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## **Species Coexistence and Periodicity in Host-Host-Pathogen Models**

Received: 22 September 2004 / Revised version: 21 March 2005 /  
Published online: 6 June 2005 – © Springer-Verlag 2005

**Abstract.** Models for the transmission of an infectious disease in one and two host populations with and without self-regulation are analyzed. Many unusual behaviors such as multiple positive equilibria and periodic solutions occur in previous models that use the mass-action (density-dependent) incidence. In contrast, the models formulated using the frequency-dependent (standard) incidence have the behavior of a classic endemic model, since below the threshold, the disease dies out, and above the threshold, the disease persists and the infectious fractions approach an endemic equilibrium. The results given here reinforce previous examples in which there are major differences in behavior between models using mass-action and frequency-dependent incidences.

### **1. Introduction**

Pathogens such as viruses, bacteria, protozoans, and helminths affect their host's population dynamics (Anderson and May, 1978, 1986; May and Anderson, 1978; Hethcote and Levin, 1989; Begon and Bowers, 1995; Grenfell and Dobson, 1995). For example, infectious diseases can change the size or density of a host population, and cross-species infections can affect community composition by allowing or restricting species coexistence. Holt and Pickering (1985) formulated a model for two host species without self-regulation, which share a directly-transmitted infectious disease. Begon et al. (1992) formulated a similar model in which each host species has density dependent regulation. In both papers there were some mathematical analyses of the models and some conjectures about the behavior of solutions. Greenman and Hudson (1997) did extensive analyses of these models

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*Key words or phrases:* Coexistence – Regulation – Host-pathogen – Infectious disease – Dynamics

and found counterexamples to some of the conjectures. Indeed, the two host models can have complicated behaviors such as one, two, or three infected coexistence equilibria and one or more attractive periodic solutions. In this paper we give formulations similar to the models of Holt-Pickering and Begon et al., which have much simpler dynamic behaviors. The significant change is that mass-action incidence in their models is replaced by frequency-dependent incidence. Thus the analyses here provide more examples of infectious disease models in which different forms of the incidence lead to significantly different behaviors.

As in the models of Holt and Pickering (1985), Begon et al. (1992), and Greenman and Hudson (1997), we consider models for directly transmitted diseases of SIS type, i.e. individuals in the susceptible class become infectious and then return to the susceptible class upon recovery, since an infection does not confer immunity. Section 2 contains detailed derivations and comparisons of the mass-action and frequency-dependent forms of the incidence in terms of both numbers and densities of infectives and susceptibles. Section 3 has new results on two models for an SIS disease in a single host population with infection-reduced reproduction and infection-related deaths, but without density dependent regulation. The threshold conditions and asymptotic behaviors are quite different for the two models with frequency-dependent and mass-action incidences.

A general model with a shared SIS disease in two host populations with exponential growth or decay (no self-regulation) is formulated in Section 4 and then two special cases are considered in the following sections. For the model in Section 5 using mass-action incidence, we describe the conjectures of Holt and Pickering (1985) and the counterexamples of Greenman and Hudson (1997). This model has unusual dynamic possibilities such as multiple equilibria that are all unstable, surfaces that separate attractive regions for different equilibria, and periodic solutions around interior or boundary equilibria. We extend the analyses of Greenman and Hudson (1997) by showing that Hopf bifurcation and periodic solutions can occur for some parameter values.

The analogue of the Holt-Pickering model with frequency-dependent incidence is analyzed in Section 6. For this new model we obtain the classic result for an endemic model (Hethcote, 1976, 2000; Anderson and May, 1991). If the modified reproduction number is below the threshold, then the disease dies out, but if the modified reproduction number is above the threshold, then the disease remains endemic (i.e. it persists) and the infective fractions approach endemic equilibrium values. Moreover, the two host population sizes grow or decay either at their usual per capita rates if the disease dies out, or at infection-reduced per capita rates when the disease remains endemic. Thus a key conceptual result is that the analog with frequency-dependent incidence of the Holt-Pickering two host model has the classic endemic threshold behavior.

Section 7 contains new formulations and analyses of models for an SIS disease in one host population with logistic growth and either frequency-dependent or mass-action incidence. For the model with frequency-dependent incidence, two threshold quantities determine the three possible asymptotic behaviors of solutions. The first possibility is that the disease dies out and the population size approaches its carrying capacity. The second possibility is that the disease remains endemic and

the population size approaches a new equilibrium value below the carrying capacity. The third possibility is that the disease remains endemic, but the infection-reduced deaths are stronger than the maximum population growth rate, so that the host population size is driven to zero (extinction). This third possibility is intuitively plausible, but does not occur in the one host model with mass-action incidence.

A general SIS model with self-regulation (logistic growth) in two host populations is formulated in Section 8. The model with logistic growth and mass-action incidence considered by Begon et al. (1992) is presented in Section 8.1. We do not do any further mathematical analyses of this model, but we briefly describe the conjectures of Begon et al. and the counterexamples with unusual behaviors found by Greenman and Hudson (1997). For example, with one parameter set they found no relevant one host equilibria, an unstable uninfected coexistence equilibrium, and three unstable infected coexistence equilibria. Other examples have no relevant stable equilibria, but have stable periodic solutions.

A similar model with self-regulation and frequency-dependent incidence is analyzed in Section 8.2. Just as in the model without self-regulation, we obtain the classic result for an endemic model. Below the threshold, the disease dies out in both host populations and the host population sizes approach their carrying capacities. Above the threshold, the disease remains endemic in both host populations and drives the two host population sizes to either zero or new equilibrium sizes below their carrying capacities. Thus the two host SIS model with logistic growth and frequency-dependent incidence has the usual endemic threshold behavior. Section 9 contains discussion and conclusions.

## 2. The mass-action and frequency-dependent incidences

The incidence of a disease is defined as the rate of new infections in susceptible individuals because of their contacts with infectious individuals. Sometimes this is called the horizontal incidence to distinguish it from vertical incidence, which is the rate at which newborns are infected by their mothers. Let  $X(t)$  be the number of susceptibles at time  $t$ ,  $Y(t)$  be the number of infectives, and  $N(t)$  be the host population size. The incidence term in the equation for  $dY/dt$  is often written as  $\lambda X = crpX$ , where the force of infection  $\lambda$  is the product of the local contact rate  $c$ , the probability  $r$  that the contact is with an infective, and the probability  $p$  that the contact with an infective is sufficient for a transmission of infection. Usually the transmission probability  $p$  is assumed to be constant. The probability  $r$  is the infectious fraction encountered locally, which is often assumed to be the same as the infectious fraction  $Y/N$  in the entire population. At this point the incidence is given by  $cpXY/N$  with the local contact rate  $c$  to be specified.

A common assumption is that the local contact rate  $c$  is proportional to the local density which is equal to the global density  $N/A$ , where  $A$  is the fixed area occupied by the population. With proportionality constant  $k$ , the incidence above becomes  $kpXY/A = \eta XY$ . This form of the incidence is often called the mass-action incidence and is widely used in epidemiology modeling (e.g. Anderson and May, 1991). Begon et al. (2002) preferred to write this incidence as  $\tilde{\beta}XY/A$  with  $\tilde{\beta} = kp$  to emphasize the dependence on the area  $A$ . Because the incidence form  $\eta XY$  assumes

that  $c$  is proportional to the density, it is sometimes called density-dependent incidence.

Let  $x = X/A$ ,  $y = Y/A$ , and  $n = N/A$  be the global densities of susceptibles, infectives, and the host population, respectively. By dividing the equation and variables by the fixed area  $A$ , we find that the density form of the mass-action incidence term in the equation for  $dy/dt$  is  $(\eta A)xy$  or  $\tilde{\beta}xy$ . Note that this form  $\tilde{\beta}xy$  is consistent with the law of mass action for chemical kinetics in a closed container, which is that the reaction rate is proportional to the product of the densities of the reacting chemicals. It is plausible for infectious disease transmission if one assumes that the animals move randomly in a region and that "collisions" correspond to adequate contacts sufficient for transmission of the infection between infective and susceptible animals.

