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Pathogen Exclusion from Eco-Epidemiological Systems

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abstract: Increasing concerns about the changing environment and the emergence of pathogens that cross species boundaries have added to the urgency of understanding the dynamics of complex ecological systems infected by pathogens. Of particular interest is the often counterintuitive way in which infection and predation interact and the consequent difficulties in designing control strategies to manage the system. To understand the mechanisms involved, we focus on the pathogen exclusion problem, using control maps (on which the network of exclusion thresholds are plotted) in order to readily identify which exclusion strategies will work and why others will not. We apply this approach to the analysis of parasite exclusion in two game bird ecologies. For higher dimensions, we propose a computational scheme that will generate the optimal exclusion strategy, taking into account all operational constraints on the pathogen invasion matrix, populations, and controls. The situation is further complicated when external forcing distorts pathogen thresholds. This distortion is highly sensitive to the lags between forcing components, a sensitivity that can be exploited by management using correctly lagged cyclically varying controls to reduce the effort involved in pathogen exclusion.

Keywords: ecological control, red grouse, apparent competition, nonlinear optimization, environmental forcing, resonance.

Introduction

Theoretical and empirical studies have provided insight into the dynamics of a specialist pathogen and its host (Anderson and May 1986, 1991). Out of these studies has emerged the important concept of invasion threshold (typically determined by the basic reproduction number R_0). Its properties reveal the various ways in which the pathogen can be excluded, for example, by vaccination, quarantine, and (for wildlife) regular culling. A more complicated situation occurs when a generalist pathogen is present in a community of competing hosts. Its presence can lead to the reversal of previous dominance relations and, on occasion, exclusion of hosts. This is what is thought to have happened with the exclusion of the rhesus monkey *Macaca mulatta* from Eastern India and Bangladesh as a result of apparent competition with the macaque *Macaca fuscularis*, mediated by the malarial parasite *Plasmodium knowlesi* (Allison 1982). The interaction here is between direct and apparent competition (Holt 1977; Hudson and Greenman 1998).

Also of importance is the occurrence of infection in predator-prey systems. There are many examples where this happens: the European tapeworm *Echinococcus multilocularis* is established in both wolf and moose on Isle Royale (Hadeler and Freedman 1989). There is heavy mortality of migrating pelicans feeding on infected fish in the highly toxic Salton Sea (Kaiser 1999), and predation affects the incidence of infection (*Trichostrongylus tenuis*) in red grouse attacked by foxes (Hudson et al. 1992). The complexity here arises from the interaction between infection and predation, where the predator may or may not be host to the pathogen.

Various approaches have been adopted to generalize pathogen exclusion theory to handle these more complicated situations. Ways have been found to generalize the basic reproduction number R_0 to handle heterogeneous host populations (Diekmann et al. 1990; Dobson 2004). Alternatively, invasion properties can be studied as an outcome of a local and global stability analysis of system equilibria (Arino et al. 2004; Hethcote et al. 2004; Bairagi et al. 2009). Our approach is to go back to basics and work with the invasion matrix in rare invader approximation to enable us to focus directly on the pathogen invasion threshold (Greenman and Hoyle 2008). In this approximation, it is assumed that the infected populations are sufficiently small in size that they can be ignored in finding the equilibrium levels of the resident (noninfected) populations (so the resident population equations can be decoupled) and sufficiently small that the invasion equations for the infected populations can be linearized and written in matrix form.

With a more complex system structure, more controls are likely to be available as well as more ways of using them to exclude a pathogen. For example, one might be able to directly control the number of predators (e.g.,

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through controlled predator breeding and release into the infected ecological system). In Machupo, a virulent virus spread by rodents was eliminated by the importation of domestic cats (Johnson et al. 1965). For those situations where the predator cannot be directly controlled, one might be able to increase its survival rate (e.g., by protecting its habitat) or increase predation efficiency by opening up or improving access to the prey habitat (e.g., by removing man-made or natural barriers). Managing infection transmission may be possible through vaccination (directly with a trap and test program or indirectly through distributed pellets), increased biosecurity measures, or earlier infection detection (Donnelly et al. 2006).

One difficulty is that in some situations particular controls, although implementable, may be counterproductive in the attempt to achieve management objectives. For example, the intuitive idea that increasing the effect of predation will always help pathogen exclusion from infected prey is shown not to be the case in a simple example presented below. This is because the interaction between the forces of infection and predation is sufficiently complex that counterintuitive behavior can frequently be observed (Sih et al. 1985; Hudson et al. 1992). When there are just two controls, many of these problems can be identified and resolved by using control maps on which the complete set of thresholds, for all participating species, are superimposed. We apply this approach to the analysis of two game bird ecologies described by the red grouse model of Hudson et al. (1992) and the pheasant-partridge model of Tompkins et al. (2000). For a general eco-epidemiological system, we show how constrained nonlinear optimization theory can be used to find the best exclusion strategy, taking into account all the difficulties discussed.

