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The exclusion problem in seasonally forced epidemiological systems

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HIGHLIGHTS

- New holistic control approach helps solve the pathogen exclusion problem.
- Results inform design of exclusion strategies in complex forced conditions.
- New method for solving the highly unstable optimal exclusion problem.
- New method to find R_0 analytically under multi-component forcing.
- Investigation of epidemiological conditions using 2-stage control analysis.

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ABSTRACT

The pathogen exclusion problem is the problem of finding control measures that will exclude a pathogen from an ecological system or, if the system is already disease-free, maintain it in that state. To solve this problem we work within a holistic control theory framework which is consistent with conventional theory for simple systems (where there is no external forcing and constant controls) and seamlessly generalises to complex systems that are subject to multiple component seasonal forcing and targeted variable controls. We develop, customise and integrate a range of numerical and algebraic procedures that provide a coherent methodology powerful enough to solve the exclusion problem in the general case. An important aspect of our solution procedure is its two-stage structure which reveals the epidemiological consequences of the controls used for exclusion. This information augments technical and economic considerations in the design of an acceptable exclusion strategy. Our methodology is used in two examples to show how time-varying controls can exploit the interference and reinforcement created by the external and internal lag structure and encourage the system to 'take over' some of the exclusion effort. On–off control switching, resonant amplification, optimality and controllability are important issues that emerge in the discussion.

1. Introduction

It is well known that variability in the environment can have a significant impact on the dynamic behaviour of epidemiological systems whether they involve humans or animals or both (Chesson, 1982; Grassly and Fraser, 2006). Of particular interest is periodic variation, especially seasonality, but there are other examples where the period is greater than a year (e.g. El Nino (Koelle et al., 2005) and African rain patterns (Wichmann et al., 2003)) or less than a year (e.g. marine life subject to tidal or light intensity cycles (Rinaldi et al., 1993)). In simple epidemiological systems environmental forcing acts primarily through infection transmission. This is the case in childhood diseases such as measles (Dietz, 1976) where the seasonal variation is caused by the term structure of the school year. In other cases several forcing components are in play. A study of conjunctivitis in house finches (Hosseini et al., 2004) found that infection is transmitted in the autumn/winter when there is population aggregation but breeding takes place in the summer when there is dispersal. These two seasonal effects are 'out of phase'. A third example, also highlighting the importance of lags, is that of a managed game-bird population subject to two forms of variable external forcing: A seasonally transmitted disease and 'harvesting' restricted to particular times of the year. The choice of lag between transmission and harvesting determines whether harvesting reduces or increases the impact of the disease (Choisy and Rohani, 2006).

Another important factor that influences how external forcing affects a system is the number and nature of the different infected host types (Diekmann et al., 1990, 2010). Unforced systems with more than one host type have received a lot of attention in the literature, for

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example Anderson and May (1981, 1986) and many others. Of particular interest recently has been the spread of bovine TB between badgers and livestock (Cox et al., 2005, Lintott et al., 2013) and the dominance of the grey over the red squirrel population because of reinforcement between direct competition and apparent competition mediated by a parapox virus (Tompkins et al., 2003). Much less work has been carried out on how external forcing affects transmission between species and there remains much more to do in this area (Brassil, 2006). However, seasonality in host-vector systems has received some attention. Bacaer and Guernaoui (2006) analysed a seasonal model for *leishmaniasis* in Chichaoua, Morocco while Wang and Zhao (2008) studied a simple seasonal model for dengue.

The specific problem studied in this paper is how to exclude a pathogen from an epidemiological system or how to maintain that exclusion if the system is already disease-free. In the absence of forcing and with constant controls the exclusion problem can be solved explicitly for a standard model in terms of its resident asymptotic state even when there are multiple host types (Diekmann et al., 1990, 2010). With forcing present the exclusion problem is much more difficult to solve (Heesterbeek and Roberts, 1995; Bacaer and Guernaoui, 2006; Wang and Zhao 2008). Most applications have been limited to the simplest cases with forcing only on infection transmission and no structure in the resident subsystem. Further advances in solution methods are necessary to study the new opportunities for bringing about exclusion that are created when these limitations are removed.

Our primary objective in this paper therefore is to contribute to the development of a sufficiently powerful coherent and insightful methodology to solve the exclusion problem for the general case of complex epidemiological systems that have a structured resident subsystem (with predation or competitive forces in play for example), multiple infected host types and subject to variable controls and multiple seasonal forcing components. Since the exclusion problem is a control problem, involving intervention with a set of control measures, we work within a control theory framework to find the levels of these controls that bring about exclusion. Our methodology involves the following three main components: An approximation procedure that replaces nonlinearities by explicitly solvable linear equations (Greenman and Pasour, 2012); monodromy theory on which to base the numerical calculations (Hale, 1969); optimal control theory of use in exploring the impact of variable controls (Lenhart and Workman, 2007). Integrating these different procedures creates an efficient 'fit for purpose' exclusion methodology and, in so doing, divides the exclusion process into two distinct stages that provide insight into the epidemiology of exclusion and connectivity with other approaches to be found in the literature.