De Jong et al. (1995) and Diekmann et al. (1995) pointed out that making contacts with neighbors that lead to transmission is often a local phenomenon involving social behavior and local densities as measured by the average distance to nearest neighbors. This concept of local density is not the same as the formal density obtained by dividing the total population by the total area, since the population may be distributed in patches within the total area. Thus an increase in population size in the total area could occur by filling in the vacant areas. In this case the local distance to nearest neighbors and hence the local contact rate could remain unchanged, even though the total population size in the fixed area increased.

If we assume that the local contact rate  $c$  is constant, so that it is independent of the global density  $N/A$ , then the incidence  $cpXY/N$  above becomes  $\beta XY/N$ , where  $\beta = cp$ . Because the force of infection  $\lambda = \beta Y/N$  depends on the frequency of infections  $Y/N$ , Begon et al. (2002) called this frequency-dependent incidence. This form of the incidence can be derived directly from basic principles as follows. Let  $\beta$  be the average number of adequate contacts (*i.e.* contacts sufficient for transmission) of one susceptible animal per unit time. Note that  $\beta$  is the product of the contact rate  $c$  per animal per unit time and the probability  $p$  of transmission per contact. If we assume that the local fraction of animals that are infectious is equal to the global infectious fraction  $Y/N$ , then  $\beta Y/N$  is the average number of adequate contacts with infectious animals per unit time of one susceptible, and  $(\beta Y/N)X$  is the number of new cases per unit time when the number of susceptibles is  $X$ . Hethcote first used this form  $\beta XY/N$  in 1976 and calls it the standard incidence (Hethcote 1976, 1994, 1996, 2000). When converted to a density form using the area  $A$ , the standard or frequency-dependent incidence term in the equation for  $dy/dt$  becomes  $\beta xy/n$ .

Another form of the incidence in terms of densities is  $c(n)pxy/n$ , where the contact rate  $c(n)$  is a non-decreasing function of the population density  $n$ . It is plausible that the contact rate  $c(n)$  is a linear function of  $n$  for low densities and that  $c(n)$  is independent of  $n$  (*i.e.* a constant) for high densities. These two extremes at low and high densities correspond to the mass-action and frequency-dependent incidences, respectively. Functions  $c(n)$  that describe the transition between low and high densities have been proposed. Dietz (1982) suggested the Holling functional response  $c(n) = an/(1 + bn)$ . By assuming a short interaction time, Heesterbeek and Metz (1993) derived  $c(n) = 2\theta n/[1 + 2\theta n + \sqrt{1 + 4\theta n}]$ . Roberts (1996)

proposed  $c(n) = n/(1 - \varepsilon + \varepsilon n)$ , which corresponds to mass-action incidence for  $\varepsilon = 0$  and frequency-dependent incidence for  $\varepsilon = 1$ . For more details and citations of other authors using incidences dependent on population size or density, see Chapter 10 in Diekmann and Heesterbeek (2000). Because models usually use either mass-action or frequency-dependent incidence, only these two forms are considered here.

Because the incidence  $\beta XY/N$  depends on the frequency of infection  $Y/N$ , we call it “frequency-dependent incidence” in this paper instead of standard incidence. For  $\eta XY$ , we use the usual name “mass-action incidence” instead of density-dependent incidence. Note that the parameter  $\eta$  in the mass-action incidence  $\eta XY$  has no epidemiological interpretation, but comparing it with the frequency-dependent incidence implies that  $\beta = \eta N$ , so that the mass-action incidence form implicitly assumes that the contact rate is a linearly increasing function of population size  $N$ . This result is consistent with the density-dependent interpretation above, since an increase in population size in a fixed region would give a corresponding increase in density. Because the frequency-dependent and mass-action incidences both have plausible derivations and interpretations, the evidence for them is now examined.

De Jong et al. (1995) used four data sets on actual disease transmission to compare the frequency-dependent (their true mass-action) and mass-action (their pseudo mass-action) incidences. For the Greenwood et al. (1936) data set on *Pasteurella muris* in mice, in which the density of the mice was kept constant, De Jong et al. (1995) found that both forms of the incidence gave good fits. Note that their analysis was more complete than that of Anderson and May (1979) and Mena-Lorca and Hethcote (1992), who had incorrectly concluded that the mass-action incidence gave a better fit to the data on *Pasteurella muris* in mice.

The frequency-dependent incidence gave a better explanation for an outbreak of smallpox in Brazil studied by Becker and Angulo (1981) and for transmission experiments on Aujeszky’s disease in pigs done by Bouma et al. (1995). Using an incidence of the form  $\eta N^v XY/N$  with data for four human diseases (measles, pertussis, diphtheria, and scarlet fever) in communities with population sizes from 1,000 to 400,000, Anderson and May (1982, 1991) inferred that  $v$  is between 0.03 and 0.07. This strongly suggests that frequency-dependent incidence corresponding to  $v = 0$  is more realistic for human diseases in populations with medium to high densities than mass-action incidence corresponding to  $v = 1$ . This result is consistent with the concept that people are infected through their daily encounters and the patterns of daily encounters are largely independent of community size within a given country (e.g. students of the same age in a country usually have a similar number of daily contacts). Populations with low densities often have a critical community size for disease endemicity. For very low densities, stochastic effects are important and the population size is critical in determining the probability of extinction of the disease. Based on the one equal fit and the three better fits described in this and the previous paragraph, De Jong et al. (1995) concluded that frequency-dependent incidence is better than mass-action incidence.

Diekmann et al. (1995) considered concepts such as local density, population number, area occupied, effective density, contact rate, and saturation in their

formulations of disease incidence for populations of varying size. For transmission of Phocid Distemper Virus among seals in northwest Europe, they obtained the frequency-dependent incidence when they used a combinatorial model for the arrangement of seals when they came onto sandbanks at the twice-daily low tides.

Dobson and Meagher (1996) found that frequency-dependent incidence more accurately predicted the observed level of brucellosis prevalence in the bison herd of Yellowstone National Park. In their model of Feline Leukemia Virus in domestic cats, Fromont et al. (1997) found that their model with frequency-dependent transmission fit the data in several feline populations. In their examination of various forms of the transmission term, McCallum et al. (2001) cited several studies in which the mass-action incidence was inadequate. Turner et al. (2003) used two cellular automata models in which they assumed that susceptibles only have contacts with adjacent neighbors or have contacts with a fixed number of nearby occupied cells. When comparing their local spatially explicit transmission simulations with global models, they found that their results with both assumptions and variable population size were far better described by frequency-dependent incidence than by mass-action (density-dependent) incidence. Lloyd-Smith et al. (2004) derived frequency-dependent transmission mechanistically from pair formation models for sexually transmitted diseases under the assumption that the pairing processes occur faster than the epidemic processes.

In this paper we consider infectious diseases in which two host populations can transmit infections during encounters, but do not have any other interactions such as a predator-prey relationship or competition for food or niches. For the two host populations indexed with  $(i, j)$  equal to  $(1, 2)$  or  $(2, 1)$ , the mass-action incidence in terms of the numbers of infectives and susceptibles is  $[(\tilde{\beta}_{ii}/A)Y_i + (\tilde{\beta}_{ij}/A)Y_j]X_i$ , where  $\tilde{\beta}_{ij}$  is a mass-action coefficient for the interactions between animals in the  $i$  and  $j$  populations.