Finally, we use our theoretical and applied models to study the distortion of the invasion thresholds caused by environmental forcing and show how this might provide an opportunity for management to ease the burden of exclusion by using cyclical controls (Chesson 1984; Greenman and Norman 2007). Most of the detailed mathematics is to be found in appendixes A–C in the online edition of the *American Naturalist*. On terminology, we will refer to the infection-causing agents as parasites since our focus will be on micro- and macroparasites. Although our concern is with exclusion, we will follow the literature and talk about invasion matrices and invasion thresholds. Our use of the term "control" is shorthand for finding ways of shifting the system from an infected to an uninfected state and does not refer to manipulation of the stability properties of equilibria, which our methodology cannot directly address.

Fundamentals

The problem we consider is how to exclude a parasite from an eco-epidemiological system using a specified set of controls. To solve this problem, we will locate in control space the threshold dividing the regions where the infected populations can and cannot successfully invade. This threshold is found from the rare invader approximation where, as previously described, the equations for the invading populations become linear. The invasion matrix defining these linear equations will be denoted by $\mathbf{J}$. The threshold lies on the curve (surface) given by $\det \mathbf{J} = 0$ (where "det" denotes determinant). This is because $\det \mathbf{J}$ is the product of the eigenvalues of $\mathbf{J}$, the leading eigenvalue being 0 at the threshold. If the leading eigenvalue is negative, the invasion attempt will fail; if positive, it will succeed.

We previously studied this problem (Greenman and Hoyle 2008) in the simpler situation of a community of species not directly interacting but all host to a parasite. Our control variables were limited to regular culling of infectious individuals, looking particularly at how many species and which species need to be culled to achieve parasite exclusion. Here we study more complex systems involving predators and immune species as well. The greater complexity leads to the possibility of new ways of managing the system, including predation as well as culling. First, we consider some simple models that show the strengths and weaknesses of these two methods of system control.

Examples with Immune Predator

Consider a simple model with prey host to the parasite but the predator immune. With infection transmission and predation density dependent (McCallum et al. 2001) and no latency or immunity for the prey, the model equations are given by

$$\frac{dS}{dt} = A(H)H - bS - \beta SI - c_1 PS + \gamma I, \tag{1a}$$

$$\frac{dI}{dt} = \beta SI - dI - c_2 PI, \tag{1b}$$

$$\frac{dP}{dt} = \theta_1 c_1 PS + \theta_2 c_2 PI - mP - c_3 PQ. \tag{1c}$$

For the prey, S and I denote the susceptible and infectious populations, respectively, and $H = S + I$ denotes the total population. Parameters a and b describe (per capita) birth rate and natural mortality, respectively, while $r = a - b$ measures the net population growth rate and $d = b + \alpha + \gamma$ the removal rate from the infectious state by natural

mortality (b), by virulence (α; i.e., additional mortality due to infection), or by recovery (γ) to the susceptible state. Self-regulation is embedded in the birth rate: $A(H) = a(1 - \mu H)$, with K the carrying capacity and $\mu = r/(aK)$. The infection transmission constant is β. For the predator, P is the population level and m its natural mortality. Parameters c_1 and c_2 are the predation constants for S and I, respectively, with θ_1 and θ_2 the corresponding biomass conversion factors. With $Q = 0$, equations (1) define for us model 1. (For the moment, we keep $Q = 0$, explaining its significance later.) In rare invader approximation, the resident equations (for S, P) can be written as

$$\frac{dS}{dt} = rS\left(1 - \frac{S}{K}\right) - c_1PS, \tag{2a}$$

$$\frac{dP}{dt} = \theta_1c_1PS - mP - c_3PQ, \tag{2b}$$

taking $I = 0$. The (per capita) growth rate, ξ, for the infectious prey I attempting to invade is then given by

$$\xi = \beta S - d - c_2P = \frac{dI/dt}{I}, \tag{3}$$

where S, P now denote the resident equilibrium population levels. With only one parasite host, the invasion matrix **J** has just one element, given by ξ in equation (3). The parasite (invasion) threshold lies on the curve $\xi = 0$.

As the first of four variations on model 1, consider model 1 with P as the single control (with eq. [2b] overridden). (This would be the case if P were to model gamekeepers or their hunting dogs.) Increasing P will always lead to pathogen exclusion through the combined effects of reducing the susceptible population and increasing mortality of the infectious population. This double effect is clear from equation (3) after substituting resident population $S = K[1 - (c_1/r)P]$ from equation (2a). With P large enough, ξ will become negative and the parasite will be excluded.

Exclusion by predation alone may not be possible if there are three levels to the food chain (Abrams 1993). Such a model can be constructed by reactivating equation (2b) for the now dynamically determined intermediate predator P and interpreting Q as the top predator acting as the single control, no longer zero. Increasing Q will decrease P and increase S, making matters worse, with ξ increasing rather than decreasing in value. (To see this, substitute $S = (c_3Q + m)/(\theta_1c_1)$ and $P = (r/c_1)(1 - S/K)$ as solutions of eqq. [2] in eq. [3].) Decreasing Q will not lead to parasite exclusion either if the two-level food chain with $Q = 0$ still supports the parasite.

