Under cooperative behaviour the level of control in region i along the optimal path explicitly takes into account the effects on marginal treatment costs in region j (i.e., the term $-\frac{a+2bu_j}{2b} p_{ij}\left(N_j - I_j\right)$ in 12).

The system (12, 1) with initial conditions given by $I_i(0) = \hat{I}_i,\ i = 1,2$ and terminal conditions given by $I_i(T) = 0,\ i = 1,2$ is a boundary value problem (BVP) and is solved numerically with the bvp4c routine. As the terminal time T is free, I use condition (17.c) to identify its optimal

value. After substituting (11.a) in (11.c), the latter implies $u_i(T)=0$. The value of T in the BVP problem is then adjusted so as to meet this condition.

For low initial infections levels, with $\hat{I}_i = 0.2$, eradication occurs in T=4 (earlier than in the OLNE case) and the NPV associated with the programme stands at £ 2.353 (per region). The infection and control paths (only for region 1) are illustrated in figures 2.a and 2.b (square marker). The level of control in this case is initially larger than in the OLNE but declines at a faster rate, while the prevalence of the infection is always lower. The NPV associated with the cooperative outcome is worse (i.e., larger) than the one obtained in the OLNE, something which is difficult to accept as two cooperative agents can at least replicate what two non-cooperative agents are doing. This result, which may be a consequence of the non-convexities in the problem and is further discussed in the last section of this paper, suggests that the internalisation strategy identified by the FONC of the cooperative outcome cannot be relied upon. For higher levels of initial infections, with $\hat{I}_i = 0.5$, eradication occurs in T=7 (earlier than in the OLNE case) and the NPV associated with the programme stands at £ 6.382 (per region). The corresponding infection and control paths (only for region 1) are presented in figures 3.a and 3.b (square marker). In this case the cooperative solution outperforms (i.e., the NPV is lower) the OLNE. This result is not in contrast with the one obtained above, as our problem is neither convex nor concave (remember that the sign of the second order differential associated with the maximised Hamiltonian for problem 9 is indefinite). Finally, for high initial levels of infection with $\hat{I}_i = 0.75$, eradication in finite time is not possible (a result analogous to the one obtained in the OLNE).

5.2.2 Convergence to steady-state

Finally problem (3.e) becomes

$$Min_{u_i} \int_0^{\infty} \sum_{i=1}^{2} [kI_i^2 + au_i + bu_i^2] e^{-\delta t} dt \quad (13.a)$$

$$\text{subject to (1)}, 0 \leq I_i(t) \leq 1, 0 \leq u_i(t) \leq \bar{u}_i \text{ and } I_i(0) = \hat{I}_i, \ i = 1,2 \quad (13.b)$$

The current value Hamiltonian is unchanged (see expression 10) and for an interior solution the FONC are given by (11.a, 11.b) and the Arrow-type transversality condition $lim_{t\to\infty} e^{-\delta t}\mu_i(t)I_i(t) = 0, \ i = 1,2$. The FONC can be manipulated to yield four differential equations given by (1) and (12) and this system can be solved for steady-state. In total 9 steady-states are identified, but after ruling out degenerate equilibria (i.e., complex roots and/or negative roots and/or $I_i>1$) only 2 are left, as indicated in Table 2. An analysis of the Jacobian matrix associated with the dynamic system reveals that both steady-states are saddle points (see Appendix A.3).

[Table 2 here]

Convergence to the steady-state is obtained numerically by implementing a shooting method with the bvp4c routine. After various attempts it turns out that for initial conditions $0 \leq \hat{I}_i \leq 1, i = 1,2$ only steady-state A can be approached. When the initial infection is low,

with $\hat{I}_i = 0.2$, the NPV of the programme stands at £ 11.256 (per region), an outcome which ranks below the one obtained in the OLNE. The associated infection and control paths (for region 1 only) are illustrated in figures 4.a and 4.b (square marker). The infection prevalence is initially higher than in the OLNE, but then reaches a lower steady-state. Control is initially lower than in the OLNE, but it finally rests on a higher steady-state. For higher levels of initial infection, with $\hat{I}_i = 0.5$, the NPV of the programme stands at £ 12.498 (again underperforming the OLNE solution) and the associated infection and control paths are illustrated in figures 5.a and 5.b (square marker). In this case infection prevalence is always lower than in the OLNE, while the level of control is always higher. Finally, for $\hat{I}_i = 0.75$, the NPV of the programme stands at £ 13.967, therefore (just) outperforming the OLNE, and the associated infection and control paths are illustrated in figures 6.a and 6.b (square marker). Even in this case infection prevalence is always lower than in the OLNE, while the level of control is always higher.

The results indicate that even under cooperative behaviour, eradication is possible only when initial levels of infections are not too high (as already noted by Barrett and Hoel 2007) and the NPV of the corresponding programme is increasing in the initial value of infection. This latter conclusion holds also along the paths converging to the steady-state. The cooperative solutions underperform the OLNE in three circumstances (i.e., in the eradication case with low initial levels of infection and in the convergence to steady-state with low and intermediate levels of infections), an aspect which leads to question the ability of the FONC associated with the non-convex cooperative problem to identify the appropriate way to internalise externalities.

6 Discussion

As noted in the early sections, the main objective of this paper is to analyze the implications of non-convexities in the OC of epidemics across two connected regions/populations. In particular two aspects deserve attention: a) whether eradication is preferable to indefinite treatment and b) how to internalize the between-region externalities.

The results of the model are summarized in Table 3, where the optimal policies (i.e., those yielding the lowest NPV) for each set of initial conditions are indicated in bold.

[Table 3 here]

With respect to point a), Lewis and Schmalensee (1977) conclude that the choice between eradication and convergence to steady-state requires the numerical evaluation of the associated payoffs. The application developed in this paper suggests that eradication in finite time turns to be optimal only when the initial levels of infection are not too high (although the optimal time of eradication is positively correlated with the initial infection levels), a result consistent with those of Barrett and Hoel (2007, pp. 638-639). For high initial levels of infection, on the other hand, the optimal solution is to converge to the steady-state. In this case, along the optimal path converging to the (cooperative) steady-state the prevalence of the disease decreases smoothly while the corresponding level of control increases gradually. This pattern, suggesting a negative relationship between the level of control and the prevalence of a disease, is illustrated in Figure 7.c and has been used as a sort of feedback rule to guide optimal management of epidemics (Goldman and Lightwood 2002). The intuition behind this 'golden rule' is that when disease prevalence is high, the risk of re-infection is also high and the return

to control is therefore low. However, for low/moderate initial levels of infections, along the respective optimal eradication paths the prevalence of the disease and the level of control decline, indicating a positive relationship between control and prevalence (as illustrated in Figures 7.a and 7.b). Therefore informing public health policies on the basis of the 'golden rule' might be inappropriate as the non-convex nature of the problem might require either eradication or convergence to the steady-state, depending on initial conditions.

[Figures 7.a, 7.b and 7.c here]

Point b) also requires careful discussion. To the best of my knowledge the existing environmental economic literature in OC has looked at the effects of non-convexity with respect to the multiplicity of steady-states and the implications for optimal management (e.g., Tahvonen and Salo 1996; Rondeau 2001; Brock and Starrett 2003)[6]. However, as the problem I consider also involves externalities between various agents, a novel aspect emerges in that one should consider both cooperative and non-cooperative solutions. Rowthorn et al. (2009), for example, look at the optimal control of epidemics in two connected populations (and show that the problem is non-convex) but only consider cooperative solutions. My results point out that cooperative solutions do not always perform better than OLNE, which is difficult to accept in concrete, as two cooperating agents should at least be able to replicate the outcome of non-cooperating agents. This could be the consequence of the non-convexities in the problem, indicating that the FONC of the cooperative solution might not be relied upon to identify a corrective mechanism to internalize the between-region externalities. Although providing a rigorous proof of this statement is beyond the remit of the paper, there are some results in

cooperative game theory that point in this direction, as it appears that when the problem is non-convex there are difficulties with the cooperative solutions. Barucci (2000), for example, considers an infinite horizon differential game of capital accumulation (with non-convexities due to positive spill-over between firms) in both the non-cooperative (OLNE) and cooperative framework. He shows that in the linear-quadratic case the OLNE exists, while the cooperative solution does not. Engwerda (2007) examines the sufficient conditions for optimal strategies (equivalent to the cooperative solution discussed here) in finite time and free terminal state cooperative differential games and shows that such conditions bear a close resemblance to the Arrow sufficiency theorem (i.e., requiring the joint convexity of the maximized Hamiltonian in the state variable) for an OC problem. Although the author is not able to generalize his results to free-time problems (as problems (2) and (3) here would require), it seems that when non-convexities are present the OC problem is not well-behaved, in which case the FONC may fail to signal the correct cooperative mechanism to internalize externalities. Perhaps this is an aspect which calls for further investigation.

