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Optimization of Control Strategies for Epidemics in Heterogeneous Populations with Symmetric and Asymmetric Transmission

Martial L. Ndeffo Mbah*[,a], Christopher A. Gilligan[a]

[a]*Department of Plant Sciences, University of Cambridge, Downing Street, Cambridge CB2 3EA, United Kingdom. Tel: +44(0)1223 330229; Fax: +44 (0)1223-333953*

Abstract

There is growing interest in incorporating economic factors into epidemiological models in order to identify optimal strategies for disease control when resources are limited. In this paper we consider how to optimize the control of a pathogen that is capable of infecting multiple hosts with different rates of transmission within and between species. Our objective is to find control strategies that maximize the discounted number of healthy individuals. We consider two classes of host-pathogen system, comprising two host species and a common pathogen, one with asymmetrical and the other with symmetrical transmission rates, applicable to a wide range of SI (susceptible-infected) epidemics of plant and animal pathogens. We motivate the analyses with an example of sudden oak death in California coastal forests, caused by Phytophthora ramorum, in communities dominated by bay laurel (Umbellularia californica) and tanoak (Lithocarpus densiflorus). We show for the asymmetric case that it is optimal to give priority in treating disease to the more infectious species, and to treat the other species only when there are resources left over. For the symmetric case, we show that although a switching strategy is an optimum, in which preference is first given to the species with the lower level of susceptibles and then to the species with the higher level of susceptibles, a simpler strategy that favours treatment of infected hosts for the more susceptible species is a robust alternative for practical application when the optimal switching time is unknown. Finally, since transmission rates are notoriously difficult to estimate, we analyze the robustness of the strategies when the true state with respect to symmetry or otherwise is unknown but one or other is assumed.

Key words: epidemiological modeling, economic modeling, control theory, species coexistence

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1. Introduction

Many plant and animal pathogens can infect more than one host species. Amongst diseases of contemporary interest that can spread in this way, are sudden oak death in plant communities (Rizzo et al., 2002; Rizzo and Garbelotto, 2003), foot and mouth disease (Ferguson et al., 2001; Keeling et al., 2001), blue-tongue virus in livestock (Bethan et al., 2005), and bird influenza that can spread between wild and domestic birds with a risk to humans (Alexander, 2000). The spread of disease in each case can be viewed as a series of coupled epidemics on sub-populations of each species, with occasional, or sometimes frequent, transmission of infection between species. It follows that targeting control of infection (and hence disease) on one of the host species influences the infection pressure and disease risk for the other species. Host species may differ in susceptibility to the pathogen, in amenability and cost of control, or in intrinsic value. The question naturally arises of how best to deploy resources for disease control, especially when resources are limited. Here, we address the problem using a combination of economic control theory (Goldman and Lightwood, 2002; Rowthorn, 2006; Forster and Gilligan, 2007) in combination with a metapopulation framework for disease dynamics (Hanski, 1998; Park et al., 2003). The metapopulation framework is a convenient devise to separate each host species into a sub-population with coupled epidemics between sub-populations. We motivate the problem for the control of sudden oak death caused by the Oomycete, *Phytophthora ramorum*, a fungal-like organism, that is mainly transmitted by rain splash. The pathogen has a wide host range and is currently

*Corresponding author

Email addresses: mln25@cam.ac.uk (Martial L. Ndeffo Mbah), cag1@cam.ac.uk (Christopher A. Gilligan)

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spreading rapidly through coastal regions of California (Rizzo et al., 2002, 2005). Here we focus initially on spread through communities dominated by two major host species with asymmetrical transmission between bay laurel (*Umbellularia californica*) and tanaok (*Lithocarpus densiflorus*) (Maloney et al., 2005).

Rowthorn et al. (2009) recently analysed optimal strategies for the deployment of disease control on a single host species comprising two or more spatially-separated sub-populations in which infected individuals recover and can be reinfected. This form of SIS (Susceptible-Infected-Susceptible) model is commonly used to describe some sexually-transmitted diseases such as gonorrhea. Rowthorn et al. (2009) revealed a counter-intuitive result for the SIS type of disease in which giving preference to the sub-population with the higher level of infection is the worst strategy for diseases of the SIS form. The optimal strategy instead involved giving preference to the species with the lower level of infected individuals and hence the higher level of susceptibles. What should happen in an SI (Susceptible-Infected) system typical of sudden oak death and many other plant and animal diseases hosts in which hosts do not recover but new susceptible hosts arise by reproduction and transmission rates within species differ? To answer this, we consider whether or not preference should be given to treating the species with the higher transmission rate, and show that it is possible to identify an analytical solution for the optimal strategy. Many epidemics, including those of sudden oak death, involve cryptic spread of infection from hosts that are infected prior to spread. Additional realism is conferred to the analysis by the introduction of a threshold for detection of visible symptoms of disease.