We formulate the frequency-dependent incidence for two host populations by using explicit definitions that are analogous to those used in the one-population derivation. The contact rate  $\beta_{ij}$  is the average number of adequate contacts of one susceptible animal in host population  $i$  with animals in host population  $j$  per unit time (cf. Hethcote, 1976, 1978, 1994, 1996, 2000). Since the fraction of animals in host population  $j$  with size  $N_j$  that are infectious is  $Y_j/N_j$ , the average number of adequate contacts of one susceptible animal in host population  $i$  with infectious animals in host population  $j$  per unit time is  $\beta_{ij}Y_j/N_j$ . Since the number of susceptibles in host population  $i$  is  $X_i$ , the average number of adequate contacts of susceptibles in host population  $i$  with infectious animals in host population  $j$  per unit time is  $(\beta_{ij}Y_j/N_j)X_i$ , so this is the number of new cases in the  $i$  population due to contacts with the  $j$  population. Thus the frequency-dependent incidence, which is the total number of new cases in the  $i$  population due to contacts with their own population  $i$  and the other population  $j$ , is given by  $[\beta_{ii}Y_i/N_i + \beta_{ij}Y_j/N_j]X_i$ . As in the one population incidences, the frequency-dependent incidence involves the infective fractions and the mass-action incidence involves the numbers of infectives.

In their studies of cowpox in populations of bank voles and wood mice, Begon et al. (1999, 2003) formulated models for the transmission within and between

these two hosts. They found that frequency-dependent incidence was much better in accounting for the dynamics than mass-action (density-dependent) incidence. When they estimated the within-species and between-species transmission rates from their data collected at two sites in north-west England, they found that the between-species rates were very low (Begon et al., 1999). They acknowledge that there might be slight competition between the bank voles and wood mice, but argue that it is insignificant in practice. Thus these two species appear to share a disease without other significant interactions as in the two host models in this paper.

As for one population, let  $x_i = X_i/A$  and  $y_i = Y_i/A$  (where  $A$  is the fixed area of the region) to convert to equations involving the densities  $x_i$  and  $y_i$ . Then the two host mass-action incidence  $[\tilde{\beta}_{ii}Y_i + \tilde{\beta}_{ij}Y_j]X_i/A$  in terms of numbers becomes  $[\tilde{\beta}_{ii}y_i + \tilde{\beta}_{ij}y_j]x_i$  in the density differential equation for  $dy_i/dt$ . This mass-action incidence was used in the density models of Holt and Pickering (1985), Begon et al. (1992), and Greenman and Hudson (1997). When converted to densities, the frequency-dependent incidence  $[\beta_{ii}Y_i/N_i + \beta_{ij}Y_j/N_j]X_i$  becomes  $[\beta_{ii}y_i/n_i + \beta_{ij}y_j/n_j]x_i$  in terms of densities, where  $n_i = N_i/A$  is the density of the  $i$ th host population. Note that the frequency-dependent incidences in terms of the numbers and densities have the same form. The mass-action incidence forms differ only in the constant  $A$  factor. Thus theoretical results for models formulated using population densities and numbers would be the same or very similar. In succeeding sections we simplify the notation by using  $\beta_{ij}$  as the coefficients in the mass-action formulations instead of  $\tilde{\beta}_{ij}/A$ .

Although Holt and Pickering (1985), Begon et al. (1992), and Greenman and Hudson (1997) used population densities in formulating their models with the mass-action incidence, we formulate our models in terms of population numbers as done in the papers on bank voles and wood mice (Begon et al. (1999, 2003) and many other papers (De Jong et al. 1995; Diekmann et al. 1995; Fromont et al. 1997; Begon et al. 2002; Turner et al. 2003; Hethcote, 1976, 1978, 1994, 1996, 2000). Because there is a large amount of evidence supporting the frequency-dependent incidence, in this paper we consider the effects of both the mass-action and frequency-dependent forms of the incidence on the asymptotic behavior in some one and two host population models. For more information about the differences in the behavior of models using the frequency-dependent (standard) and mass-action forms of the incidence in one population models, see Gao and Hethcote (1992), Mena-Lorca and Hethcote (1992), and Gao et al. (1995, 1996). Multiple group models with frequency-dependent and proportionate mixing are considered in Hethcote and Van Ark (1987) and Hethcote (1996, 2000).

### 3. The SIS model with exponential growth

Before looking at models with two hosts, we analyze new SIS models in one host population with infection-reduced reproduction and infection-related deaths. Let  $X(t)$  be the number of susceptibles and  $Y(t)$  be the number of infectives in a host population with size  $N(t)$  with  $N = X + Y$ . The SIS model with exponential growth is

$$\begin{aligned}
 dN/dt &= a[X + (1 - f)Y] - bN - \alpha_0 Y, \\
 dX/dt &= a[X + (1 - f)Y] - bX - g(X, Y, N) + \gamma Y, \\
 dY/dt &= g(X, Y, N) - (\gamma + b + \alpha_0)Y,
 \end{aligned}
 \tag{3.1}$$

where  $a$  is the per capita birth rate for susceptibles and  $f$  is the reduction in birth rate in infectious people, so that  $a(1 - f)$  is the per capita birth rate for infectives. The per capita natural death rate is  $b$  and the per capita infection-related death rate is  $\alpha_0$ . The incidence  $g(X, Y, N)$  is either frequency-dependent incidence  $\beta XY/N$  or mass-action incidence  $\beta XY$ , and the per capita recovery rate is  $\gamma$ . The analogous SIRS model without infection-reduced reproduction was studied for both frequency-dependent (standard) and mass-action incidence by Mena-Lorca and Hethcote (1992).

The model (3.1) can be reduced to the following system of two equations by using  $X = N - Y$  and the infectious fraction  $I = Y/N$ .

$$\begin{aligned}
 dN/dt &= [r - (af + \alpha_0)I]N, \\
 dI/dt &= g^*(I, N) - [\gamma + a + \alpha_0 - (af + \alpha_0)I]I,
 \end{aligned}
 \tag{3.2}$$

Here the positive disease-free per capita net growth rate is  $r = a - b$ , and the incidence  $g^*(I, N) = g(X, Y, N)/N$  is frequency-dependent incidence  $\beta I(1 - I)$  or mass-action incidence  $\beta I(1 - I)N$ . This model is well posed in the region  $D = \{(N, I) : N \geq 0, 0 \leq I \leq 1\}$ . The thresholds and asymptotic behaviors are summarized in Table 1 and then proved in the following paragraphs.

For frequency-dependent incidence  $g^*(I, N) = \beta I(1 - I)$ , the  $dI/dt$  equation is independent of  $N$  and is quadratic in  $I$ . The threshold quantity is the modified reproduction number  $R_1 = \beta/(\gamma + a + \alpha_0)$ , which is the daily contact rate  $\beta$  times a modified average infectious period  $1/(\gamma + a + \alpha_0)$  in model (3.2); note that this is not the same as the average infectious period  $1/(\gamma + b + \alpha_0)$  in model (3.1). Analysis of the equation for  $dI/dt$  shows that  $I(t) \rightarrow 0$  as  $t \rightarrow \infty$  if  $R_1 \leq 1$  and  $I(t) \rightarrow I_e$  as  $t \rightarrow \infty$  if  $R_1 > 1$ , where the equilibrium endemic fraction is  $I_e = [\beta - (\gamma + a + \alpha_0)]/(\beta - af - \alpha_0)$ . When  $R_1 \leq 1$  and  $I(t) \rightarrow 0$ , the limiting