Notes

[1] In 2009 the National Science Foundation in the US opened a call for interdisciplinary research to look at the Ecology of Infectious Diseases (National Science Foundation, 2009). Also in 2009, an initiative was launched in the UK by various Research Councils led by the Medical Research Council, to undertake interdisciplinary research to look at the Environmental and Social Ecology of Human Infectious Diseases (Medical Research Council, 2009).

[2] A metapopulation consists of a group of spatially separated populations (i.e. local demes), interacting with each other at some level.

[3] The use of two regions greatly simplifies both the analysis and the notation, while it still allows one to think about a general n regions case.

[4] Notice that as the total population in each region is constant, the dynamics of the susceptible populations can be obtained simply by changing the sign of (1).

[5] As our model describes the dynamics of a disease in a region, the control must be qualified as public/collective. In this model treatment removes infected/infectious individuals. In an alternative model treatment could affect the infectiousness of the disease (β) and/or the probability of between-regions transmission (p) and/or the recovery rate (ω).

[6] The papers show that when multiple steady-states exist, optimal management trajectories may depend on initial conditions. Similarly in my model multiple steady-states exist, but for plausible initial conditions only one steady-state can be approached.

APPENDICES

A.1 Existence Theorems

In what follows I prove the existence of solutions to problems (2) in both free finite terminal time (as implemented in problem 4) and infinite horizon (as implemented in problem 8). The proof for the cooperative case (i.e., problem 3 and its implementations in finite and infinite horizon) is omitted as it is be entirely analogous to the one here presented.

A.1.1 Free finite terminal time

This proof is based on theorem 5.5 in Seierstad and Sydsaeter (1987). Let the control space be $U_i = [0, \bar{u}_i]$. First of all notice that as $D_i(I_i)$, $C_i(u_i)$, $\dot{I}_i$ are continuous function, the first requirement of the theorem is met. Also, by assumption in problem (2) and its implementation in finite time (4), $0 \leq I_i \leq 1$. Therefore by setting b=1, the second requirement of the theorem is also met. The final requirement calls for the convexity of the set

$$N(\mathbf{I}, \mathbf{u}, t) = \{(n_o, n_1) = [(D_i + C_i)e^{-\delta t} + \gamma, \beta_i(N_i - I_i)I_i - \alpha_i u_i - \omega_i I_i + p_{ji}(N_i - I_i)I_j] : u_i \in U, \gamma \geq 0, i = 1,2 \ \ and \ j \neq i\}$$

which I will now prove, drawing on Seierstad and Sydsaeter (1987).

Keeping (I_1, I_2, t) constant let x and y be two arbitrary points in N defined as

$$x = \{[(D_i + C_i(u_i'))e^{-\delta t} + \gamma', \beta_i(N_i - I_i)I_i - \alpha_i u_i' - \omega_i I_i + p_{ji}(N_i - I_i)I_j] : u_i' \in U, \gamma' \geq 0, i = 1,2 \ \ and \ j \neq i\}$$

and

$$y = \{[(D_i + C_i(u_i''))e^{-\delta t} + \gamma'', \beta_i(N_i - I_i)I_i - \alpha_i u_i'' - \omega_i I_i + p_{ji}(N_i - I_i)I_j] : u_i'' \in U, \gamma'' \geq 0, i = 1,2 \ \ and \ j \neq i\}$$

Let $\lambda \in [0,1]$, then it is sufficient to prove that $z = \lambda x + (1-\lambda)y = (z_0, z_1) \in N(\mathbf{I}, \mathbf{u}, t)$. By definition

$$z_0 = \lambda\left[\left(D_i + C_i(u_i')\right)e^{-\delta t} + \gamma'\right] + (1-\lambda)\left[\left(D_i + C_i(u_i'')\right)e^{-\delta t} + \gamma''\right] = \left\{\lambda\left(D_i + C_i(u_i')\right) + (1-\lambda)\left(D_i + C_i(u_i'')\right)\right\}e^{-\delta t} + \lambda\gamma' + (1-\lambda)\gamma''$$

The term in the curly brackets can be developed into

$$D_i + \lambda C_i(u_i') + (1-\lambda)C_i(u_i'') \geq D_i + C_i[\lambda u_i' + (1-\lambda)u_i''] = D_i + C_i(u_i''')$$

where $u_i''' = \lambda u_i' + (1-\lambda)u_i'' \in U$. Then it follows that

$z_0 \geq \left(D_i + C_i(u_i''')\right)e^{-\delta t} + \lambda\gamma' + (1-\lambda)\gamma''$ which in turn implies that

$$\gamma''' = z_0 - \left(D_i + C_i(u_i''')\right)e^{-\delta t} \geq \lambda\gamma' + (1-\lambda)\gamma'' \geq 0.$$

By definition

$$z_1 = \lambda\left[\beta_i(N_i - I_i)I_i - \alpha_i u_i' - \omega_i I_i + p_{ji}(N_i - I_i)I_j\right] + (1-\lambda)\left[\beta_i(N_i - I_i)I_i - \alpha_i u_i'' - \omega_i I_i + p_{ji}(N_i - I_i)I_j\right] = \beta_i(N_i - I_i)I_i - \alpha_i u_i''' - \omega_i I_i + p_{ji}(N_i - I_i)I_j$$

.

Then we found a $\gamma''' \geq 0$ and a $u_i''' \in U$ such that for two arbitrary points in N, x and y, and for $\lambda \in [0,1]$,

$$z = \lambda x + (1-\lambda)y = \left\{[D_i + C_i(u_i''')]e^{-\delta t} + \gamma''', \beta_i(N_i - I_i)I_i - \alpha_i u_i''' - \omega_i I_i + p_{ji}(N_i - I_i)I_j\right\} \in N(\mathbf{I}, \mathbf{u}, t)$$

.

A.1.2 Infinite time horizon

I extend theorem 5.5 to infinite horizon by using theorem 3.15 in Seierstad and Sydsaeter (1987). In this case the existence of a solution has some additional requirements to those presented in A.1.1. First of all notice that in our case $(D_i + C_i)e^{-\delta t} \geq 0$ and therefore setting

$\varphi(t) = 0$, it follows that $\int_0^\infty \varphi(t)dt = 0 < \infty$ which satisfies the requirement of the theorem. Also by setting $a(t) = 0$, the last requirement of the theorem becomes $\left|\beta_i(N_i - I_i)I_i - \alpha_i u_i' - \omega_i I_i + p_{ji}(N_i - I_i)I_j\right| \leq b(t)$. As in our case $0 \leq I_i \leq 1$ and $u_i \in [0, \bar{u}_i]$, even this requirement is trivially satisfied.

A.2 Sufficiency Conditions

Here I openly test Arrow-type sufficiency conditions for the OLNE (problems 4 and 8) and cooperative solution (problems 9 and 13).

A.2.1 OLNE

The current value Hamiltonian associated with problems (4) and (8) is

$$\tilde{H}_i = kI_i^2 + au_i + bu_i^2 + \mu_i \dot{I}_i \quad \text{(A.1)}$$

First of all notice that the necessary Legendre-Clebesh condition is satisfied, as $\frac{\partial^2 \tilde{H}_i}{\partial u_i^2} = 2b > 0$. After substituting the maximum condition (6.a) into (A.1) the corresponding Maximised Hamiltonian is

$$\tilde{H}_i^0 = kI_i^2 + a\left(\frac{\alpha_i\mu_i - a}{2b}\right) + b\left(\frac{\alpha_i\mu_i - a}{2b}\right)^2 + \mu_i\left[\beta_i(N_i - I_i)I_i - \alpha_i\left(\frac{\alpha_i\mu_i - a}{2b}\right) - \omega_i I_i + p_{ji}(N_i - I_i)I_j\right]$$

(A.2)

The Arrow-type sufficiency requires the Maximised Hamiltonian to be jointly convex in the state variables I_1 and I_2 $\forall t$, which in turn requires the two principal minors of the Hessian matrix associated with (A..2) to be positive (Caputo 2005). Focusing on region 1 (as the analysis for region 2 is symmetric), the Hessian matrix is

$$Hessian = \begin{bmatrix} \tilde{H}^0_{I_1 I_1} & \tilde{H}^0_{I_1 I_2} \\ \tilde{H}^0_{I_2 I_1} & \tilde{H}^0_{I_2 I_2} \end{bmatrix} = \begin{bmatrix} 2(k - \beta_1 \mu_1) & -\mu_1 p_{21} \\ -\mu_1 p_{21} & 0 \end{bmatrix} \quad \text{(A.3)}$$

As the determinant is $-(\mu_1)^2(p_{21})^2 < 0$, the quadratic form associated with the second order differential will never be positive semidefinite. Moreover the first principal minor will be positive if and only if $\mu_1 < \frac{k}{\beta_1}$, which in turn would require $u_1 < 0$ and therefore is never satisfied. Therefore the quadratic form associated with the second order differential is indefinite, suggesting that the Maximised Hamiltonian is neither convex nor concave, and the sufficient conditions are not met.