The differential transmission rates for *P. ramorum* for bay laurel and tanoak, and several other species (Meentemeyer et al., 2004), can be inferred from simple pathology experiments. The relative transmission rates may not be known in advance for some emerging epidemics prior to the implementation of control strategies. Accordingly, we generalize the methods for asymmetric transmission to consider a two-species model for SI epidemics with births of susceptibles, in which there is symmetrical transmission of infection between host species. The additional analysis serves two purposes. Firstly, it provides a lower bound to the (zero) difference between transmission rates from which it is possible to test the consistency of the results for asymmetrical and symmetrical transmission. Secondly, it allows a test of the robustness of the optimal control strategies when transmission rates are erroneously assumed to be asymmetric when in fact they are not, and *vice versa*.

2. Methods

2.1. The model

We consider a community comprising two susceptible species with a pathogen that can infect both hosts. The model is motivated and parameterized for the spread of sudden oak death through mixed species stands of bay laurel and tanoak, in which there is asymmetrical transmission of infection between species. Parameterization (Table 1) was derived from Meentemeyer et al. (2004). The model is then generalized to consider what happens when there is symmetrical infection between the two host species. The disease dynamics on each species are described by a simple SI compartmental model, in which the vital dynamics and natural competition between host species are taken into consideration. Disease dynamics in the absence of control are described by the following set of differential equations:

$$\begin{aligned} \dot{S_1} &= g_1 - \beta_{11} S_1 I_1 - \beta_{21} S_1 I_2 - d_1 S_1 \\ \dot{I_1} &= \beta_{11} S_1 I_1 + \beta_{21} S_1 I_2 - \mu_1 I_1 - d_1 I_1 \end{aligned} \tag{1}$$

$$\begin{aligned} \dot{S_2} &= g_2 - \beta_{22} S_2 I_2 - \beta_{12} S_2 I_1 - d_2 S_2 \\ \dot{I_2} &= \beta_{22} S_2 I_2 + \beta_{12} S_2 I_1 - \mu_2 I_2 - d_2 I_2 \end{aligned} \tag{2}$$

in which $i = 1, 2$ denotes species 1 and species 2, respectively. The host dynamics are characterised by a recruitment function (g_i) and a death rate (d_i) for each species. For the sake of simplicity, we characterise the recruitment function with a simple monomolecular form,

$$g_i(S_1, I_1, S_2, I_2) = b_i(\kappa - S_1 - I_1 - S_2 - I_2),$$

where κ is the carrying capacity, b_i is the rate of recruitment of species i, and all trees are assumed to exhibit equivalent competitive effects irrespective of species or disease status (Holt and Pickering, 1985; Preedy et al., 2007; Borer et al., 2007). However, the results of the optimization problem remain unchanged for the use of more complex growth functions such a logistic function. We also assume identical death rates for each species, $d_1 = d_2$, without loss of generality. The pathogen is characterised by transmission rates within (β_{11}, β_{22}) and between (β_{12}, β_{21}) species, with different infectious periods $1/\mu_i$ on each species.

Control is introduced by culling of infected individuals. Only those individuals that have been detected as infected elicit culling and so control is introduced in the

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model by adding the term $-\alpha f_i I_i$ to the infection term of Eq. 1 and Eq. 2 in which α reflects the rate of detection of infected individuals and f_i is the proportion of detected individuals that is culled in species i ($i = 1, 2$).

2.2. Optimal Control

We assume that expenditure on control is subject to a budget constraint $c\,\alpha\,(f_1 I_1 + f_2 I_2) \leq M$, where c is the cost of culling per detected infected individual, and M is the expenditure limit. This constraint encompasses the amount of logistic and human resources at the point of infection. We also assume that finance is not transferable through time, so that money which is not spent immediately cannot be saved for future use. If there are sufficient resources, all detected individuals will be culled. Otherwise, resources are allocated so as to maximize the total utility attached to healthy individuals of both species over time. Therefore, we choose f_1 and f_2 in order to maximize the following integral,

$$J = \int_0^\infty e^{-rt}(p_1 S_1 + p_2 S_2)dt. \tag{3}$$

by optimizing the current value of the Hamiltonian (Pinch, 1993; Seierstad and Sydsaeter, 1986) for the disease dynamics equations subject to the constraints of the epidemiological and economic system. Here, we denote respectively by p_1 and p_2 the intrinsic value attached to a healthy individual of species 1 and 2: r is the discount rate. The discount rate represents the rate the policymaker is willing to pay to trade-off the value of controlling today against the ensuing cost of increased infection in the future (measured by loss of healthy individuals) (Dixit and Pindyck, 1994). Here we assume the p_1 and p_2 are of order one, i.e. that the intrinsic values of healthy individuals of each species are similar. We also assume that the total populations of each species are initially of similar size.

We investigate the optimal culling strategies for two scenarios that differ in reciprocal transmission rates between species in mixed, two-species populations. In the first scenario, we assume asymmetric rates of transmission in which species 1 is the one mainly driving the epidemic. Accordingly: $\beta_{11} > \beta_{12} \geq \beta_{22}$ and $\beta_{11} \geq \beta_{21}$. Moreover, we also assume that $\mu_2 \geq \mu_1$, consistent with a positive correlation between transmissibility and infectious period. This positive correlation can be observed in many natural systems such as the spread of *P. ramorum* in bay laurel-tanoak communities (Meentemeyer et al., 2004), and that of foot-and-mouth disease between dairy cattle and sheep (Orsel et al., 2009). In the second scenario, we assume that the model is symmetric with respect to the disease dynamics, so that $\beta_{11} = \beta_{22}$ and $\beta_{12} = \beta_{21}$, with $\beta_{11} > \beta_{12}$. In the symmetric case, the condition $\beta_{11} > \beta_{12}$ implies that infection in each species is mainly the result of intra-species rather than cross-species infection.