**Table 1.** Asymptotic behaviors for the SIS exponential model.

frequency-dependent incidence	$g = \beta XY/N \Rightarrow g^* = \beta(1 - I)I$
$R_1 = \beta/(\gamma + a + \alpha_0) \leq 1$	$I(t) \rightarrow 0, N(t)$ grows like $e^{rt}$
$R_1 = \beta/(\gamma + a + \alpha_0) > 1$	$I(t) \rightarrow I_e, N(t)$ decays or grows like $e^{\rho t}$
mass-action incidence	$g = \beta XY \Rightarrow g^* = \beta(1 - I)IN$
$r < af + \alpha_0$	$I(t) \rightarrow r/(af + \alpha_0), N(t) \rightarrow N_e$
$r > af + \alpha_0$	$I(t) \rightarrow 0, N(t)$ grows like $e^{rt}$

equation is  $N' = rN$ , so that  $N(t)$  has asymptotically exponential growth with the usual per capita rate  $r = a - b$  by Corollary 4 on asymptotically autonomous systems in Hethcote et al. (2004), which is based on a result in Thieme (1992). When  $R_1 > 1$  and  $I(t) \rightarrow I_e$ , the limiting equation is  $N' = [r - (af + \alpha_0)I_e]N$ , so that the same Corollary 4 implies that  $N(t)$  has asymptotically exponential decay or growth with the rate constant  $\rho$ , which is less than  $r$  and given by

$$\rho = r - (af + \alpha_0)I_e = \frac{r\beta - (af + \alpha_0)[\beta - (\gamma + b + \alpha_0)]}{\beta - (af + \alpha_0)}. \tag{3.3}$$

Thus the host population size  $N$  approaches extinction if  $\rho < 0$  and grows exponentially if  $\rho > 0$ .

For mass-action incidence  $g^*(I, N) = \beta I(1 - I)N$ , the  $dI/dt$  equation depends on  $N$ , so the system does not uncouple. Note from the equation for  $dI/dt$  that  $I(t)$  cannot go to 1, since  $I = 1$  implies that  $I' < 0$ . Thus if  $\psi = r/(af + \alpha_0) \geq 1$ , then  $N' = [r - (af + \alpha_0)I]N > 0$ , so that  $N(t) \rightarrow \infty$  as  $t \rightarrow \infty$ . In this case the only bounded solution of  $dI/dt$  equation is  $I = 0$ , so that we must have  $I(t) \rightarrow 0$  as  $t \rightarrow \infty$ . The quantity  $af + \alpha_0$  is interpreted as the infection-induced death rate occurring directly through infection-related deaths ( $\alpha_0$ ) and indirectly through infection-reduced reproduction ( $af$ ). Hence if  $\psi = r/(af + \alpha_0) \geq 1$ , so that the per capita natural growth rate  $r$  exceeds the infection-induced death rate  $af + \alpha_0$ , then the disease dies out and  $N$  grows exponentially with the usual per capita rate  $r$ . In this case the infection-induced death rate is less than the natural growth rate, so that it is expected that the population size would still grow indefinitely. If  $\psi = r/(af + \alpha_0) < 1$ , then there is a locally stable endemic equilibrium given by  $I_e = r/(af + \alpha_0)$  and  $N_e = (\gamma + b + \alpha_0)/\{\beta[1 - r/(af + \alpha_0)]\}$ . Global stability is proved using a Liapunov function in Appendix A. In this case the infection-induced death rate  $af + \alpha_0$  is greater than the natural growth rate  $r$ , so that the endemicity of the disease changes the exponential growth of the host population into an approach to a steady state host population size. Note that this SIS model with mass-action incidence does not have a reproduction number as a threshold.

#### 4. The SIS exponential model with two hosts

Now consider the generalization of the SIS model in the previous section to two exponentially growing host populations, which interact only through the transmission of infections between the host populations.

$$\begin{aligned} dN_1/dt &= a_1[X_1 + (1 - f_1)Y_1] - b_1N_1 - \alpha_{10}Y_1, \\ dX_1/dt &= a_1[X_1 + (1 - f_1)Y_1] - b_1X_1 - g_1(X_1, Y_1, N_1, X_2, Y_2, N_2) + \gamma_1Y_1, \\ dY_1/dt &= g_1(X_1, Y_1, N_1, X_2, Y_2, N_2) - (\gamma_1 + b_1 + \alpha_{10})Y_1, \\ dN_2/dt &= a_2[X_2 + (1 - f_2)Y_2] - b_2N_2 - \alpha_{20}Y_2, \\ dX_2/dt &= a_2[X_2 + (1 - f_2)Y_2] - b_2X_2 - g_2(X_1, Y_1, N_1, X_2, Y_2, N_2) + \gamma_2Y_2, \\ dY_2/dt &= g_2(X_1, Y_1, N_1, X_2, Y_2, N_2) - (\gamma_2 + b_2 + \alpha_{20})Y_2. \end{aligned} \tag{4.1}$$

In host population  $i$  with  $i = 1, 2$ ,  $N_i$  is the population size,  $X_i$  is the number of susceptibles,  $Y_i$  is the number of infectives,  $a_i$  is the birth rate constant,  $b_i$

is the natural death rate constant,  $\alpha_i$  is the infection-induced death rate constant of infected individuals,  $\gamma_i$  is the per capita recovery rate, and  $f_i$  is the fraction corresponding to the infection-reduced reproduction rate of infected individuals. The incidence  $g_i(X_1, Y_1, N_1, X_2, Y_2, N_2)$  is either frequency-dependent incidence  $(\beta_{ii}Y_i/N_i + \beta_{ij}Y_j/N_j)X_i$  or mass-action incidence  $(\beta_{ii}Y_i + \beta_{ij}Y_j)X_i$ .

The system (4.1) can be reduced to the following system of four equations by using  $X_i = N_i - Y_i$  and infectious fractions  $I_i = Y_i/N_i$ .

$$\begin{aligned} dN_1/dt &= [r_1 - \alpha_1 I_1]N_1, \\ dI_1/dt &= g_1^*(I_1, N_1, I_2, N_2) - [d_1 - \alpha_1 I_1]I_1, \\ dN_2/dt &= [r_2 - \alpha_2 I_2]N_2, \\ dI_2/dt &= g_2^*(I_1, N_1, I_2, N_2) - [d_2 - \alpha_2 I_2]I_2, \end{aligned} \quad (4.2)$$

where the positive per capita net growth rates are  $r_i = a_i - b_i$ , the sum of the per capita infection-related death rates and the infection-reduced reproduction rates are  $\alpha_i = \alpha_{i0} + a_i f_i$ , the per capita rates of recovery and death are  $d_i = \gamma_i + a_i + \alpha_{i0}$ , frequency-dependent incidence is  $g_i^* = (\beta_{ii}I_i + \beta_{ij}I_j)(1 - I_i)$ , and mass-action incidence is  $g_i^* = (\beta_{ii}I_i N_i + \beta_{ij}I_j N_i)(1 - I_i)$ . For this model the region  $D = \{(N_1, I_1, N_2, I_2) : N_i \geq 0, 0 \leq I_i \leq 1\}$  is positively invariant.

The equivalent density system (4.1) with mass-action incidence and  $f_i = 0$  was studied by Holt and Pickering (1985), who conjectured that the coexistence equilibrium exists and is asymptotically stable whenever all other relevant equilibria are unstable. Greenman and Hudson (1997) showed that this conjecture is not true for some parameter sets in which the coexistence equilibrium is unstable and solutions go to a stable periodic solution. In the next section we extend this result of Greenman and Hudson (1997) by doing a complete Hopf bifurcation analysis on the existence of periodic solutions and obtaining a Hopf bifurcation surface in parameter space. Then in Section 6 we analyze the analogous model with frequency-dependent incidence and find that periodic solutions do not arise by Hopf bifurcation.