A.2.2 Cooperative Solution

The current value Hamiltonian associated with problems (9) and (13) is

$$\tilde{H} = \Sigma_{i=1}^{2}\left[kI_i^2 + au_i + bu_i^2 + \mu_i \dot{I}_i\right] \quad \text{(A.4)}$$

Even in this case the necessary Legendre-Clebesh condition is satisfied, as $\frac{\partial^2 \tilde{H}_i}{\partial u_i^2} = 2b > 0$. After applying conditions (11.a), the Maximised Hamiltonian is given by

$$\sum_{i=1}^{2} kI_i^2 + a\left(\frac{\alpha_i\mu_i - a}{2b}\right) + b\left(\frac{\alpha_i\mu_i - a}{2b}\right)^2 + \mu_i\left[\beta_i(N_i - I_i)I_i - \alpha_i\left(\frac{\alpha_i\mu_i - a}{2b}\right) - \omega_i I_i + p_{ji}(N_i - I_i)I_j\right]$$

(A.5)

The corresponding Hessian Matrix is

$$Hessian = \begin{bmatrix} \tilde{H}^0_{I_1I_1} & \tilde{H}^0_{I_1I_2} \\ \tilde{H}^0_{I_2I_1} & \tilde{H}^0_{I_2I_2} \end{bmatrix} = \begin{bmatrix} 2(k - \beta_1\mu_1) & -\mu_1 p_{21} - \mu_2 p_{12} \\ -\mu_1 p_{21} - \mu_2 p_{12} & 2(k - \beta_2\mu_2) \end{bmatrix} \quad \text{(A.6)}$$

Positive definitiveness of the quadratic form associated with the second order differential of (A.5) again requires the two principal minors of (A.6) to be positive $\forall t$. For our parameter values this implies $\mu_i < 5$ (which is never satisfied, as it would require $u_i < 0$) and $4(1 - 0.2\mu_1)(1 - 0.2\mu_2) - 0.01(\mu_1 + \mu_2)^2 > 0$. The second inequality will be satisfied in regions I and III of figure A.1. Given the values of μ_i along the solution paths presented in Table A.1, it follows that the sign of the second-order differential associated with (A.5) is indefinite. Therefore the sufficient conditions are not satisfied.

[Figure A.1 here]

[Table A.1 here]

A.3 Dynamic stability of the Steady-State solutions

A.3.1. OLNE

The FONC for problem (8) can be reduced to expressions (1) and (7), which evaluated in steady-state define a system of 4 equations in 4 variables (u_i, I_i, i=1,2). The system has 9 steady-states of which only two are non-degenerate: A = {u_i=0.032, I_i=0.8} and B = { u_i=0.26, I_i=0.42}. For our parameter values the eigenvalues of the Jacobian matrix associated with the FONC, evaluated at steady-state A are $\{-0.286, -0.208, 0.278, 0.317\}$, suggesting that steady-state A is a saddle point. For steady-state B the corresponding eigenvalues are given by $\{-0.091, 0.054 - 0.18i, 0.054 + 0.18i, 0.083\}$. As the real parts of the eigenvalues have alternate signs, even steady-state B is a saddle point.

A.3.2. Cooperative Solution

In the cooperative solutions also two non-degenerate steady-states emerge: A = {u_i=0.11, I_i=0.73} and B = { u_i=0.17, I_i=0.67}. The corresponding eigenvalues of the Jacobian matrix associated with the FONC (12, 1) are $\{-0.243, 0.025 - 0.097i, 0.025 + 0.097i, 0.293\}$ and $\{-0.269, -0.081, 0.131, 0.319\}$ respectively. Both A and B are saddle points.

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TABLES AND FIGURES

Table 1: Steady-states solutions under the OLNE

Steady-States	Values of the variable				Dynamic Stability Properties
	u_1	I_1	u_2	I_2	
A	0.032	0.8	0.032	0.8	Saddle Point
B	0.26	0.42	0.26	0.42	Saddle Point

Table 2: Steady-states solutions under cooperative behaviour

Steady-States	Values of the variable				Dynamic Stability Properties
	u_1	I_1	u_2	I_2	
A	0.11	0.73	0.11	0.73	Saddle Point
B	0.17	0.67	0.17	0.67	Saddle Point

Table 3: summary of model results and optimal policies

	Eradication		Steady-State
	T	*NPV*	*NPV*
$\hat{I}_i = 0.2$			
OLNE	**7**	**2.196**	10.116
Coop Sol	4	2.353	11.256
$\hat{I}_i = 0.5$			
OLNE	14	6.588	12.179
Coop Sol	**7**	**6.382**	12.498
$\hat{I}_i = 0.75$			
OLNE	n.a.	n.a.	13.977
Coop Sol	n.a.	n.a.	**13.967**

Table A.1: values of μ_i, i=1,2 in the cooperative solutions

time	$I_i(0)$=0.2, i=1,2		$I_i(0)$=0.5, i=1,2		$I_i(0)$=0.75, i=1,2
	Eradication	Steady-State*	Eradication	Steady-State*	Steady-State*
0	11.14375	7.607431	12.88127	7.512677	6.03758
1	9.742151	6.739839	12.86498	7.265778	6.046541
2	8.258388	6.135221	12.24647	7.033097	6.054693
3	6.856293	5.744482	11.13645	6.827313	6.062119
4	5	5.512353	9.734023	6.655766	6.068888
5	-	5.390732	8.250473	6.519624	6.075064
6	-	5.342375	6.84924	6.414529	6.080704
7	-	5.340357	5	6.332864	6.085858
8	-	5.36611	-	6.266625	6.090572
9	-	5.407291	-	6.209591	6.094885
10	-	5.455957	-	6.158116	6.098834
11	-	5.507175	-	6.110756	6.102452
12	-	5.558004	-	6.067366	6.105767

13	-	5.606777	-	6.028255	6.108807
14	-	5.652631	-	5.993676	6.111596
15	-	5.695187	-	5.963644	6.114154
16	-	5.734356	-	5.937986	6.116502
17	-	5.770217	-	5.91644	6.118658
18	-	5.802939	-	5.898745	6.120638
19	-	5.832734	-	5.884675	6.122457
20	-	5.859833	-	5.87403	6.124127
21	-	5.884465	-	5.866612	6.125661
22	-	5.906853	-	5.862208	6.127071
23	-	5.927204	-	5.860577	6.128366
24	-	5.94571	-	5.861454	6.129556
25	-	5.962547	-	5.864555	6.130649
26	-	5.977874	-	5.869586	6.131652
27	-	5.991836	-	5.876254	6.132573
28	-	6.004563	-	5.884279	6.133418

29	-	6.016172	-	5.893395	6.134193
30	-	6.026769	-	5.903361	6.134902
31	-	6.036448	-	5.913958	6.135551
32	-	6.045297	-	5.924994	6.136145
33	-	6.05339	-	5.936305	6.136686
34	-	6.060798	-	5.94775	6.137178
35	-	6.067584	-	5.959211	6.137624
36	-	6.073804	-	5.970595	6.138027
37	-	6.079509	-	5.981825	6.13839
38	-	6.084746	-	5.992846	6.138713
39	-	6.089557	-	6.003617	6.139
40	-	6.09398	-	6.01411	6.13925
41	-	6.098051	-	6.024311	6.139466
42	-	6.101802	-	6.034216	6.139647
43	-	6.105261	-	6.043832	6.139794
44	-	6.108456	-	6.053173	6.139907

45	-	6.111411	-	6.062263	6.139985
46	-	6.11415	-	6.07113	6.140028
47	-	6.116694	-	6.079813	6.140033
48	-	6.119063	-	6.088354	6.14
49	-	6.121275	-	6.096804	6.14
50	-	6.123349	-	6.10522	6.14
51	-	6.125301	-	6.113669	6.14
52	-	6.127147	-	6.122224	6.14
53	-	6.128904	-	6.130969	6.14
54	-	6.130587	-	6.14	6.14
55	-	6.132211	-	6.14	6.14
56	-	6.133791	-	6.14	6.14
57	-	6.135344	-	6.14	6.14
58	-	6.136885	-	6.14	6.14
59	-	6.138431	-	6.14	6.14
60	-	6.14	-	6.14	6.14

* In any numerical simulation a steady-state will be approached in finite time.