As the third example, consider this two-level food chain (with $Q = 0$) controlled by u (infectious prey culling) and v (immune predator culling) and modeled by model 1 with the following substitutions: $d \to d + u$ and $m \to m + v$. The immune predator "culling" (v) can be negative to model enhancement of predator survival. The equilibrium populations are $S = (m + v)/(c_1\theta_1)$, $P = (r/c_1)(1 - S/K)$, yielding a linear parasite threshold AA* ($\xi = 0$) with positive gradient when plotted against controls u, v, as shown in the "control map" of figure 1*A*. This threshold divides the control map into two regions defined by which of the three populations are present: uninfected prey H_0, infected prey H_1, and predator P. Possible parasite exclusion options are cull the prey ($u > 0$), increase predator survival by reducing v ($v < 0$), or some combination of these strategies. Increasing v is clearly not an option since this will reduce the number of predators and increase the prey population and hence the reservoir of infection. A possible control constraint to be aware of is that reducing v might reduce predator mortality to negative values, although this could be interpreted and remodeled as controlled immigration.

The story is very different if two changes are made in the previous model. First, suppose the predator strongly "prefers" (or, more likely, can more easily catch) the infectious prey (i.e., $c_2 > c_1$). Second, suppose it is not easy to differentiate between the infectious and the susceptible prey. Both of these populations would then have to be culled, but this imposes the constraint $u \leq r$ on control u to avoid the prey becoming extinct because of a negative growth rate. The control map of figure 1*B* shows the difficulties that can be encountered. For the parameter values specified in appendix A, culling only the prey will not work because increasing u will lead first to predator exclusion (as the predator threshold BB* is crossed) and then to simultaneous prey and parasite exclusion, since the prey extinction barrier CC* ($r = u$) is crossed before the parasite exclusion threshold AA*. However, enhancing predator survival (by lowering v) will work, with less effort needed the greater the preference for infectious prey. This is apparent from the threshold algebra set out in appendix B.

These examples show that control through predation can be counterproductive because the network structure matters (example 2) while culling can lead to the unwanted exclusion of predator or prey (example 4). So other invasion thresholds can be relevant as well, which is why control maps (in which we superimpose all thresholds) are an important visual tool.

Red Grouse

Hudson et al. (1992) propose a dynamic model describing the behavior of red grouse infected by the cecal nematode

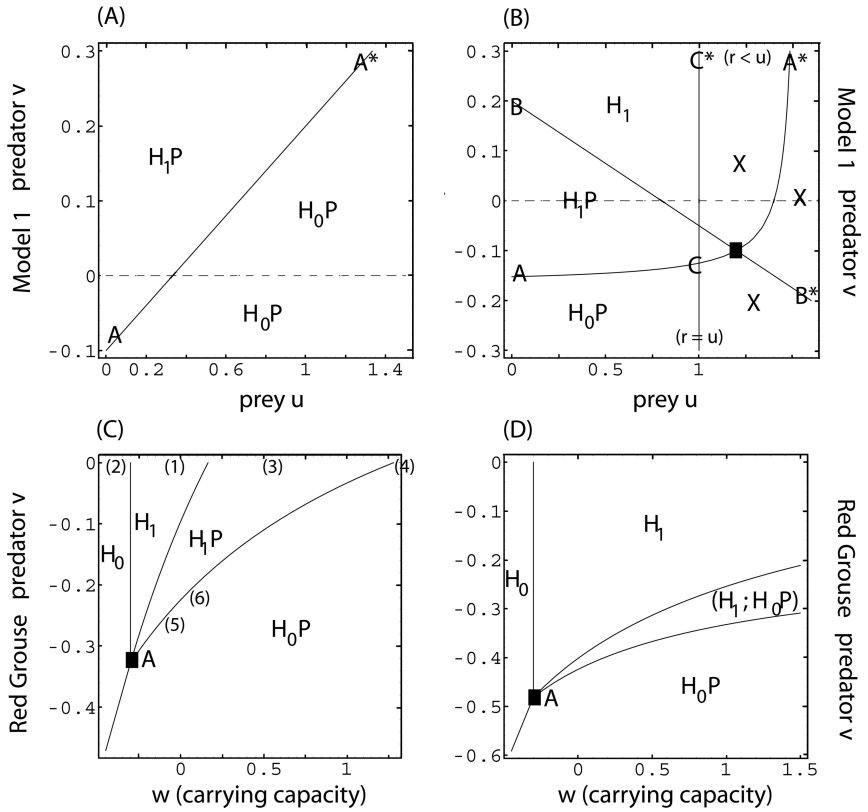

Figure 1: Control maps for systems with an immune predator and a single host prey. Control u denotes prey culling, v denotes predator culling, and w denotes proportionate change in carrying capacity K. Model 1: only infectious prey culled (A) and all prey culled (B). Red grouse model: with infectious prey preference (C) and with no preference (D). Region labeling: H_0, prey uninfected; H_1, prey infected; P, predators; X, empty region.