## 5. The Holt-Pickering model

With mass-action incidence the model (4.2) becomes

$$\begin{aligned} dN_1/dt &= [r_1 - \alpha_1 I_1]N_1, \\ dI_1/dt &= (\beta_{11}I_1 N_1 + \beta_{12}I_2 N_2)(1 - I_1) - [d_1 - \alpha_1 I_1]I_1, \\ dN_2/dt &= [r_2 - \alpha_2 I_2]N_2, \\ dI_2/dt &= (\beta_{21}I_1 N_1 + \beta_{22}I_2 N_2)(1 - I_2) - [d_2 - \alpha_2 I_2]I_2. \end{aligned} \quad (5.1)$$

This is a formulation with different variables of the model of Holt and Pickering (1985). As in the model with one host, the quantity  $\alpha_i = a_i f_i + \alpha_{i0}$  can be interpreted as the infection-induced death rate occurring directly through infection-related deaths ( $\alpha_{i0}$ ) and indirectly through infection-reduced reproduction ( $a_i f_i$ ). If the per capita natural growth rate  $r_i$  exceeds the per capita infection-induced death rate  $\alpha_i$ , then the differential equation for  $N_i$  in the system (5.1) implies that

$N_i$  grows to infinity, and  $I_i$  must approach 0 as  $t \rightarrow \infty$ , since a positive limit would contradict the differential equation for  $I_i$ . The coefficients of the terms involving the infectives are  $e_i = a_i(1 - f_i) + \gamma_i$  and  $-d_i^* = -(\gamma_i + b_i + \alpha_{i0})$  in the differential equations for the sizes of susceptibles and infectives, respectively, so we could call  $e_i$  the feedback coefficient and  $d_i^*$  the net removal rate (as in Greenman and Hudson, 1997). Since  $\alpha_i - r_i = d_i^* - e_i$ , the condition that  $r_i > \alpha_i$  is equivalent to  $e_i > d_i^*$ . If  $r_i > \alpha_i$ , then  $dN_i/dt > 0$ , so that  $N_i(t) \rightarrow \infty$  as  $t \rightarrow \infty$ . In order to focus on bounded solutions, we assume that the inequalities  $r_1 < \alpha_1$  and  $r_2 < \alpha_2$  hold in the following analysis.

This model always has the equilibrium  $E_0 = (0, 0, 0, 0)$ . Since  $r_1 < \alpha_1$ , the model has the equilibrium  $E_1 = (N_1^*, r_1/\alpha_1, 0, I_2^*)$  on a boundary of  $D$ , where  $N_1^* = d_1^*/[\beta_{11}(1 - r_1/\alpha_1)]$ , and  $I_2^*$  is the root in the interval  $(0, 1)$  of the quadratic equation  $Q_1(I_2) = A(1 - I_2) - (d_2 - \alpha_2 I_2)I_2 = 0$  with  $A = \beta_{21}(r_1/\alpha_1)N_1^*$ ,  $Q_1(0) > 0$ , and  $Q_1(1) < 0$ . Since  $r_2 < \alpha_2$ , the model has the analogous equilibrium  $E_2 = (0, I_1^*, N_2^*, r_2/\alpha_2)$  on a boundary of  $D$  with symmetric definitions of  $N_2^*$  and  $I_1^*$ .

The model also has the equilibrium  $E_3 = (N_1^e, r_1/\alpha_1, N_2^e, r_2/\alpha_2)$ , where the solutions of two simultaneous linear equations in  $N_1$  and  $N_2$  are found by Cramer's rule to be

$$\begin{aligned}
 N_1^e &= \frac{\alpha_1}{r_1} \left[ \frac{\beta_{22}d_1^*r_1}{\alpha_1 - r_1} - \frac{\beta_{12}d_2^*r_2}{\alpha_2 - r_2} \right] / (\beta_{11}\beta_{22} - \beta_{21}\beta_{12}), \\
 N_2^e &= \frac{\alpha_2}{r_2} \left[ \frac{\beta_{11}d_2^*r_2}{\alpha_2 - r_2} - \frac{\beta_{21}d_1^*r_1}{\alpha_1 - r_1} \right] / (\beta_{11}\beta_{22} - \beta_{21}\beta_{12}).
 \end{aligned}
 \tag{5.2}$$

This equilibrium  $E_3$  is in the relevant region  $D$  if  $r_1 < \alpha_1$ ,  $r_2 < \alpha_2$ ,  $N_1^e > 0$ , and  $N_2^e > 0$ .

A local stability analysis shows that the equilibrium  $E_0 = (0, 0, 0, 0)$  is repulsive in the  $N_1$  and  $N_2$  directions and is attractive in the  $I_1$  and  $I_2$  directions. A local stability analysis is also used to identify the conditions under which the shared pathogen leads to the extinction of one of the hosts, so that solutions go to  $E_1$  or  $E_2$ . At the boundary equilibrium  $E_1 = (N_1^*, r_1/\alpha_1, 0, I_2^*)$ , the characteristic equation is  $Q_2(\lambda)(j_{33} - \lambda)(j_{44} - \lambda) = 0$ , where  $Q_2(\lambda) = \lambda^2 - j_{22}\lambda + r_1d_1^*$ ,  $j_{22} = -r_1[\gamma_1 + a_1(1 - f_1)]/(\alpha_1 - r_1) < 0$ ,  $j_{33} = r_2 - \alpha_2 I_2^*$ , and  $j_{44} = -[\gamma_2 + a_2(1 - f_2)]/(1 - I_2^*) - \alpha_2(1 - I_2^*) < 0$ . The quadratic equation  $Q_2(\lambda) = 0$  always has roots with negative real parts, so that the equilibrium  $E_1$  is locally asymptotically stable if  $r_2 - \alpha_2 I_2^* < 0$  and is unstable with repulsion in the  $N_2$  direction if  $r_2 - \alpha_2 I_2^* > 0$ . We cannot find the solution  $I_2^*$  of the quadratic equation  $Q_1(I_2) = 0$  explicitly, but if  $p = r_2 - \alpha_2 I_2^*$ , then  $p$  satisfies the quadratic equation  $Q_3(p) = p^2 + p(A - d_2^* - r_2) + A(\alpha_2 - r_2) - d_2^*r_2$ . If  $Q_3(0) = A(\alpha_2 - r_2) - d_2^*r_2 < 0$ , then this quadratic has a positive solution  $p$  and hence the equilibrium  $E_1$  is repulsive into  $D$  in the  $N_2$  direction. Also the equilibrium  $E_1$  is attractive in the  $N_2$  direction if  $A(\alpha_2 - r_2) - d_2^*r_2 > 0$ . This condition is equivalent to

$$\frac{r_2d_2^*}{\beta_{21}(\alpha_2 - r_2)} < \frac{r_1d_1^*}{\beta_{11}(\alpha_1 - r_1)}.
 \tag{5.3}$$

By symmetry the equilibrium  $E_2 = (0, I_1^*, N_2^*, r_2/\alpha_2, )$  is repulsive into  $D$  in the  $N_1$  direction if  $B(\alpha_1 - r_1) - d_1^*r_1 < 0$ , where  $B = \beta_{12}(r_2/\alpha_2)N_2^*$ . Also the equilibrium  $E_2$  is attractive in the  $N_1$  direction if  $B(\alpha_1 - r_1) - d_1^*r_1 > 0$ . This condition is equivalent to

$$\frac{r_1 d_1^*}{\beta_{12}(\alpha_1 - r_1)} < \frac{r_2 d_2^*}{\beta_{22}(\alpha_2 - r_2)}. \quad (5.4)$$