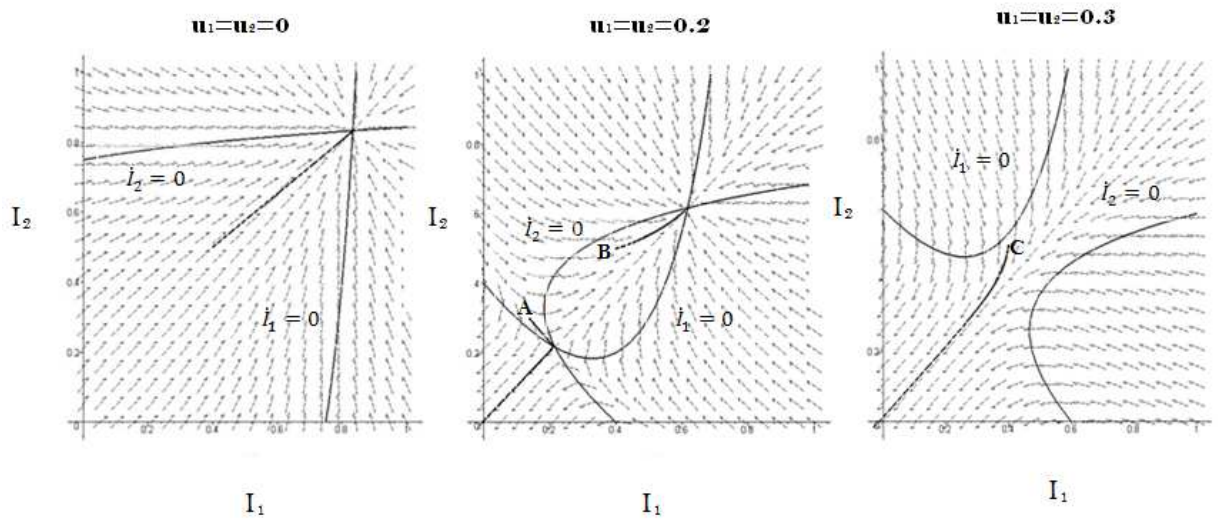

Figure 1: Phase-plane diagram of system (1). The following parameter values have been used: α=0.2; β=0.2; ω=0.05; p=0.1; $N_1=N_2=1$. In the left panel, $u_1=u_2=0$ and the system converges to the only equilibrium point (a locally asymptotically stable node). The central panel is drawn for $u_1=u_2=0.2$ and two equilibria appear: a high infection one (which is a local asymptotically stable node) and a low infection one (which is a saddle). For initial conditions given by point A, exerting a constant level of control equal to $u_1=u_2=0.2$ will lead to eradication in finite time. However for different initial conditions, as indicated by point B, the specified level of control will move the system towards the stable steady-state. The panel on the right is drawn for $u_1=u_2=0.3$, where the steady-state equilibria are complex. However for certain initial conditions, as indicated by point C, the specified level of control will lead to eradication in finite time.

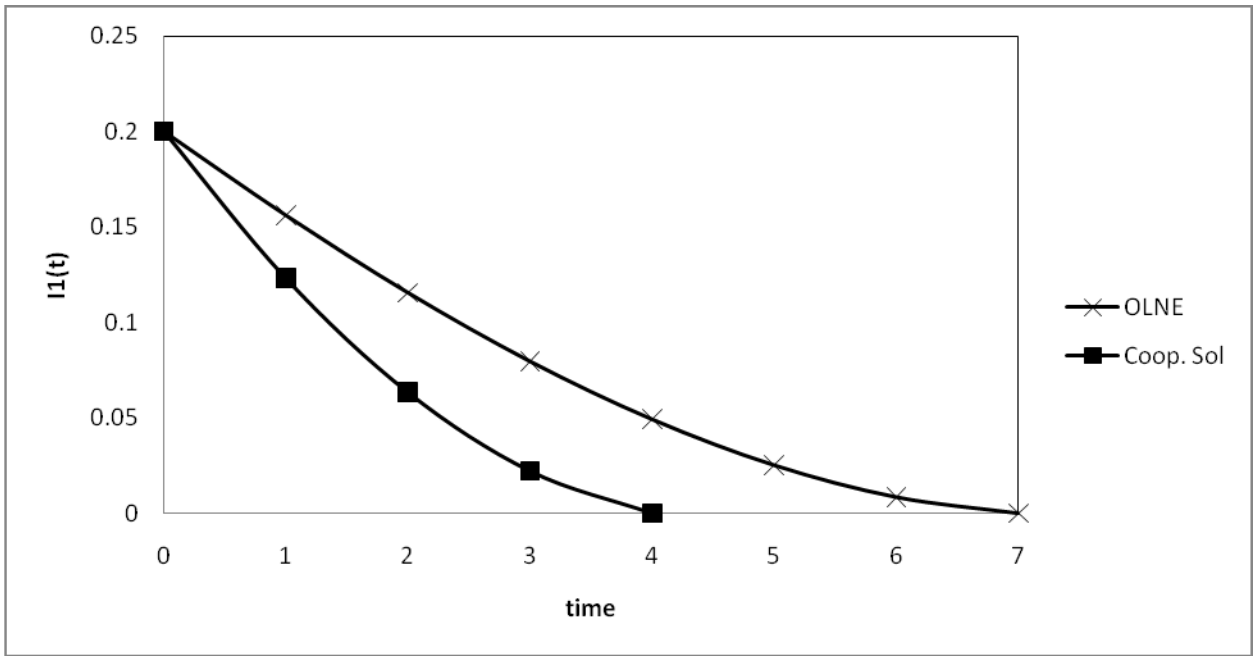

Figure 2.a: infection prevalence in region 1 along the OLNE (cross marker) and the Cooperative Solution (square marker) eradication path for low initial levels of infection.

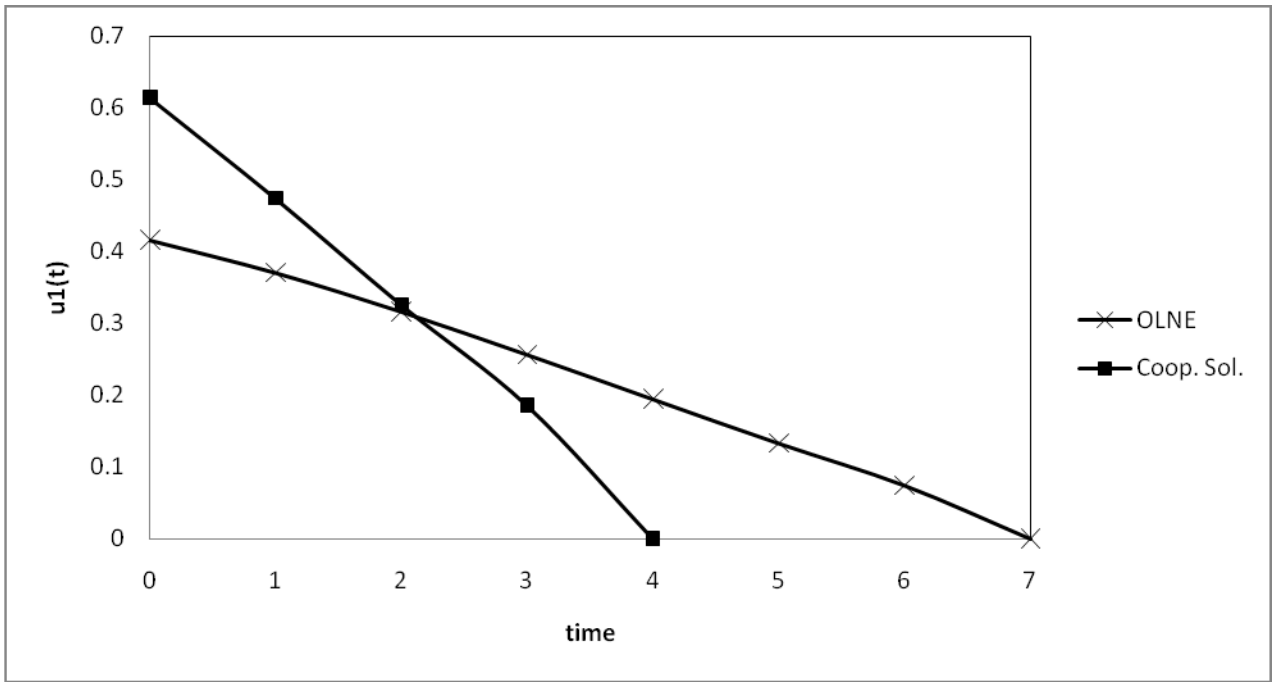

Figure 2.b: control in region 1 along the OLNE (cross marker) and the Cooperative Solution (square marker) eradication path for low initial levels of infection.