2.3. Optimization

Our objective is to maximize the discounted utilities of healthy (i.e. susceptible) individuals (Eq. 3) subject to the disease dynamics equations and the constraint,

$$((S_1, I_1, S_2, I_2), (f_1, f_2)) \in A(t) \quad \forall\, t \geq 0,$$

where

$$A = \{(x, y) \in \mathbb{R}_+^4 \times [0,1]^2 : \text{ if } \alpha\,(x_2 + x_4) \leq M/c,$$
$$y_1 = y_2 = 1; \text{ otherwise } \alpha\,(y_1 x_2 + y_2 x_4) = M/c\}.$$

The above constraint implies that all detected individuals will be culled as long as there are resources available to do so. Hence, if $\alpha\,(I_1 + I_2) \leq M/c$, then $f_1 = f_2 = 1$ and it is optimal to remove all detected individuals.

The main challenge is to find the trajectory for optimal control strategies when there is insufficient resource to remove all detected individuals. We denote by $B = \{(S_1, I_1, S_2, I_2) : \alpha(I_1 + I_2) \leq M/c\}$ the region within which all detected individuals can be culled. In other words, so long as the total level of infection in the community is within B, there are enough resources to cull every single individual that is detected as infected. If the following condition for detection of visible symptoms of disease is satisfied,

$$\frac{\beta_{11} S_1^* + \beta_{12} S_2^*}{\mu_1 + d_1 + \alpha} \leq 1 \tag{4}$$

(where $(S_1^*$ and $S_2^*)$ are the pathogen-free equilibrium densities of the susceptible hosts), it is possible to bring the epidemic under control and eliminate the pathogen [see Supporting information, Appendix A]. Under this boundary condition of B, any path that enters B must remain permanently within the set. The criterion is analogous to the epidemic reproductive criterion, R_0 (Anderson and May, 1979; Van den Driessche and Watmough, 2002) and is a necessary but not sufficient criterion to prevent invasion of an epidemic.

We now consider two cases in which the efficiency of detection is set so that α either does or does not satisfy the condition Eq. 4. When α satisfies the condition (cf Eq. 4), the pathogen may be eliminated and all admissible paths fall into two categories: those that never enter region B, and those that enter this region and never leave it again [see Supporting information, Appendix A]. When α does not satisfy Eq. 4 the disease may not be eliminated.

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2.4. First Case: α satisfies Eq. 4

The current value of the Hamiltonian (Pinch, 1993) is given by:

$$\begin{aligned} H &= e^{-rt}(p_1 S_1 + p_2 S_2) + m_1 \dot{S}_1 \\ &\quad + m_2 \dot{I}_1 + m_3 \dot{S}_2 + m_4 \dot{I}_2 \end{aligned} \tag{5}$$

where m_i are the costate variables. We are only interested in the case where $\alpha(I_1 + I_2) \geq M/c$, and since $\alpha f_1 I_1 = M/c - \alpha f_2 I_2$ under this condition, the Hamiltonian can be written as

$$\begin{aligned} H = {} & e^{-rt}(p_1 S_1 + p_2 S_2) + m_1\Big(b_1(\kappa - S_1 - I_1 \\ & - S_2 - I_2) - d_1 S_1 - \beta_{11} S_1 I_1 - \beta_{21} S_1 I_2\Big) \\ & + m_2\Big(\beta_{11} S_1 I_1 + \beta_{21} S_1 I_2 - d_1 I_1 - \mu_1 I_1 - (M/c \\ & - \alpha f_2 I_2)\Big) + m_3\Big(b_2(\kappa - S_2 - I_2 - S_1 - I_1) - d_2 S_2 \\ & - \beta_{12} S_2 I_1 - \beta_{22} S_2 I_2\Big) + m_4\Big(\beta_{12} S_2 I_1 \\ & + \beta_{22} S_2 I_2 - d_2 I_2 - \mu_2 I_2 - \alpha f_2 I_2\Big) \end{aligned}$$

f_2 (and hence f_1) has to be chosen so as to maximize the Hamiltonian (Seierstad and Sydsaeter, 1986). Maximization yields the following result:

$$\begin{aligned} &\text{If } m_2 - m_4 > 0 \text{ then } f_2 = \min(1, M/c\alpha I_2) \\ &\qquad\qquad \text{and } \alpha f_1 I_1 = M/c - \alpha f_2 I_2, \\ &\text{If } m_2 - m_4 < 0 \text{ then } f_1 = \min(1, M/c\alpha I_1) \\ &\qquad\qquad \text{and } \alpha f_2 I_2 = M/c - \alpha f_1 I_1. \end{aligned} \tag{6}$$

And it must be the case that

$$\dot{m}_i = -\frac{\partial H}{\partial x_i}, \tag{7}$$

where x_i is the state variable corresponding to m_i.