Greenman and Hudson (1997) formulated the Holt-Pickering model in terms of the susceptibles  $X_i = (1 - I_i)N_i$  and infectives  $Y_i = I_i N_i$  (which they interpreted as densities instead of numbers). In these variables the equilibria are  $E_1 = (X_{11}, Y_{11}, 0, 0)$  and  $E_2 = (0, 0, X_{21}, Y_{21})$ , where  $X_{i1} = d_i^*/\beta_{ii}$  and  $Y_{i1} = r_i d_i^*/[\beta_{ii}(\alpha_i - r_i)]$ . Their coexistence equilibrium is  $E_3 = (X_{12}, Y_{12}, X_{22}, Y_{22})$ , where  $Y_{i2} = \beta_{jj}(\beta_{ii}Y_{i1} - \beta_{ij}Y_{j1})/\Delta$  and  $X_{i2} = Y_{i2}(\alpha_i - r_i)/r_i$  with  $\Delta = \beta_{11}\beta_{22} - \beta_{21}\beta_{12}$ . The advantage of our formulation is that one can see that the infective fractions  $I_2^*$  and  $I_1^*$  are positive when the population sizes  $N_2$  and  $N_1$  are zero at the equilibria  $E_1$  and  $E_2$ . In their notation the condition (5.3) is  $\beta_{22}Y_{21} < \beta_{21}Y_{11}$  and condition (5.4) is  $\beta_{11}Y_{11} < \beta_{12}Y_{21}$ . Biological interpretations of these inequalities are given in the survey paper of Begon and Bowers (1995). For example, condition (5.3) for the local asymptotic stability of  $E_1$  is interpreted as host 2 being affected more by interspecific competition for pathogen free space than by intraspecific competition.

Note that  $\beta_{11}\beta_{22} - \beta_{21}\beta_{12}$  is less than 0 if conditions (5.3) and (5.4) both hold, and it is greater than 0 if both conditions are reversed. Thus the equilibrium  $E_3$  exists in  $D$  if conditions (5.3) and (5.4) both hold or both conditions are reversed. Four possible cases with bounded solutions follow. In case 1 condition (5.3) is satisfied and condition (5.4) is reversed, so that boundary equilibrium  $E_1$  is asymptotically stable, boundary equilibrium  $E_2$  is unstable, and equilibrium  $E_3$  is not in  $D$ . One might expect that bounded solutions with  $N_1(0) > 0$ , and  $I_1(0) > 0$  or  $I_2(0) > 0$  would approach the equilibrium  $E_1$  as  $t \rightarrow \infty$ . This occurs for some parameter values, but Greenman and Hudson (1997) found a parameter set (A4 in their Table 1) for which some solution paths approach a limit cycle.

In case 2 condition (5.3) is reversed and condition (5.4) is satisfied, so that boundary equilibrium  $E_1$  is unstable, boundary equilibrium  $E_2$  is asymptotically stable, and equilibrium  $E_3$  is not in  $D$ . Analogous to case 1, for some parameter sets bounded solutions approach the equilibrium  $E_2$  as  $t \rightarrow \infty$ , but for other parameter sets, solution paths approach periodic solutions.

For cases 3 and 4 when the equilibrium  $E_3$  exists in the interior of  $D$ , we make the following changes to simplify the equations. First replace  $N_1$  and  $N_2$  by  $\bar{N}_1 = \beta_{21}N_1$  and  $\bar{N}_2 = \beta_{12}N_2$ . Next for  $i = 1, 2$  replace  $d_i$  by  $d_i^* + r_i$  and replace  $\alpha_i$  by  $r_i(1 + \frac{d_i^*}{g_i + r_i})$ , where  $g_i + r_i = \frac{r_i d_i^*}{\alpha_i - r_i}$ , so that the new parameters  $g_i$  satisfy  $g_i = r_i \frac{\gamma_i + a_i(1 - f_i)}{\alpha_i - r_i}$ . Finally replace  $\beta_{11}$  by  $\beta_{21}\beta_1(g_1 + r_1)/(g_2 + r_2)$  and  $\beta_{22}$  by  $\beta_{12}\beta_2(g_2 + r_2)/(g_1 + r_1)$ , where  $\beta_i > 0$  are new parameters. Then the

system (5.1) with 10 parameters becomes

$$\begin{aligned}
 \frac{d\bar{N}_1}{dt} &= r_1 \left[ 1 - \left( 1 + \frac{d_1^*}{g_1 + r_1} \right) I_1 \right] \bar{N}_1, \\
 \frac{dI_1}{dt} &= \left[ \frac{\beta_1(g_1 + r_1)}{g_2 + r_2} I_1 \bar{N}_1 + I_2 \bar{N}_2 \right] (1 - I_1) \\
 &\quad - \left[ d_1^* + r_1 - r_1 \left( 1 + \frac{d_1^*}{g_1 + r_1} \right) I_1 \right] I_1, \\
 \frac{d\bar{N}_2}{dt} &= r_2 \left[ 1 - \left( 1 + \frac{d_2^*}{g_2 + r_2} \right) I_2 \right] \bar{N}_2, \\
 \frac{dI_2}{dt} &= \left[ I_1 \bar{N}_1 + \frac{\beta_2(g_2 + r_2)}{g_1 + r_1} I_2 \bar{N}_2 \right] (1 - I_2) \\
 &\quad - \left[ d_2^* + r_2 - r_2 \left( 1 + \frac{d_2^*}{g_2 + r_2} \right) I_2 \right] I_2,
 \end{aligned} \tag{5.5}$$

with 8 parameters. Moreover, the conditions (5.3) and (5.4) simplify to

$$\begin{aligned}
 \beta_1 &< 1, \\
 \beta_2 &< 1.
 \end{aligned} \tag{5.6}$$

Conditions  $\beta_1 < 1$  and  $\beta_2 < 1$  hold in case 3 and conditions  $\beta_1 > 1$  and  $\beta_2 > 1$  hold in case 4, so that the interior equilibrium  $E_3$  exists in  $D$ . For these cases the characteristic equation  $P_4(\lambda) = 0$  for the eigenvalues of the Jacobian at the equilibrium  $E_3$  is a fourth degree polynomial that is analyzed in Appendix B. In case 3 the conditions in (5.6) both hold, so that the boundary equilibria  $E_1$  and  $E_2$  are both locally asymptotically stable and interior equilibrium  $E_3$  is in  $D$ . Greenman and Hudson (1997) proved the Holt and Pickering (1985) conjecture that this coexistence equilibrium  $E_3$  is unstable. If the coefficients of the characteristic polynomial in Appendix B satisfy  $c_1 c_2 c_3 - c_3^2 - c_1^2 c_4 > 0$ , then one eigenvalue is positive and the other three eigenvalues have negative real parts. In this subcase of case 3, there is a 1 dimensional unstable manifold and a 3 dimensional stable manifold near  $E_3$ , so the latter is a local separating hypersurface. Thus we conjecture that in this subcase there may be a global separating hypersurface in  $N_1 I_1 N_2 I_2$  space passing through the saddle-like, interior equilibrium  $E_3$  and the equilibrium  $E_0 = (0, 0, 0, 0)$  with solution paths on one side approaching the boundary equilibrium  $E_1$  and solution paths on the other side approaching the other boundary equilibrium  $E_2$ .

In the other subcase of case 3 where the coefficients satisfy  $c_1 c_2 c_3 - c_3^2 - c_1^2 c_4 < 0$ , the real part of a complex conjugate pair of eigenvalues is positive. Since the real part switches from negative to positive at  $c_1 c_2 c_3 - c_3^2 - c_1^2 c_4 = 0$ , this defines a Hopf bifurcation parameter surface. Complete details for showing Hopf bifurcation are not given here, but are given in case 4 below. We have not calculated the stability of the periodic solutions arising by Hopf bifurcation, but there is a 3 dimensional manifold containing the periodic solution and the eigenvector for

the negative real eigenvalue. The unstable manifold contains the eigenvector corresponding to the positive real eigenvalue, so that this subcase could also have a separating hypersurface, or it could have some solutions paths approaching a limit cycle.