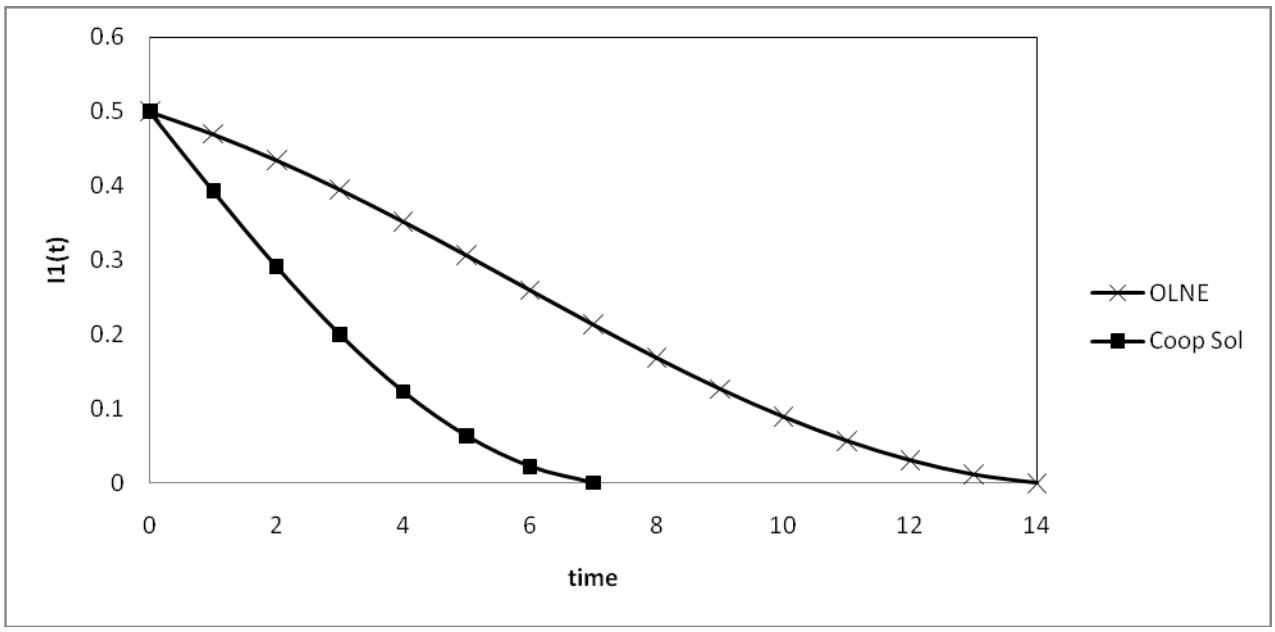

Figure 3.a: infection prevalence in region 1 along the OLNE (cross marker) and the Cooperative Solution (square marker) eradication path for intermediate initial levels of infection.

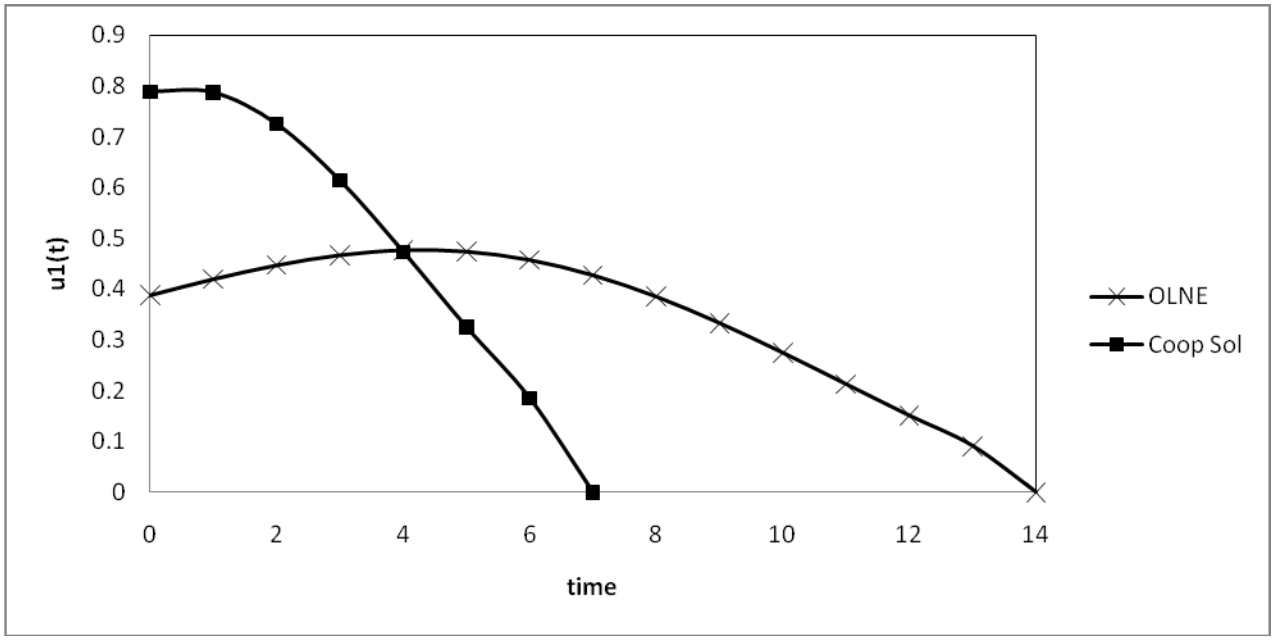

Figure 3.b: infection prevalence in region 1 along the OLNE (cross marker) and the Cooperative Solution (square marker) eradication path for intermediate initial levels of infection.

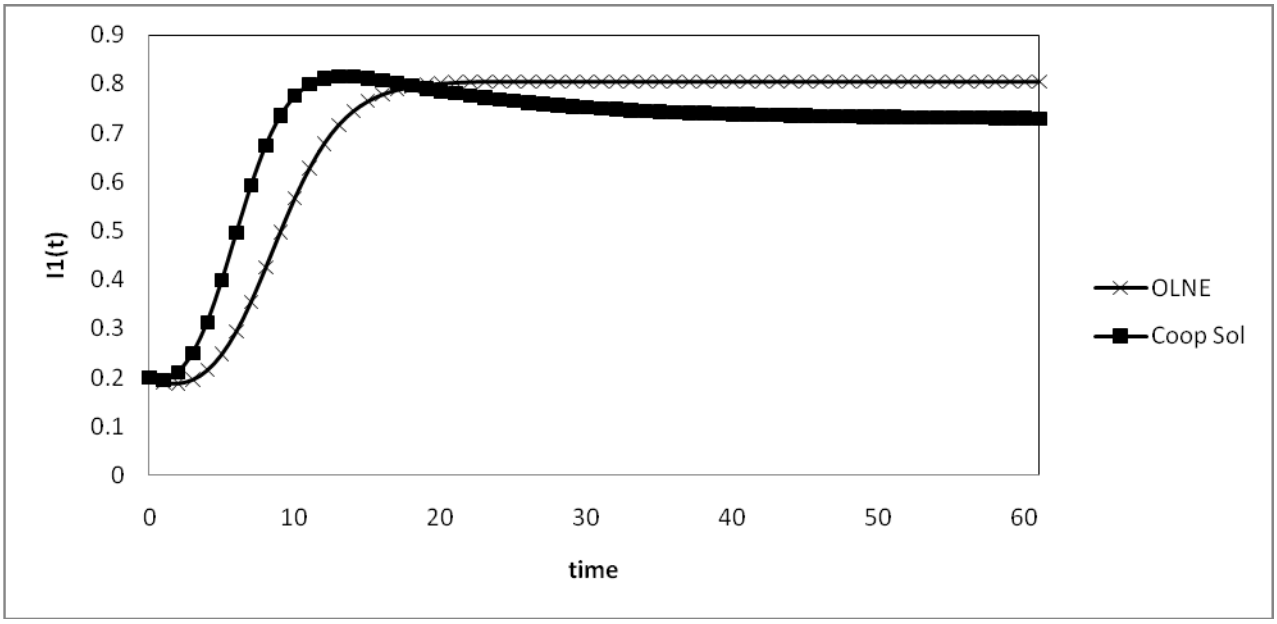

Figure 4.a: infection prevalence in region 1 along the OLNE (cross marker) and the Cooperative Solution (square marker) paths converging to steady-state for low initial levels of infection.