2.5. Interior solution

We suppose that there exists an allowable path that satisfies the above maximal conditions on the Hamiltonian, and for which there exists an open interval where we have $m_2 = m_4$. By differentiating $m_2 - m_4$ over that open interval, we obtain

$$\begin{aligned} \dot{m}_2 - \dot{m}_4 = {} & (m_1 - m_2)(\beta_{11} - \beta_{21}) S_1 - m_2 \mu_2 \\ & + m_2 \mu_1 + (m_3 - m_4)(\beta_{12} - \beta_{22}) S_2 \\ & = 0. \end{aligned} \tag{8}$$

From an economical view point, the co-state variables can be interpreted as shadow prices. The variables m_i indicate respectively the marginal benefit to society of increasing by one unit the stock of the corresponding state variable (Behncke, 2000; Dorfman, 1969; Rowthorn and Brown, 2003). Because infection is harmful, and increasing the stock of infected individuals decreases the stock of susceptibles, the shadow prices m_2 and m_4 must be negative. $-m_j\,(j = 2, 4)$ represent the amount that society is willing to invest for control, that would result in reducing the stock of infected individuals by one unit respectively in the first and second species. The shadow prices m_1 and m_3 must be positive. $(m_1 - m_2) \geq 0$, $(m_3 - m_4) \geq 0$ and $-m_2 \geq 0$.

2.6. Asymmetric case

Here, we assume that the dynamics of infection in the community are mainly driven by the first species and $\beta_{11} > \beta_{12} \geq \beta_{22}$ and $\beta_{11} \geq \beta_{21}$. From the previous section on interior solutions, if $\mu_2 \geq \mu_1$ (cf Eq. 8), then the sign of $m_2 - m_4$ is either constant or switches only once from negative to positive. Therefore according to the maximal condition on the Hamiltonian given by Eq. 6, whenever $\alpha(I_1 + I_2) > M/c$, the optimal culling strategy is one of the following:

$$\begin{cases} \text{High } \beta \text{ strategy:} \\ f_1 = \min(1, M/c\alpha I_1);\ \alpha f_2 I_2 = M/c - \alpha f_1 I_1. \\ \\ \text{Low } \beta \text{ strategy:} \\ f_2 = \min(1, M/c\alpha I_2);\ \alpha f_1 I_1 = M/c - \alpha f_2 I_2. \\ \\ \text{Switching high to low } \beta \text{ strategy:} \\ \text{with a single switch from implementing} \\ \text{the high } \beta \text{ strategy to implementing} \\ \text{the low } \beta \text{ strategy.} \end{cases}$$

2.7. Symmetric case

Here we assume that the dynamics of infection are equally driven by both species (i.e. $\beta_{11} = \beta_{22}$, $\beta_{12} = \beta_{21}$ and $\mu_1 = \mu_2$). From Eq. 8 and the economical interpretation of costate variables as shadow prices, we easily show that if an interior solution exists it will satisfy at least one of the following condition on the open interval [see Supporting information]:

$$\begin{aligned} &\text{If } S_1 = S_2 \text{ on the interval, then} \\ &\qquad \alpha f_1 I_1 = \alpha f_2 I_2 = M/2c, \end{aligned} \tag{9}$$

$$\begin{aligned} &\text{If } S_i > S_j \text{ on the interval, then} \\ &\qquad f_j = \min(1, M/c\alpha I_j) \text{ and} \\ &\alpha f_i I_i = M/c - \alpha f_j I_j, \text{ with } i, j = 1, 2. \end{aligned} \tag{10}$$

We assume that adding infecteds to the species with the higher level of susceptibles is more harmful to the system than adding infecteds to the species with lower level

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of susceptibles. Such an assumption can be justified by the fact that the rate of infection within is greater than the rate between species. Increasing the amount of infected individuals in the species with the higher level of susceptibles will surely generate more infection than the same increase in the other species. Therefore, the following equation satisfies Eq. 6,

$$\text{If } S_j > S_i \text{ then } f_j = \min(1, M/c\alpha I_j)$$
$$\alpha f_i I_i = M/c - \alpha f_j I_j. \quad (11)$$

Accordingly we derive the following strategies as candidates for optimality, in addition to the reciprocal switching strategies from one to the other:

1. give priority to the species with higher level of susceptibles;
2. give priority to the species with lower level of susceptibles.

2.8. Second Case: α does not satisfy Eq. 4

Now we assume that α does not satisfy Eq. 4. Under this condition, it is not possible to prove that if an admissible path enters region B it will never leave again. Because of the difficulty in undertaking any analytical investigation, we rely on numerical simulation to gain some insights on the optimal strategy of control. For the Asymmetric case, using the same method as described in the First Case, it is evident that on every interval on which an admissible solution enters region B just once, the optimal strategy of control is one of those obtained when Eq. 4 is satisfied. For the symmetric case, we compare the strategies which were derived for α satisfying Eq. 4.