Trichostrongylus tenuis and subject to predation. The predator is supposed a generalist, justifying the constancy of predator numbers in an otherwise dynamically varying system. Among other issues, the authors discuss what is, in effect, a control problem with predation and prey carrying capacity the control variables. We generalize their analysis, focusing on how best to exclude the macroparasite with these controls by taking the predator now to be a specialist with grouse as its primary resource. The dynamic equations for the host prey (reproduced in app. A) are augmented by equation (1c) for the now dynamic predator, with parameters suggested by field data for foxes (Anderson et al. 1981). The control map for the extended system is shown in figure 1*C*, with v the "culling" rate for the predator ($m \rightarrow m + v$) and w the proportionate change in prey carrying capacity ($K \rightarrow K(1 + w)$). Figure 1*C* shows four thresholds (marking the exclusion of predator or parasite) all emerging from "anchor point" A and defining four regions, each defined by whether the parasite or predator is present.

Suppose the system is initially in state H_1 at the control origin ($w = v = 0$; point 1 in fig. 1*C*), with the predator not able to establish itself. There are three basic ways of excluding the parasite: reduce carrying capacity sufficiently (e.g., $1 \rightarrow 2$) that the prey can no longer support the parasite; progressively increase carrying capacity (e.g., $1 \rightarrow 3 \rightarrow 4$) so that initially both predator and parasite can be supported until the predator eventually wins out; or enhance predator survival (i.e., reduce v) along path $1 \rightarrow 5$, for example. In the last two cases, prevalence progressively decreases, driven largely by the predator's strong "preference" for infectious prey. This reduces the infectious population and increases the susceptible population, an effect partly offset by reduction in the resources available for the predator. The third case is "counterintuitive" in that the number of prey rises with increase in predation (see Hudson et al. 1992; Packer et al. 2003).

If we replace our assumption that the predator prefers infectious over susceptible prey by assuming no preference between these populations, then the control map can be

radically different (fig. 1*D*), with no region (H_1P) of coexistence between prey, predator, and parasite. There is instead a region with H_1, H_0P as coexisting point attractors. In this region, the parasite can be excluded by an initial shock to switch the system to the H_0P basin of attraction, that is, the set of initial conditions that lead to coexistence of H_0 and P.

Building Complexity

In our second application, we consider macroparasite exclusion from a two host prey and one immune predator system using a different pair of controls: infection transmission (β) and predation efficiency (c). In so doing, we will illustrate the diversity of control map structure and test the effectiveness of these particular controls. To enable us to continue to use (two-dimensional) control maps, we will take our control variables to be the "scaling factors" for transmission and predation. Precisely, for predation, if c_{i0} is the precontrol value and c_i the postcontrol value of the ith predation constant, then scaling factor y is defined as $c_i = yc_{i0}$ and is the same for all constants, c_i. In the same way, we can define the scaling factor x for infection transmission.

Pheasants and Partridges

One hypothesis for the declining partridge population in the United Kingdom is that it is the weaker species under apparent competition between pheasant and partridge, mediated by the shared nematode *Heterakis gallinarum*. Supporting this hypothesis is a dynamical model (Tompkins et al. 2000) listed in appendix A with parameter values determined from field data. To study how the parasite might be excluded, we add an immune dynamic predator (e.g., foxes) and take the control variables to be the predation scaling factor y and the scaling factor x for parasite establishment within the game birds (app. A). We suppose that x can be reduced, for example, by pellet-distributed biological or chemical agents. The control map for the system with these particular controls is shown in figure 2*A* for a predator with the characteristics specified in appendix A. There are now three anchor points (A, B, C) defining five regions defined by the populations present. (H_{ij} denotes species i in state j, where $i = 1$ = pheasant, $i = 2$ = partridge, $j = 0$ = uninfected, and $j = 1$ = infected.)

There are two basic ways of excluding the parasite when the infected pheasant is initially alone (i.e., in state H_{11} at $x = 1.0$) with the partridge excluded by force of infection. The first is the obvious strategy of reducing transmissibility (x). This weakens the dominance of the pheasant and allows the partridge to reestablish ($H_{11} \rightarrow H_{11}H_{21}$). However,