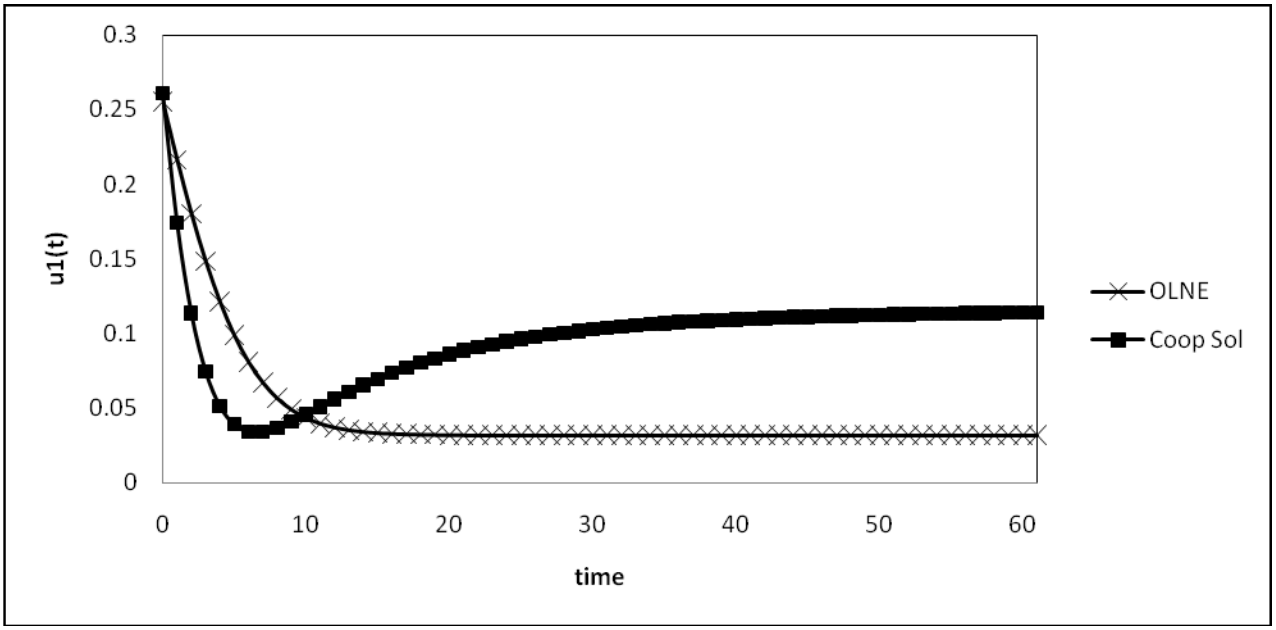

Figure 4.b: control in region 1 along the OLNE (cross marker) and the Cooperative Solution (square marker) paths converging to steady-state for low initial levels of infection.

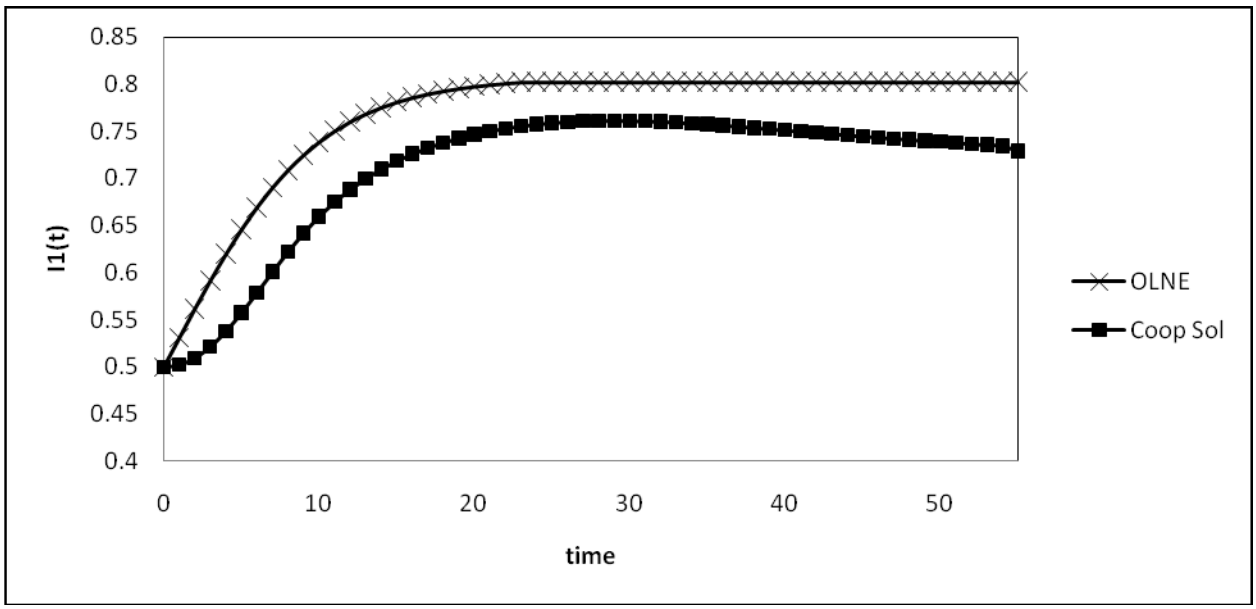

Figure 5.a: infection prevalence in region 1 along the OLNE (cross marker) and the Cooperative Solution (square marker) paths converging to steady-state for intermediate initial levels of infection.

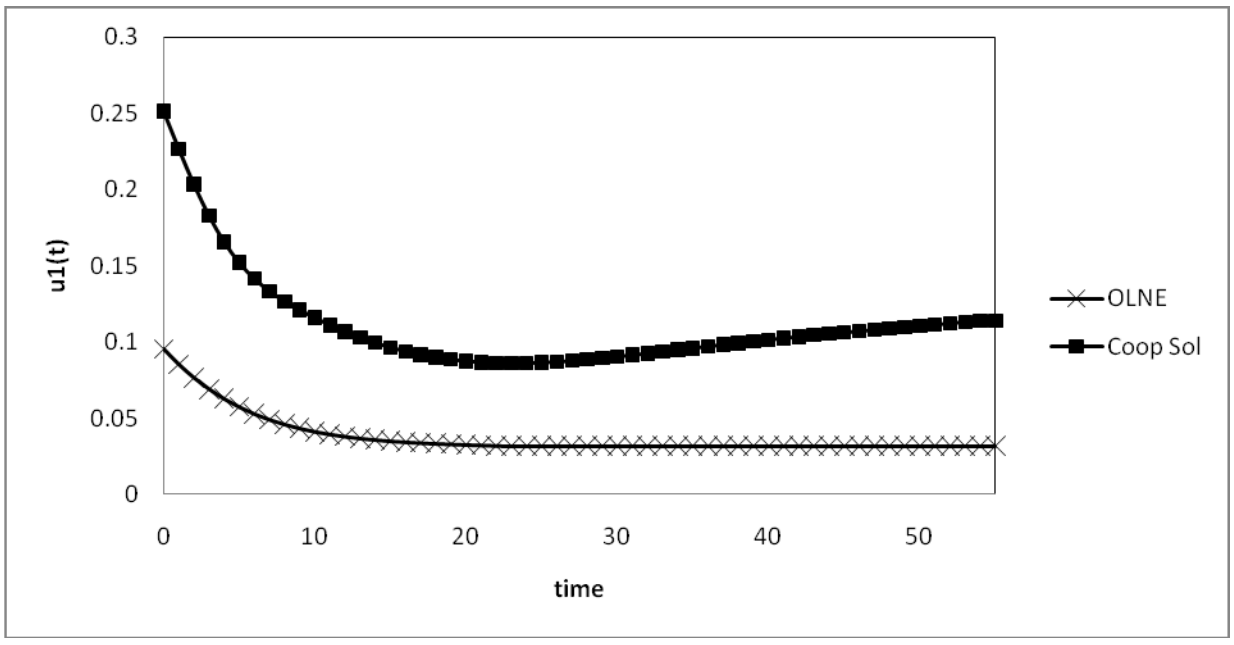

Figure 5.b: control in region 1 along the OLNE (cross marker) and the Cooperative Solution (square marker) paths converging to steady-state for intermediate initial levels of infection.