2.9. Numerical test

Simulations were done for different initial levels of infection. We used a large set of initial conditions to test the robustness of the ranking of control strategies. To build the set of initial condition, we consider two scenarios. Firstly, we assume a disease outbreak starts on one of the species with a very small proportion of individuals being infected. We run the epidemic until equilibrium, and record the values of the state of the system at 50 different points in time so as to span the trajectory of the epidemic. we use these to build a 50×50 array of initial conditions. Secondly, we assume that the disease outbreak starts simultaneously on both species with an equal level of infection. We repeat the same process as above, and build another 50×50 array of initial conditions [see Supporting information for more details].

3. Results

3.1. Asymmetric case

When there are more detected individuals than can be culled, a systematic analysis shows that there are only three candidates for optimality:

1. 'High β strategy': give priority to the species with the higher transmission rate;
2. 'Low β strategy': give priority to the species with the lower transmission rate;
3. 'Switch high to low β strategy': a single switch from giving priority to species with the higher transmission rate to giving priority to the species with the lower transmission rate.

Numerical simulation shows that the 'High β strategy' outperforms the other two strategies (Figure 1).

3.2. Symmetric case

Here we assume equality of the rates of infections thus $\beta_{11} = \beta_{22}$ and $\beta_{12} = \beta_{21}$. Without loss of generality, we also assume that $\beta_{11} > \beta_{12}$ and that $\mu_1 = \mu_2$. Regardless of the value of α, we were able to derive analytically four candidates for optimality:

1. 'High susceptibles strategy': give priority to the species with the higher level of susceptibles;
2. 'Low susceptibles strategy': give priority to the species with the lower level of susceptibles;
3. 'Single switch from high to low susceptibles strategy': single switch from giving priority to the species with the higher level of susceptibles to giving priority to the species with the lower level of susceptibles;
4. 'Single switch from low to high susceptibles strategy': single switch from giving priority to the species with the lower level of susceptibles to giving priority to the species with the higher level of susceptibles.

Following the analysis of an SIS model by Rowthorn et al. (2009) we also added the following two strategies

5. 'Low infectives strategy': give priority to the species with the lower level of infection;
6. 'High infectives strategy': give priority to the species with the higher level of infection.

By giving priority, it means that resources for control are used preferentially to treat (i.e. to cull detected individuals) on the target species (e.g. the one with the higher level of susceptibles): only when there are resources left over, are detected individuals from the

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other species treated. We note that the 'low susceptible strategy' effectively results in equalizing the levels of susceptibles of both species, while the 'high infectives strategy' effectively results in equalizing the levels of infectives of both species. Switching strategies involve fixed but *a priori* unknown switching times.

Using a range of values to explore parameter space, simulations show that the 'single switch from low to high susceptibles strategy' always outperforms the other five candidates for optimality. Although it was not possible to prove this analytically, extensive numerical simulation supports the hypothesis [see Supporting information, Appendix B].

Further numerical exploration identified two classes of solution; one in which the optimal switching time occurs when control is initiated, the other, accounting for only $\sim$ 10% of the range of initial conditions, occurs at some later time. It follows that, since the optimal switching occurs at time zero, the optimal switching strategy is equivalent to the 'high susceptibles strategy' (cf Case 1 in Figure 2) for the majority of initial conditions.

4. Conclusions and discussion

We have used a simple SI two-species model with vital host dynamics to describe an epidemic spreading through a mixed two-species stand of host plants that are susceptible to a common pathogen. For simplicity, the vital dynamics of the species are described by a simple monomolecular-type function to limit the total population size. Our results, however, hold for more complex functions such as a logistic function and incorporating Lotka-Volterra competition to describe the intrinsic host dynamics. Our investigation was done for two different conditions involving asymmetric and symmetric scenarios in the dynamics of transmission between the two species. Assuming that resources available for the control of disease outbreaks are limited, we first identify a simple epidemiological threshold for invasion of the pathogen that incorporates α, the rate of detection of infected individuals. Below this threshold there are sufficient resources to control all infected individuals. Above the threshold, we seek to identify optimal strategies for the deployment of control when there are not enough resources to treat all infected individuals. The asymmetric scenario is motivated by contemporary concerns for the control of sudden oak death in bay laurel - tanoak communities, an example of a devastating disease of natural communities (Rizzo and Garbelotto, 2003). It also allows rigorous analysis to identify the optimal culling strategy when resources for control are limited. The symmetrical scenario generalises to SI epidemics of plant and animal pathogens in which the transmission rates are similar on different hosts and susceptible hosts are replenished by births.