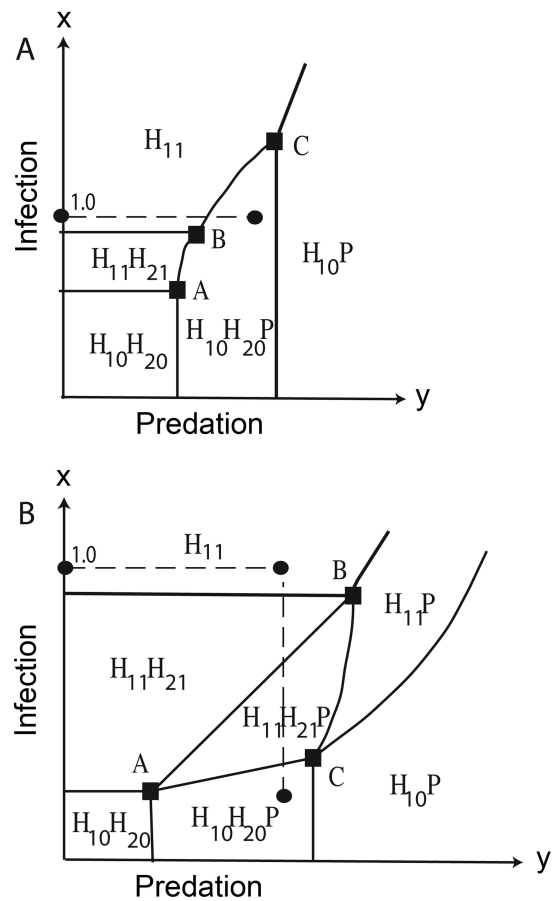

Figure 2: Control maps for two host prey, one immune predator. Controls are infection transmission scaling (x) and predation scaling (y). *A*, Pheasant-partridge model. *B*, Standard microparasite model. Region labels: H_{ij} denotes prey species i ($i = 1$ = pheasant, $i = 2$ = partridge) in state j ($j = 0$ = uninfected, $j = 1$ = infected). P denotes the predator. Dashed lines indicate possible exclusion paths.

further effort is required to exclude the parasite ($H_{11}H_{21} \rightarrow H_{10}H_{20}$). The alternative is to introduce a predator of sufficient strength to shift the system to region $H_{10}H_{20}P$ with the partridge reestablished and the parasite exchanged for the predator. In the situation where there is a possible candidate predator but it can only shift the system close to but not beyond threshold BC, it would not require much effort in predation efficiency enhancement to exclude the parasite because there is no broad region $H_{11}H_{21}P$ that has to be traversed first before exclusion. This is surprising because for most two-prey/one-parasite models, this particular region is central to the threshold structure of the control map. This is the case (fig. 2*B*) for the standard dynamical model with microparasite, two host prey, and one immune predator, where

infection transmission and predation are both density dependent.

The difference in threshold structure and anchor point positioning between figure 2*A* and figure 2*B* means that an exclusion strategy that works for one situation may not work for another. For example, in figure 2*B*, uninfected prey coexistence cannot be achieved through predation alone as it can in figure 2*A*. A hybrid strategy, with both infection transmission and predation being used as controls, is required (e.g., $H_{11} \rightarrow H_{11}H_{21} \rightarrow H_{11}H_{21}P \rightarrow H_{10}H_{20}P$) unless a different set of control variables were to be considered.

In our game bird model, we assumed that the predator had a preference for the pheasant sufficient to make the partridge weaker under predation as well as infection transmission. This explains the fact (fig. 2*A*) that if the predation is exceptionally strong, only the uninfected pheasant coexists with the predator ($H_{10}P$). If the predator's preference were for the partridge, then it would be the uninfected partridge that would survive ($H_{20}P$).

General Methods for Solving an Exclusion Problem

The essential step in solving the problem of how to exclude a population is to locate the relevant invasion threshold in control space. The invasion threshold lies on that part of the surface $\det \mathbf{J} = 0$ (where $\mathbf{J}$ is the invasion matrix in rare invader approximation) that satisfies three additional sets of constraints. First, none of the resident populations can be negative; second, there may be limits on the values that a control can take; and third, there are additional stability conditions to be imposed on matrix $\mathbf{J}$. (This is because $\det \mathbf{J} = 0$ guarantees a zero eigenvalue but not a leading zero eigenvalue.)

For example, in figure 1*B*, the parasite invasion threshold is just section AC of the upper part AA* of the curve $\det \mathbf{J} = 0$. (Curve $\det \mathbf{J} = 0$ is in fact a hyperbola. Only on its upper branch AA* is the zero eigenvalue leading.) Constraints $0 \leq u \leq r$ define the boundary points A, C of this invasion threshold. Constraint $P \geq 0$ imposes no further restriction. (For ease of exposition, we will ignore additional stability conditions in setting up a problem, choosing to check whether they are satisfied [by finding the eigenvalues] after a possible solution has been found.)

When there are more than two controls or two scaled sets of controls, then control maps are no longer practicable and algebraic and numerical methods have to be used. Consider again the three-level food chain but now with the intermediate predator host to the parasite as well. With three controls in place—Q (top predator), u (culling the infectious prey), v (culling the intermediate infectious predator)—the parasite invasion matrix is given by

$$\mathbf{J} = \begin{bmatrix} S\beta_{11} - (d_1 + u) - c_2 P & S\beta_{12} \\ P\beta_{21} & P\beta_{22} - (d_2 + v) - c_4 Q \end{bmatrix}, \tag{4}$$

where $S = (b_2 + c_3 Q)/(\theta_1 c_1)$, $P = (r_1/c_1)(1 - S/K)$ are the resident populations and c_4 measures predation on the infectious intermediate predator by Q. (See "Model 2" in app. A for the model equations and notational details.) Because there are two infectious populations, $\mathbf{J}$ is a 2×2 matrix.