The paper is set out as follows. In Section 2 there is a general discussion on how to solve the exclusion problem for a special control u that will later provide the link to all other controls of interest. In Section 3 the exclusion procedure is applied to invasion systems with one infected state and in Section 4 to systems with 2 or more such states. It is in Sections 3.4 and 4.4 where it is shown how to extend the theory to handle a general set of pre-emptive controls. Examples illustrate what difference forcing can make to the exclusion dynamics and what mechanisms are activated during forcing to explain the changes. This involves comparing systems with single or multiple host types, forcing with single or multiple components and controls that are constant or variable.

2. The pathogen exclusion problem from a control theory perspective

In Section 2.1 we introduce the rare invader approximation that simplifies the solution of the exclusion problem by dividing it into two stages. Further we introduce the special control u that removes a proportion of the newly infecteds and define the 'effort' required to remove the pathogen using this control. In Section 2.2 we describe how to apply the zero invader growth condition for exclusion by relating this condition to the eigenvalues of the monodromy matrix. We discuss the relationship between exclusion effort and the basic reproduction number R_0 when control u is constant and highlight the strengths of the control approach.

2.1. The rare invader approximation

Consider the controlled epidemiological system modelled by the following equations:

$$\frac{d\underline{x}}{dt} = \underline{f}(\underline{x}, \underline{y}, \underline{u}, t) \tag{1a}$$

$$\frac{d\underline{y}}{dt} = \underline{g}(\underline{x}, \underline{y}, \underline{u}, t) \tag{1b}$$

where $\underline{x}$ is the vector of uninfected (resident) populations (for example the susceptibles and the immune), $\underline{y}$ the vector of the infected (invader) populations and $\underline{u}$ the vector of controls. Eq. (1a) are the 'resident equations' and (1b) the 'invasion equations'. This system is subject to periodic environmental forcing as indicated by the explicit time dependence t of functions $\underline{f}, \underline{g}$. We are particularly interested in the case that control $\underline{u}$ is variable in time but first we consider the simpler case where it is constant.

The solution of the (pathogen) exclusion problem (to exclude or prevent invasion of a pathogen) is simplified by using the Rare Invader Approximation (RIA) which assumes that the number of infecteds is so small that they can be ignored in the resident Eq. (1a) and so small that the invasion Eq. (1b) can be linearised about the disease free equilibrium. This approximation holds in the early stage of an invasion or in the final stage of exclusion. The RIA defines a two-stage solution procedure: First solve the decoupled resident equations: $d\underline{x}/dt = \underline{f}(\underline{x}, \underline{0}, \underline{u}, t)$ for $\underline{x}$. Then solve the linear invasion equations after substitution of the asymptotic resident solution, $\underline{x}_\infty$, i.e. solve: $d\underline{y}/dt = G(\underline{x}_\infty, \underline{0}, \underline{u}, t)\underline{y}$ where $G(\underline{x}, \underline{y}, \underline{u}, t) = \partial \underline{g}/\partial \underline{y}$ is the matrix of derivatives of vector function $\underline{g}$. Matrix G is the Jacobian for the invasion subsystem and will be labelled more simply as J

$$\frac{d\underline{y}}{dt} = J.\underline{y} \tag{2}$$

The problem is to find controls $\underline{u}$ where the asymptotic growth rate of the infected populations in (2) is zero. These solutions define the 'pathogen threshold' separating solutions where the growth rate is negative (i.e. the pathogen is excluded) and positive (i.e. the pathogen invades). On this threshold the RIA becomes exact and so its use in solving the exclusion problem is appropriate.

In epidemiological models with compartmental structure and with the controls inactive, matrix J in (2) can be written as $J = F - V$ where F is the transmission matrix specifying the number of newly infecteds (per infected individual) for each host type and V is the transition matrix that specifies the flow rates between compartments and with the external world. The term 'host type' identifies the state a host enters at the point of infection and hence the different ways in which infection can occur (Diekmann and Heesterbeek (2000); Hartemink et al. 2008). We will also use the term 'infected state' to identify the states a host can be in throughout its infected lifetime. The host types identify a subset of the infected states. For example, for the SEIR model there is one host type (the latent state E), but two infected states (the latent state E and the infectious state I). For the SISI model, describing the transmission of disease without latency within and between two host species, there are two host types corresponding to the I states and these are also the infected states. This model is discussed in Section 4.