In case 4 conditions (5.6) are both reversed, i.e.  $\beta_1 > 1$  and  $\beta_2 > 1$ , so that the boundary equilibria  $E_1$  and  $E_2$  are both unstable and equilibrium  $E_3$  is in  $D$ . Holt and Pickering (1985) conjectured that in this case the coexistence equilibrium  $E_3$  is always asymptotically stable. But Greenman and Hudson (1997) showed that this conjecture is not always true by using Lienard-Chipman theory to show that  $E_3$  is unstable for some parameter sets. Moreover, they found a parameter set (A3 in their Table 1) for which there are no stable equilibria and solution paths are attracted to a stable limit cycle. For other parameter sets, all equilibria are unstable and solutions diverge to infinity. Greenman and Hudson (1997) also showed that the coexistence equilibrium  $E_3$  is locally asymptotically stable if  $r_1 d_1 = r_2 d_2$ , so that the Holt-Pickering conjecture is true in this case.

We extend the analysis of Greenman and Hudson (1997) by showing that Hopf bifurcation can occur at the coexistence equilibrium  $E_3$  in case 4. The Hopf bifurcation theorem states that under certain conditions a branch of periodic solutions splits off from an equilibrium when the real part of a complex conjugate pair of eigenvalues changes sign as the parameters change (Guckenheimer and Holmes, 1983). In Appendix C we show that all conditions for Hopf bifurcation are satisfied. Hence for parameter values near the Hopf surface, the Hopf bifurcation theorem guarantees that there is a one parameter family of periodic solutions of the rescaled system (5.5) branching off from the equilibrium  $E_3$ . Figure 1 shows a slice of the surface at which Hopf bifurcation occurs, and Figure 2 shows a periodic solution for a specific set of parameter values.

## 6. The Holt-Pickering model with frequency-dependent incidence

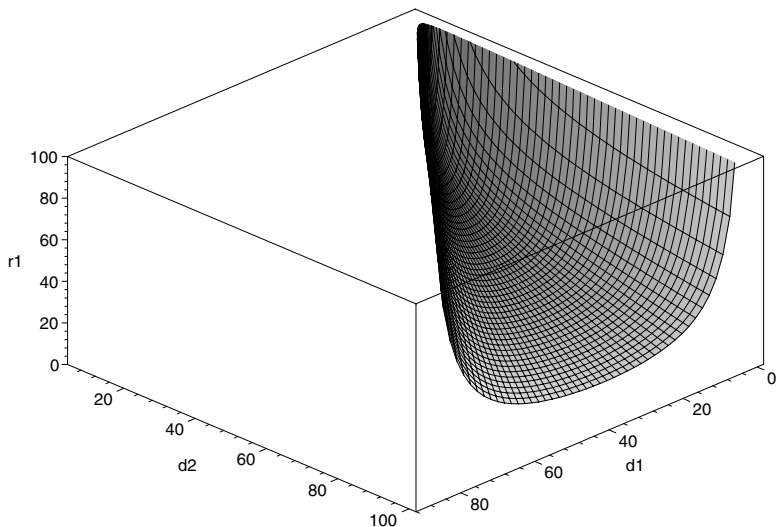
With frequency-dependent incidence the model (4.2) becomes

$$\begin{aligned} dN_1/dt &= [r_1 - \alpha_1 I_1]N_1, \\ dI_1/dt &= (\beta_{11} I_1 + \beta_{12} I_2)(1 - I_1) - [d_1 - \alpha_1 I_1]I_1, \\ dN_2/dt &= [r_2 - \alpha_2 I_2]N_2, \\ dI_2/dt &= (\beta_{21} I_1 + \beta_{22} I_2)(1 - I_2) - [d_2 - \alpha_2 I_2]I_2. \end{aligned} \quad (6.1)$$

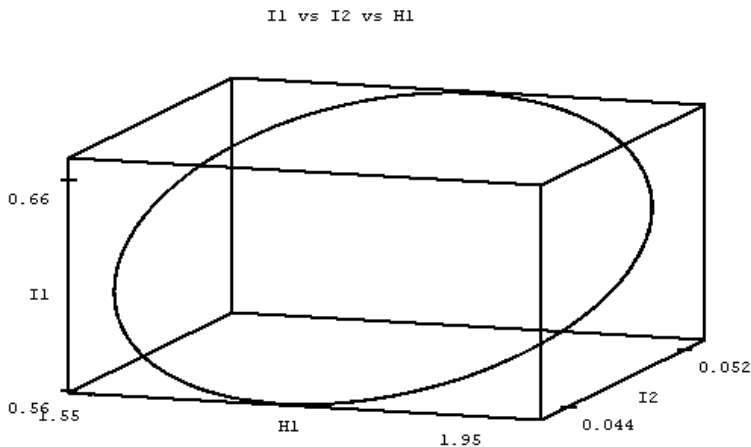
The equations for the infective fractions do not involve the host population sizes, so that the system uncouples and we can consider the following two dimensional subsystem

$$\begin{aligned} dI_1/dt &= (\beta_{11} - d_1)I_1 + \beta_{12} I_2(1 - I_1) + (\alpha_1 - \beta_{11})I_1^2, \\ dI_2/dt &= \beta_{21} I_1(1 - I_2) + (\beta_{22} - d_2)I_2 + (\alpha_2 - \beta_{22})I_2^2. \end{aligned} \quad (6.2)$$

The feasible region for (6.2) is the unit square  $\hat{D} = \{(I_1, I_2) : 0 \leq I_1 \leq 1, 0 \leq I_2 \leq 1\}$ . Since the off diagonal entries in the Jacobian matrix of the system (6.2) are positive, the system is cooperative in  $\hat{D}$ . Hence, solutions must approach



**Fig. 1.** The Hopf bifurcation surface in  $d_1 d_2 r_1$  parameter space when  $r_2 = 1$ ,  $\beta_1 = 19/18$ ,  $\beta_2 = 16/15$ ,  $g_1 = 2$ , and  $g_2 = 1$ .



**Fig. 2.** An example of a periodic orbit when  $r_1 = 30$ ,  $r_2 = 1$ ,  $d_1^* = 20$ ,  $d_2^* = 40$ ,  $\beta_1 = 1.05$ ,  $\beta_2 = 1.06$ ,  $g_1 = 2$ , and  $g_2 = 1$  with initial values  $H_1 = 1.9259$ ,  $H_2 = 293.53$ ,  $I_1 = 0.57580$ ,  $I_2 = 0.044753$ .

equilibria (Smith, 1995; Hirsch et al., 2001). One could also show this by using Poincaré-Bendixson Theory and Dulac's criterion with multiplier  $1/(I_1 I_2)$  to rule out periodic solutions (Strogatz, 1994).

For this model the modified reproduction number  $R_1$  is the spectral radius  $\rho$  (the maximum absolute value of an eigenvalue) of the next generation matrix (Diekmann et al., 1990; Hethcote, 1996) given by

$$R_1 = \rho \left[ \begin{array}{cc} \beta_{11}/d_1 & \beta_{12}/d_2 \\ \beta_{21}/d_1 & \beta_{22}/d_2 \end{array} \right] = \frac{1}{2} \left\{ \frac{\beta_{11}}{d_1} + \frac{\beta_{22}}{d_2} + \sqrt{\left( \frac{\beta_{11}}{d_1} - \frac{\beta_{22}}{d_2} \right)^2 + \frac{4\beta_{12}\beta_{21}}{d_1 d_2}} \right\}. \quad (6.3)$$

From the trace and determinant of the Jacobian, we find that the equilibrium at the origin is asymptotically stable if

$$\beta_{12}\beta_{21} < (d_1 - \beta_{11})(d_2 - \beta_{22}), \quad (6.4)$$

where the factors on the right side must be positive. As expected, this condition is equivalent to  $R_1 < 1$ .