One strategy is to use only controls u, v to exclude the parasite. However, additional options arise if we use control Q as well. In particular, we can shift the burden of culling away from the intermediate predator (v) to the prey (u). This is an advantage if the intermediate predator is more difficult to cull, for example, if it is avian rather than terrestrial or if it is protected. To see how this shift comes about, we use the observation that for the parasite to be excluded, neither the predator nor the prey can act as a "reservoir" for the parasite; that is, both diagonal elements in $\mathbf{J}$ must be zero or negative (Greenman and Hoyle 2008). From the formulas for S and P above, increasing Q increases the (1, 1) element because of a higher S, lower P. This has to be compensated for by increasing u. However, increasing Q decreases the (2, 2) element, easing the burden on v. So the use of Q need not be counterproductive when the intermediate predator is a parasite host.

As this example shows, of the many strategies that are available, the strategy that is finally chosen is likely to depend on the amount of effort required, as measured, for example, by economic cost. The problem of finding the least-effort strategy that excludes the parasite becomes a problem in optimization theory. As an example, consider the three-food chain model with invasion matrix (4) and the parameter values specified in appendix A. The problem to be solved is the following: minimize

$$E = h_1 u + h_2 v + h_3 Q \tag{5}$$

($h_i > 0$) subject to the following constraints: $\det \mathbf{J} = 0$ (necessary condition for the invasion threshold with $\mathbf{J}$ given in eq. [4]); $u \geq 0$, $v \geq 0$, $Q \geq 0$, $P \geq 0$ (bounds on controls and populations). The constant h_i is the per unit effort involved in using the ith control and E the total effort required. Problem (5) is not a linear programming problem (since $\det \mathbf{J}$ is quadratic in the controls), so it cannot be solved by the simplex algorithm but can be solved by Lagrangian techniques (see app. C; Lenhart and Workman 2007). This approach yields the optimal (least effort) solutions:

$$(u, v, Q, E) = (1.68, 0, 3.07, 4.75) \tag{6a}$$

when $(h_1, h_2, h_3) = (1, 10, 1)$ and

$$(u, v, Q, E) = (0.79, 0.51, 0, 9.81) \tag{6b}$$

when $(h_1, h_2, h_3) = (6, 10, 1)$ after checking for invasion matrix stability. So use only controls u, Q when the intermediate predator is costly to cull (eq. [6a]) and only controls u, v when the costs for prey and predator are comparable (eq. [6b]). The least-effort solution corresponds to a point on the threshold itself, but in practice, one would want a point in the interior of the exclusion region to make the strategy robust to parameter variation, but this will cost extra. Note also that we are determining where we want to get to in control space but not considering the transitional problem of how we might get there.

This Lagrangian approach can still be used when there is nonlinearity in the control or population bounds or in the effort required. As an example, consider again the red grouse control problem, supposing that the controls are increasingly more difficult to apply as their strength is increased (Anderson et al. 1981). Precisely, let the total effort be given by $E = h_1v^2 + h_2w^2$, where $h_1 = m^{-2}$ (to remove dimensionality from v) and $h_2 = 1$. The best strategy to exclude the parasite is located at point 6 on the parasite threshold (fig. 1*C*) with $(v/m, w) = (-0.21, 0.057)$, that is, increase carrying capacity by 6% and enhance predator survival by 21%. We can also handle situations where the effort is cross-linked, yielding economies of scale; for example, the effort to cull two species at the same time may be less than the total effort involved in culling them separately.

The Impact of External Forcing

In many situations, there are factors affecting the system dynamics that cannot easily be modeled explicitly and are typically approximated by regular (e.g., seasonal) or irregular (e.g., stochastic) temporal fluctuations of the model parameters. This "external" forcing of parameters can have a major impact on the invasion properties of populations in an ecological system (Chesson 1984; Greenman and Norman 2007). The forcing can distort the invasion thresholds in a way that could work with efforts to bring about exclusion but, equally, could have the opposite effect. To see what can happen and what might be the consequences for parasite exclusion, consider again the red grouse model with just carrying capacity control, w, being used.

In the absence of external forcing, we found that if the carrying capacity is increased sufficiently, then the parasite can be excluded ($w \geq 1.29$; fig. 1*C*). If the per capita birth rate a is now seasonally forced, then there is little or no effect on parasite invasion unless predation strength is seasonally forced as well. Then there is a dramatic impact, the effect of which depends crucially on the lag between these forcing components. If birth rate lags predation by a quarter cycle, then the effort required to exclude the parasite increases by about 50% ($w \geq 1.95$), but if, instead, predation lags birth rate by a quarter cycle, then the effort is reduced by a substantial 30% ($w \geq 0.88$; for more details, see app. A). There is a control opportunity here. If predation is under management control (rather than environmentally driven), then annual cyclical variation of predation strength, when appropriately lagged, could reduce the effort of expanding carrying capacity to exclude the parasite. If the lag is not chosen carefully, the situation can be made much worse. So the lag matters. The key to understanding this phenomenon is that the important lag is between the red grouse population and the managed predator strength forcing. With predation lagging birth rate, the red grouse population and the cyclic predation control are in synchrony, but if predation leads, then they are almost exactly out of phase.