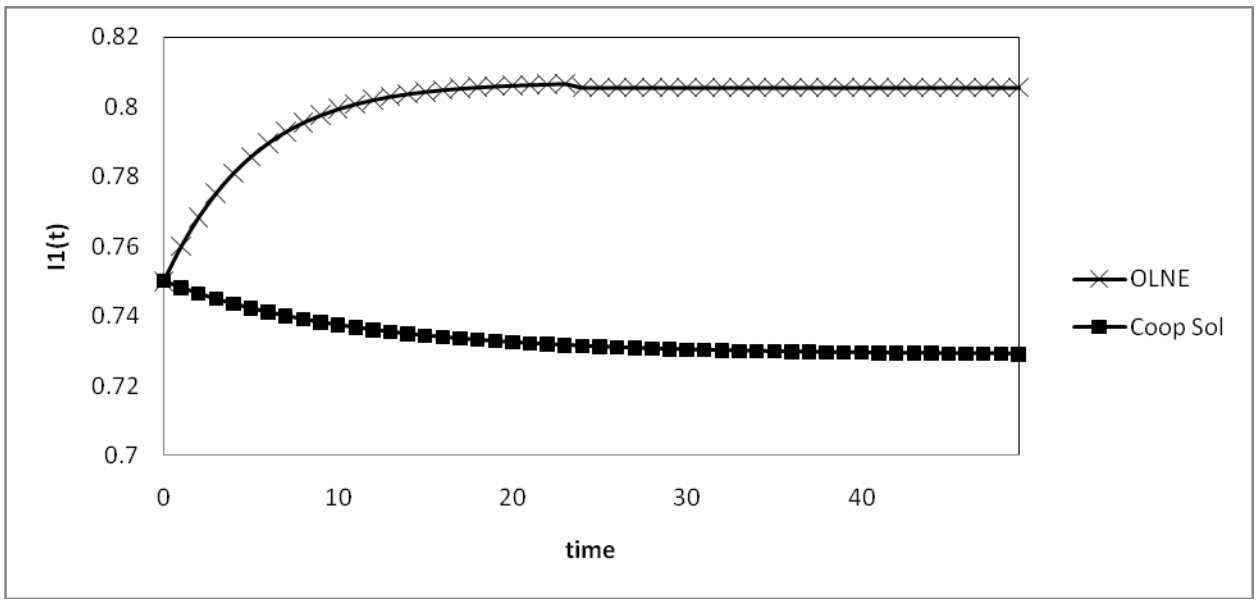

Figure 6.a: infection prevalence in region 1 along the OLNE (cross marker) and the Cooperative Solution (square marker) paths converging to steady-state for high initial levels of infection.

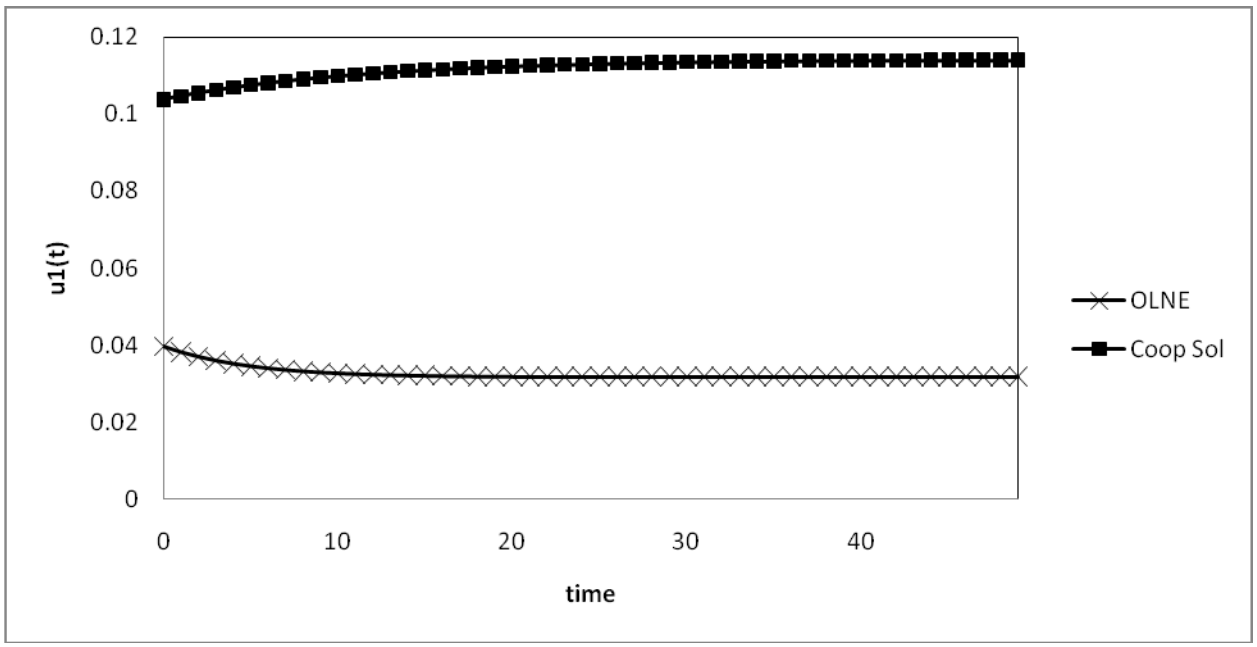

Figure 6.b: control in region 1 along the OLNE (cross marker) and the Cooperative Solution (square marker) paths converging to steady-state for high initial levels of infection.

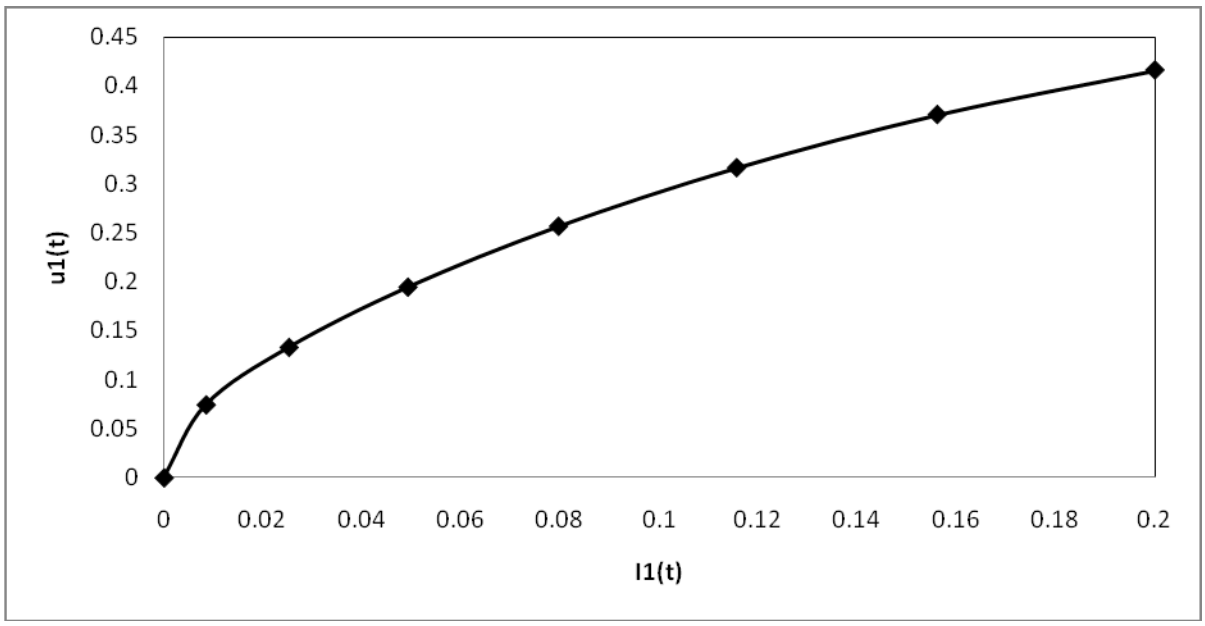

Figure 7.a: relationship between control effort and disease prevalence (for region 1) along the optimal eradication path for low initial levels of infection.