We were able to find an optimum solution for both the asymmetric and symmetric scenarios when the detection rate, α, is chosen to satisfy condition Eq. 4, whereby it is possible to bring the epidemic under control and eliminate the pathogen. For the asymmetric scenario, we have shown that it is optimal to give priority to the more infectious species. In the symmetric case, an optimum solution ordinarily consists of a single switch strategy in which priority is first given to the species with the lower level of susceptibles before switching at a critical switching time to give priority to the species with the higher level of susceptibles. The switching time is critical in implementing this optimum control strategy. Even though our numerical results show that the switching time frequently occurs when control begins, the optimal switching time cannot usually be determined in advance (Forster and Gilligan, 2007), in common with many optimal solutions for disease control (Behncke, 2000; Greenhalgh, 1988; Morton and Wickwire, 1974). Implementing a switching strategy is always subject to the risk of missing the optimal switching time, with the result, confirmed here, that the switching strategy then fails to outperform simpler alternative, if non-optimal, strategies. Our results show that giving priority to the species with more susceptibles is always the second best strategy for the symmetric case (cf Figure 2). We conclude that though this may be sub-optimal it is is the most robust control strategy for practical implementation. It is tempting to suppose that further analysis of epidemics arising from different initial conditions would identify conditions for the switching time to correspond with the onset of control. In practice, this is difficult because it involves exploring four-dimensional space for the state variables, with the additional complexities of births and deaths. Further progress may, however, be made for a simplified model.

When α does not satisfy Eq. 4, analytical investigation is not possible because of the complexity of the long term behavior of the trajectories of disease propagation. Numerical results show that giving priority to the more infectious (high β) species is optimal. We were unable to establish an unequivocal result for the symmetric case but again numerical simulation shows that the single switch strategy (from targeting low to high susceptible sub-populations) is locally optimum. Once again, following extensive numerical investigation we showed the sensitivity of the optimal strategy to errors in the switching time, and the robustness of adopting the

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next best alternative (the 'high susceptibles strategy') when, as would usually be the case, the switching time is not known.

Our models assume some knowledge of the system and in particular the relative magnitude of the transmission rates for each species. We now consider what should be done if the relative transmission rates are not known before control is implemented (Table 2) Suppose that we assume the system to be symmetric when it is indeed asymmetric. The analyses suggest that for a robust strategy, the 'high susceptibles strategy' ought to be preferred. The outcome depends upon two factors, the initial conditions (which sub-population is infected first) and the conditions at the time control is initiated (which sub-population has the higher level of susceptibles) (Table 2). If infection started in the high β species, the 'high susceptibles strategy' is equivalent to the 'low β strategy' and hence is the *worst* strategy.

The error is modified when infection is initiated in the low β species, and depends upon the state of system when control is started (Table 2). If the level of susceptibles is greater in the low β species when control is initiated, the 'high susceptibles strategy' remains the worst policy. The result is transformed, however, to the best (i.e. optimal) policy when the condition is reversed and there are more susceptibles available for infection in the high β species. The corresponding solutions when the transmission rates are assumed to be asymmetric are also summarised in Table 2. We conclude that prior knowledge of the relative magnitudes for transmission rates in metapopulations are essential to avoid serious errors in implementing policies based upon optimal control theory.

The optimality of the 'high β strategy' for the asymmetric case is based upon a rather general assumption $\beta_{11} > \beta_{12}$. However, numerical simulation shows that if $\beta_{12} > \beta_{11}$, the 'switch high to low β strategy' would instead be optimal.

In this analysis, we have used the conventional economic device of a discount rate to give more weight for the criterion of optimization to shorter than long-term control. The choice of the discount rate (r) affects the relative valuation of the present and future disease. For different value of r, other than the default value 0.05, the qualitative nature of our results remain unchanged.

Our models make two important assumptions. The first concerns the absence of a delay between detection and culling. This assumption can be easily relaxed by adding delays between detection and culling, and subdividing the infected compartment into two subcompartments: infected but not yet detected, and detected. The introduction of a delay increases the number of states variables. It makes the analysis more voluminous in handling the extra variables, but still tractable. Our exploratory analyses show that the qualitative nature of the results remains unchanged. One logical and profitable extension of these analyses would be to consider the balance between detection and eradication. The second assumption concerns the way in which the treatment affects the epidemiological dynamics. While we use culling as a means of control, our analyses also hold for treatment of infects, for example by application of an eradicant pesticide or drug, to shorten the infectious period.

Our results here are established for deterministic systems using optimal control theory. Methods to incorporate uncertainty in our knowledge of the state of the system will be the subject of a separate investigation.

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Figure 1: Strategies for optimizing control in asymmetric two-species model. The 'high β strategy' outperforms the 'low β' and the 'switching high to low β' strategies. The switching strategy is shown for a range of arbitrarily-selected switching times extending from the onset of control to the time, ($\tau = 1$)), at which the the combined path for the disease trajectories enters region B, in which it is possible to treat all detected individuals (see Methods and Supplementary Information for details). The value of the control strategy is expressed relative to the value of the 'high β strategy'). Default parameters are given in Table 1 with $\alpha = 0.25$, $M = 0.02$ and $c = 1$.

Figure 2: Effect of switching time on the relative performance of the 'single switch from low to high susceptibles strategy' compared with the high susceptibles strategy. Two possible classes of solution are indicated: Class 1, in which the optimal switching time occurs at the onset of control (denoted by switching time = 0) ; Class 2 in which the the optimal switching occurs at some later time. The relative performance of the switching strategy for each class is shown for a range of arbitrarily-selected switching times. These extend from the onset of control to the time, ($\tau = 1$), at which the combined path for the disease trajectories enters region B, in which it is possible to treat all detected individuals (see Methods and Supplementary Information for details). Default parameters are given by Table 1 with $\alpha = 0.25$, $M = 0.02$ and $c = 1$.