Further insight into the effects of forcing can be gained if the infection transmission constant β is increased from 0.10 to 0.15. Then the unforced system will become unstable for large enough w and the parasite will not be excluded (for realistic values of w). However, if we cyclically control predation strength, we can bring about parasite exclusion. The required threshold value of w first decreases as we increase the external period p, reaching as low as $w = 1.32$ at $p = 10$ before rising to a large $w = 2.4$ at $p = 17$. Why the minimum? This correlates with the natural period of the resident subsystem (~10), that is, the period of the oscillatory decay mode that the system takes to equilibrium in the absence of forcing. This correlation suggests that resonance is occurring, the phenomenon where the external forcing has a disproportionately large effect on the system, most familiarly in the amplitude of the population oscillations but also, as here, in the distortion of the invasion thresholds. The distortion is largest when the natural and forcing periods match.

The effect of resonance on threshold structure can be seen more clearly in model 1 (with eqq. [1]; app. A). We suppose that cyclic control through predation scaling y is arranged to lag environmental forcing on infection transmission by half a cycle. Figure 3 shows the dramatic effect of this forcing, an effect strongly dependent on the external forcing period p. The unforced (parasite) threshold AH is distorted into the threshold ABCDFG, with two inclusion peaks deeply penetrating into what was previously the parasite exclusion region. Except for a weak trend for low p, the effect of the forcing here is to work strongly against parasite exclusion. This threshold peak structure is very reminiscent of the resonance peak structure obtained when population amplitude is plotted against forcing period (Greenman et al. 2004). The broad right-hand threshold

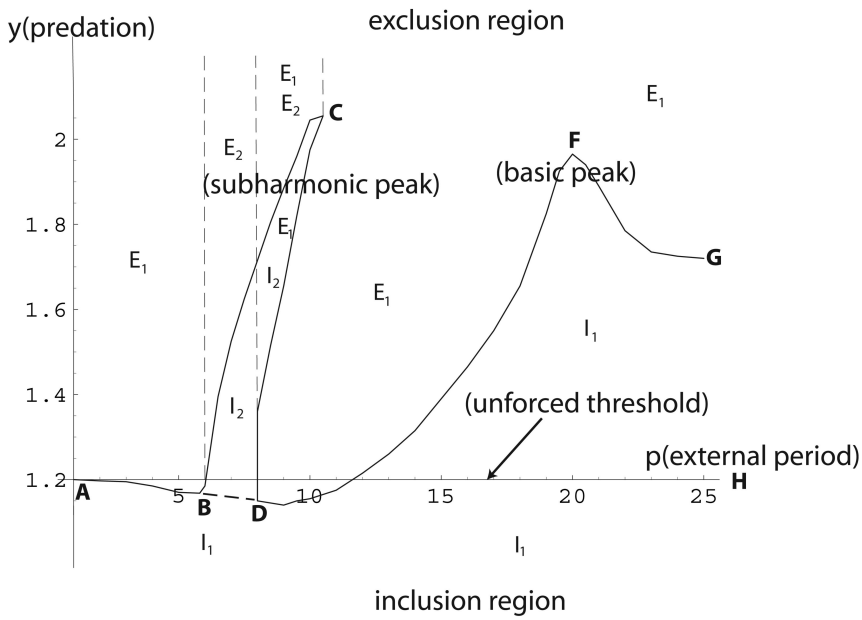

Figure 3: Distorted parasite exclusion threshold as a function of forcing period p for model 1. Shown are the regions of parasite exclusion and inclusion and the overhanging "subharmonic" peak BCD that generates multiple attractors. Region labeling: X_i indicates that the parasite is excluded ($X = E$) or included ($X = I$), with population period equal to ($i = 1$) or twice ($i = 2$) the forcing period.

peak in figure 3 is centered about the natural period p_0 of the system ($p_0 \sim 17$) and the narrow left-hand peak about $p_0/2$. Within this left-hand peak, the infectious population oscillates at twice the forcing period (reflecting subharmonic behavior in the resonance peak structure). In figure 3, we indicate precisely which modes of oscillation occur in which regions of this "threshold map." In particular, we note that because of the overhang in peak BCD, there are multiple attractors, where exclusion can be achieved by shocking the system.

For other lags, the threshold distortion can be significantly different. With control lagging forcing by a quarter cycle, the underlying trend is upward, and there is no possibility of the environment helping the exclusion effort. For zero lag, there is cancellation between forcing and control, with little or no distortion in the threshold. So exclusion threshold distortion can be highly sensitive to both lag and period and, as one can also show, to the relative strengths of the forcing components.