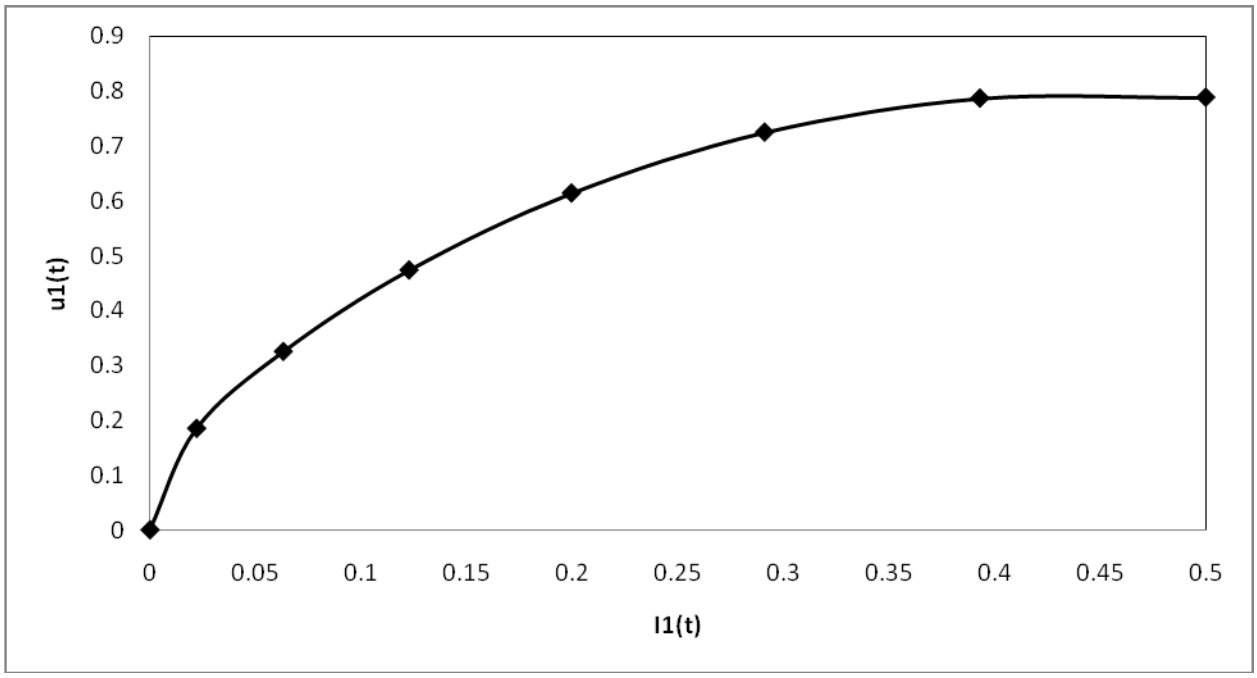

Figure 7.b: relationship between control effort and disease prevalence (for region 1) along the optimal eradication path for intermediate initial levels of infection.

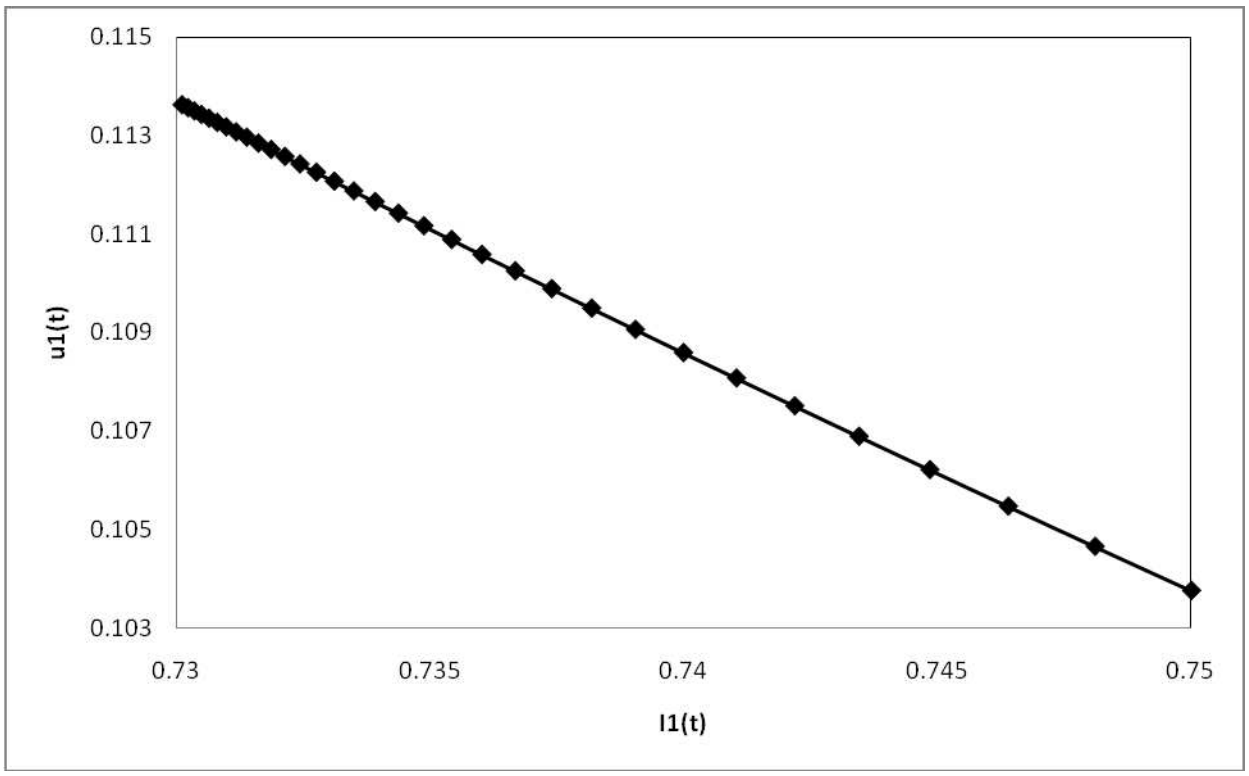

Figure 7.c: relationship between control effort and disease prevalence (for region 1) along the optimal path converging to steady-state for high initial levels of infection.

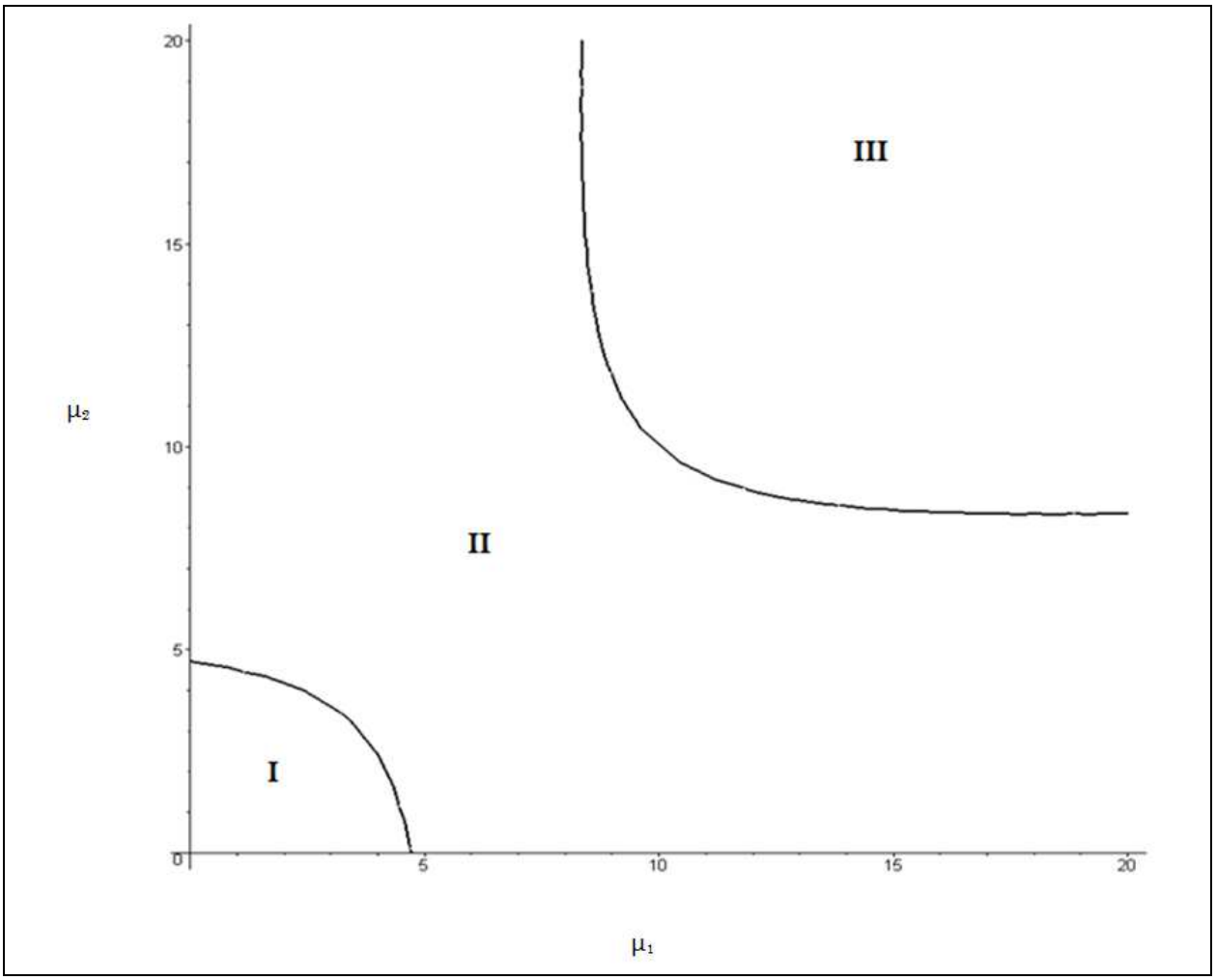

Figure A.1: the determinant of A.6 is positive in regions (I) and (III), while it is negative in region (II).