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Table 1: Default parameters used in simulations

Symbol	Description	Asym*	Sym$^\perp$
κ	carrying capacity	3	3
b_i	birth rate $(i = 1, 2)$	1/100	1/100
d_i	natural death rate $(i = 1, 2)$	1/100	1/100
β_{11}	rate of infection within species 1	0.2	0.2
β_{12}	rate of infection from species 1 to species 2	0.16	0.1
β_{22}	rate of infection within species 2	0.14	0.2
β_{21}	rate of infection from species 2 to species 1	0.12	0.1
${\mu_1}^{-1}$	infection period of species 1	1/80	1/5
${\mu_2}^{-1}$	infection period of species 2	1/5	1/5
p_1	utility of species 1 per individual/time	1	1
p_2	utility of species 2 per individual/time	1	1
r	discount rate	0.05	0.05

*Asymmetric
$^\perp$Symmetric

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Table 2: Outcome of control strategies when the assumed and true epidemiological states differ.

True state			Assumed state	
			Symmetric	Asymmetric
	LIC*	Control initiated	DS$^{\perp}$: priority high S	DS$^{\perp}$: priority low S
Asymmetric	High β species		Worst	Best‡
	Low β species	Before $S_{low} > S_{high}$	Best	Worst
		After $S_{low} > S_{high}$	Worst	Best
Symmetric			Robust$^{\mp}$	Locally worst$^{\pm}$

*Location of initial infection.