It might be thought that there is little chance of observing this resonant threshold distortion in practice, since environmental forcing is typically seasonal and the resident predator-prey subsystem has a high natural period. However, there are important examples of multiannual environmental forcing (Wichmann et al. 2003), and strong forcing can generate lower-period subharmonic modes. Further, stochastic forcing can excite high-period natural modes of the system if its power spectrum allows, as it would with white noise (Adams et al. 2006). Finally, we note that the discussion also covers the case where there is no environmental forcing; that is, all forcing components are part of a carefully designed cyclic control strategy.

We have not discussed how to solve an exclusion problem for a general system regularly or irregularly forced. The simplest approach is to assume a particular functional form (e.g., sinusoidal) for the time-varying control and optimize with respect to the control parameters (e.g., p, ϕ, δ). There are, however, more sophisticated approaches that can be taken (Lenhart and Workman 2007), which we hope to report on and give examples of in due course.

Discussion

A central theme has been the controllability of an eco-epidemiological system, that is, whether a particular management objective can be achieved with a particular set of controls. It is not only the issue of which controls are available but how they are to be applied. For example, regular culling would work if applied only to infectious populations but might not if applied to the susceptibles as well. We also observed that a managed predator would be effective in a two-level food web but might not be in a three-level web unless the intermediate predator was a parasite host. So key characteristics of the ecological system—such as network

structure, which species are hosts, and which species are immune to the parasite—are important.

One recurring cause of noncontrollability is the unwitting exclusion of other species (or parasites) by crossing their thresholds as well. So the invasion threshold of interest should not be analyzed in isolation from other thresholds, hence the usefulness of control maps that show the positioning and intersections of all relevant thresholds. Control maps can be constructed rapidly from algebraic formulas or simple numerical algorithms for the required thresholds and updated rapidly with a change of model parameters. For those thresholds derived from formulas, an analysis of their properties and their sensitivity to parameter change can be carried out algebraically (app. B).

For both of our game bird applications, we noted that modest changes in certain parameters can lead to qualitative changes in the contour maps, as indicated by the relative positioning of the anchor points and the curvature of the threshold curves. In figure 1*C* and 1*D*, qualitative change was brought about by changes in predator food preferences, and in figure 2*A*, which bird species survived depended on the relative strengths of apparent competition mediated by the parasite or by the predator. As a result of such qualitative change, a previously feasible control strategy might no longer work (cf. fig. 2*A*, 2*B*).

In general, there are many solutions to the exclusion problem, and in practice, the optimal solution would be one that minimizes "effort" as measured, for example, by economic cost. This optimal solution may involve more controls than absolutely necessary. This can be the case if effort increases more than proportionately with increase in control, as was assumed in the red grouse model. A second example is provided by two-stage control, where apparent competition is used to resize resident populations ahead of culling the infectious populations.

Controls that are varied in time can also be an important part of management's weaponry. They can be especially effective when the ecological system is already forced environmentally. Cyclical controls can be designed to work with the environmental forcing to ease the burden of parasite or population exclusion but only if the lag between forcing components is carefully chosen; otherwise the situation could be made much worse (Choisy and Rohani 2006). The distorting impact of environmental forcing on invasion thresholds can become much greater in the presence of resonance, that is, when the forcing period relates to a natural period of the system (e.g., fig. 3). So the interaction between environment and control is highly sensitive to forcing period as well as the lag.

Of increasing interest are those ecological systems affected by the environment in more than one way, for example, breeding and infection taking place at different times of the year (e.g., house finches [Hosseini et al. 2004] and red grouse [Cattadori et al. 2005]). Recently, Lello et al. (2008) have studied out-of-phase cyclic patterns of multiple parasites. This additional structure complicates the problem of finding an optimal control but may also open up new ways of managing the system.

Complementary to the problem of exclusion is that of coexistence and biodiversity, an issue that, to an extent, can be studied with the threshold methodology we have discussed. As noted, the additional presence of the parasite may be necessary for a predator to coexist with its prey if the predator has too strong a preference for infectious prey. The issue of coexistence is especially important when the interaction is frequency dependent (Rudolph and Antonovics 2005). Haque (2010), for example, argues that to avoid immune prey exclusion, the parasite may have to be present to offset predation. Infection persistence is also the main issue in recent modeling of genetically engineered viruses in pest–natural enemy systems (Ghosh et al. 2007). External forcing, in its ability to distort thresholds, can also be a factor in promoting coexistence by making it more difficult to exclude particular species (Chesson 1984). Again, there are opportunities here for management to intervene by imposing cyclically varying controls.

One of the problems in understanding eco-epidemiological systems is that it can be difficult to work out which (if any) species are carriers of the parasite (Cleaveland and Dye 1995; Hudson et al. 2002). Even if the infection pathways are well understood (e.g., the Salton Sea ecology [Kaiser 1999]), there may be insufficient field data to construct a fully determined dynamic population model that can be used for detailed exploration and analysis. For our purposes, we have created two models by splicing together data for the host prey (game birds) and immune predator (e.g., foxes) with unfitted parameters used as controls or used for sensitivity testing. In our view, lack of data does not invalidate the building of generic models to explore what might happen and to identify dangers to avoid and opportunities to exploit in designing efficient management strategies, even if the objective of providing firm predictions is not achievable.

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