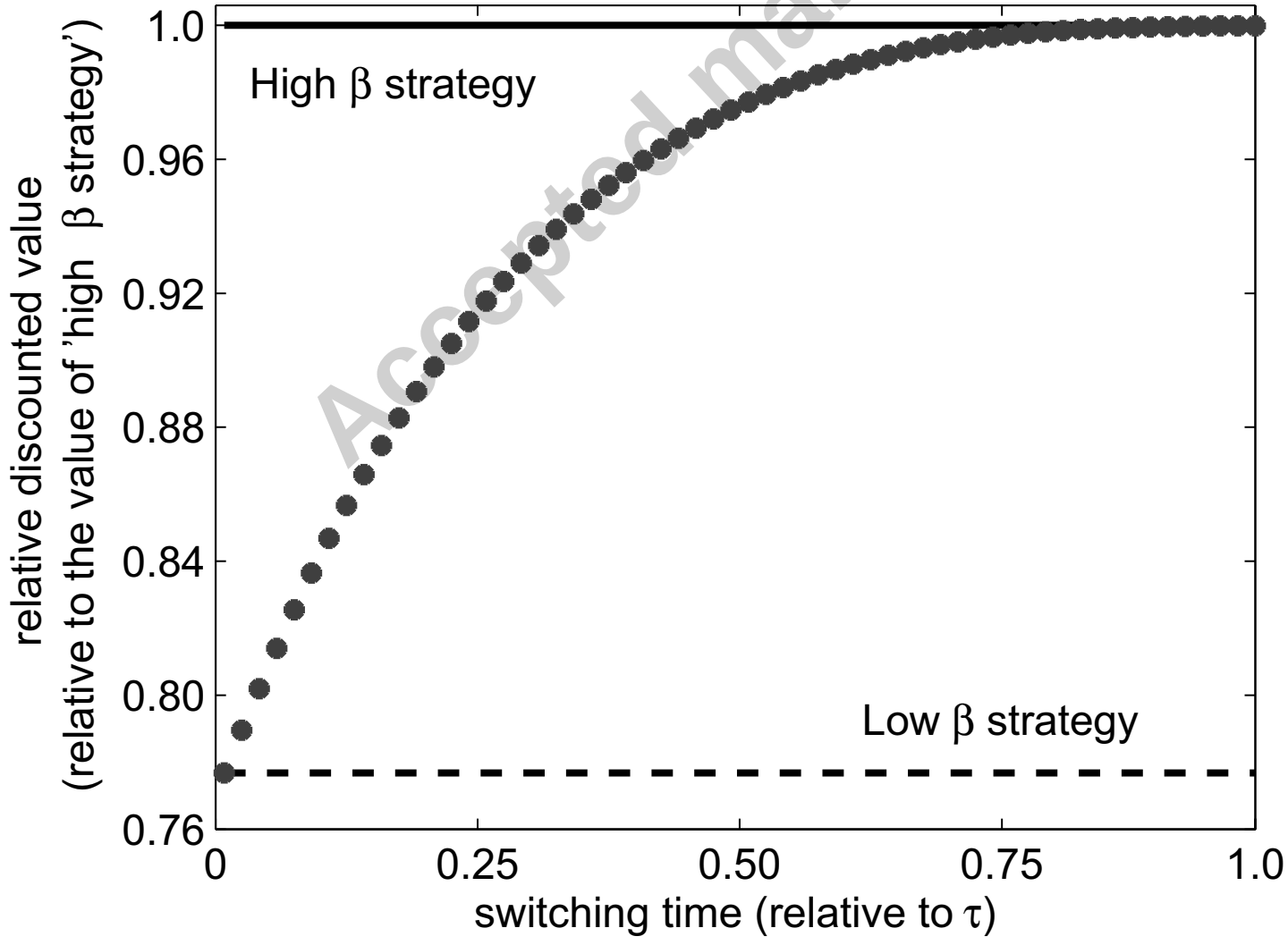
$^{\perp}$Default strategy

‡Giving priority to the sub-population with the lower level of susceptibles is consistent with the biologically plausible consequence that the high β species (sub-population) is the main source of infection, hence 'high β' is analogous to 'low susceptibles' and 'low β' is analogous to 'high susceptibles', providing the epidemic is initiated in the high β species.

$^{\mp}$Giving priority to the sub-population with high susceptibles is robust in that it outperforms the optimal (switching) strategy, when the switching time is unknown (see text for details).

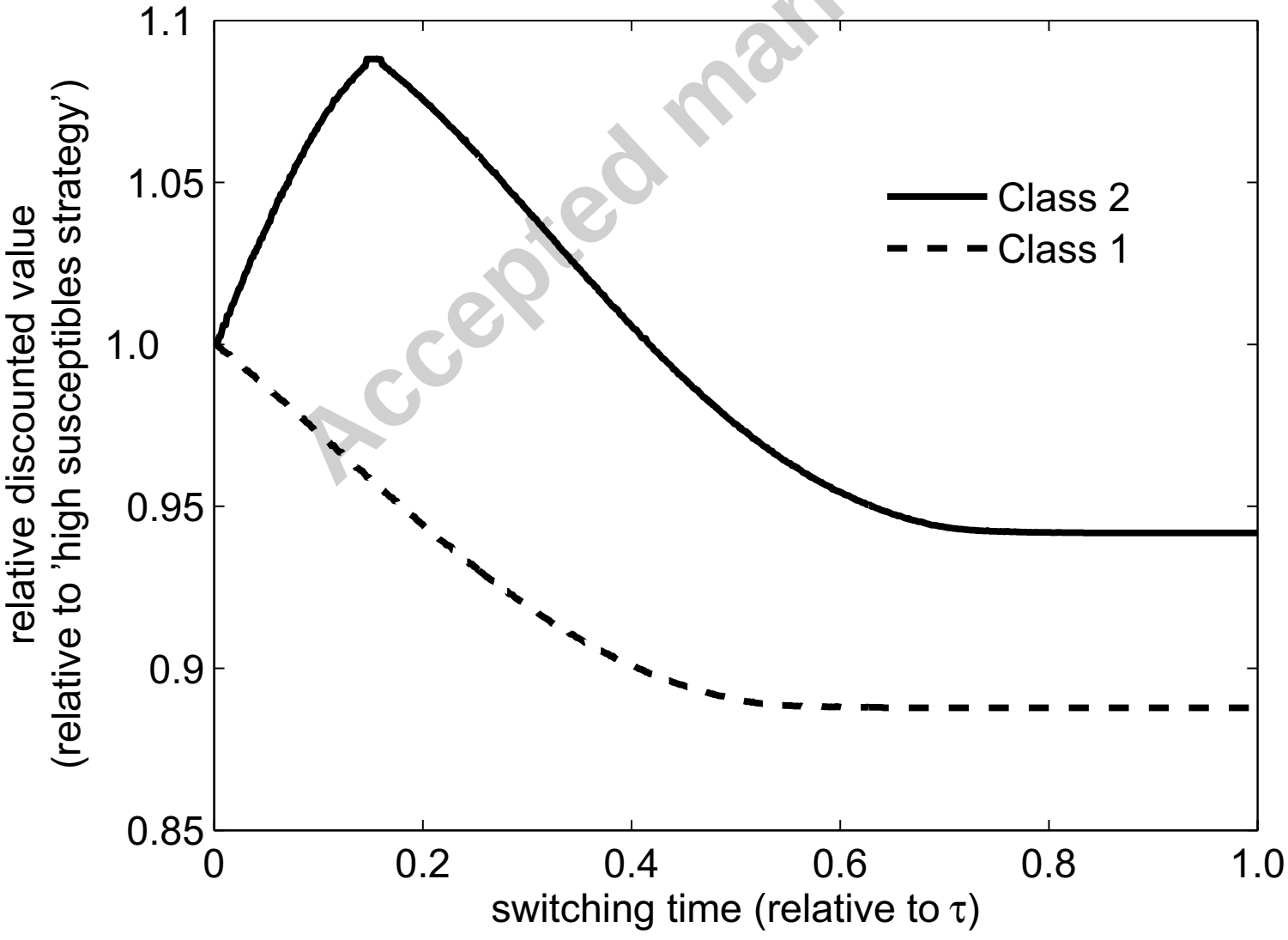
$^{\pm}$Locally worst strategy amongst six strategies tested.

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