The nullclines of (6.2) are

$$I_2 = \frac{I_1 [d_1 - \alpha_1 I_1 - \beta_{11}(1 - I_1)]}{\beta_{12}(1 - I_1)}, \quad (6.5)$$

$$I_1 = \frac{I_2 [d_2 - \alpha_2 I_2 - \beta_{22}(1 - I_2)]}{\beta_{21}(1 - I_2)}.$$

The second derivatives of the expressions above are positive (since  $d_i > \alpha_i$ ), so that the first nullcline is concave and the second is convex. These two nullclines pass through the origin of  $\hat{D}$  and pass out the top and right side of  $\hat{D}$ , respectively, since they approach infinity as  $I_1$  or  $I_2$  approaches 1. It is clear geometrically that these nullclines do not intersect in  $\hat{D}$ , if at the origin the slope  $(d_1 - \beta_{11})/\beta_{12}$  of the first nullcline is greater than the slope  $\beta_{21}/(d_2 - \beta_{22})$  of the second nullcline, which is the same as condition (6.4). However, the nullclines do intersect inside  $\hat{D}$ , if the slope of the first nullcline at the origin is less than the slope of the second nullcline. Thus if  $R_1 \leq 1$ , then  $\hat{E}_1$  is the only equilibrium in  $\hat{D}$  and it is locally asymptotically stable. By the result that cooperativity implies monotonicity above, all solution paths in  $\hat{D}$  must approach  $\hat{E}_1$ . If  $R_1 > 1$ , then the infection-free equilibrium  $\hat{E}_1 = (0, 0)$  is unstable with a repulsive direction into  $\hat{D}$ , since the Perron Theorem implies that the spectral radius is a real positive eigenvalue and the corresponding eigenvector has positive entries (Horn and Johnson, 1990). Moreover,  $R_1 > 1$  implies that there is a unique endemic equilibrium  $\hat{E}_2 = (I_1^e, I_2^e)$  in  $\hat{D}$ , which must be globally attracting in  $\hat{D} - \{(0, 0)\}$  by the monotonicity result above.

For the system (6.1), the limiting differential equations when  $R_1 \leq 1$  are  $N_i' = r_i N_i$ , so by Corollary 4 in Hethcote et al. (2004),  $N_i(t)$  has asymptotically exponential growth with per capita growth rate  $r_i$ . If  $R_1 > 1$ , then the limiting differential equations are  $N_i' = [r_i - \alpha_i I_i^e] N_i$ , so that  $N_i(t)$  has asymptotic per capita rate equal to  $r_i - \alpha_i I_i^e$ . Thus  $N_i(t)$  has asymptotic exponential decay to zero when  $r_i < \alpha_i I_i^e$ , goes to a constant when  $r_i = \alpha_i I_i^e$ , and has asymptotic exponential

growth to infinity when  $r_i > \alpha_i I_i^e$ . In contrast with the Holt-Pickering system in the previous section, solutions of this system (6.1) almost never go to an infected, coexistence equilibrium. Moreover, this system never has a nontrivial periodic solution.

### 7. The SIS model with logistic growth

The SIS model with limited growth of one host population and the usual meanings for  $X$ ,  $Y$ , and  $N$  is

$$\begin{aligned}
 dN/dt &= \left[ a - \frac{\chi r N}{K} \right] [X + (1 - f)Y] - \left[ b + \frac{(1 - \chi)rN}{K} \right] N - \alpha_0 Y \\
 &= r(1 - N/K)N - (\alpha_0 + af)Y + f\chi rYN/K \\
 dX/dt &= \left[ a - \frac{\chi r N}{K} \right] [X + (1 - f)Y] \\
 &\quad - \left[ b + \frac{(1 - \chi)rN}{K} \right] X - g(X, Y, N) + \gamma Y, \\
 dY/dt &= g(X, Y, N) - \left[ \gamma + b + \alpha_0 + \frac{(1 - \chi)rN}{K} \right] Y,
 \end{aligned}
 \tag{7.1}$$

where  $a$  is a per capita birth rate for susceptibles at very low population size and  $f$  is the reduction in birth rate due to infections, so that  $a(1 - f)$  is a per capita birth rate for infectives at very low population size. Here  $b$  is the natural per capita death rate at very low population size,  $r = a - b$  is the positive per capita net growth rate,  $\chi$  is the convex combination constant with  $0 \leq \chi \leq 1$ ,  $K$  is the environmental carrying capacity,  $\gamma$  is the per capita recovery rate, and  $\alpha_0$  is the per capita infection-related death rate. The incidence  $g(X, Y, N)$  is either frequency-dependent incidence  $\beta XY/N$  or mass-action incidence  $\beta XY$ . This SIS model and the analogous SIRS model with frequency-dependent (standard) incidence and vertical transmission, but without infection-reduced reproduction, were studied by Gao and Hethcote (1992).

In the absence of disease the  $dN/dt$  equation is the logistic differential equation for restricted growth, so that solutions with  $N(0) > 0$  approach the carrying capacity  $K$ . For  $0 < \chi < 1$ , the per capita birth rate  $a - \chi r N/K$  decreases and the per capita death rate  $b + (1 - \chi)rN/K$  increases as the population size  $N$  increases; these are consistent with limited resources corresponding to density dependence. The birth rate is density independent when  $\chi = 0$  and the death rate is density independent when  $\chi = 1$ . The birth rate does not make sense for very large values of  $N$ , so that we consider the positively invariant subset of the first quadrant with  $N < aK/\chi r$ . Since  $N' < 0$  for  $N > K$ , all solution paths in the subset above approach, enter, or stay in the subset with  $N \leq K$ . Thus it suffices to analyze solution paths with  $N = X + Y \leq K$ .

The model (7.1) can be reduced by using  $I = Y/N$  and  $X/N = 1 - I$  to the following system

$$\begin{aligned}
 dN/dt &= [r(1 - N/K) - (af + \alpha_0)I + f\chi rIN/K]N, \\
 dI/dt &= g^*(I, N) - [\gamma + a + \alpha_0 - (af + \alpha_0)I - \chi r(1 - f)I]I.
 \end{aligned}
 \tag{7.2}$$

Here the incidence  $g^*(I, N) = g(X, Y, N)/N$  is frequency-dependent incidence  $\beta I(1 - I)$  or mass-action incidence  $\beta I(1 - I)N$ . This model is well posed in  $D = \{(N, I) : 0 \leq N \leq K, 0 \leq I \leq 1\}$ . The asymptotic behaviors are summarized in Table 2 with the threshold quantity definitions and proofs given in the following subsections.

7.1. The SIS logistic model with frequency-dependent incidence

For frequency-dependent incidence the model (7.2) becomes

$$\begin{aligned} dN/dt &= [r(1 - N/K) - (af + \alpha_0)I + f\chi rIN/K]N, \\ dI/dt &= [\beta(1 - I) - (\gamma + a + \alpha_0) + (af + \alpha_0)I + \chi r(1 - fI)N/K]I. \end{aligned} \tag{7.3}$$

The behavior of this system is governed by the three threshold quantities:

$$\begin{aligned} R_2 &= \beta/(\gamma + a + \alpha_0 - \chi r), \\ R_1 &= \beta/(\gamma + a + \alpha_0), \\ \phi &= \frac{r}{(af + \alpha_0)[1 - (\gamma + b + \alpha_0)/\beta]}. \end{aligned} \tag{7.4}$$

Note that  $R_2 \geq R_1$ . The system always has the equilibrium points  $E_1 = (0, 0)$  and  $E_2 = (K, 0)$ . If  $R_1 > 1$ , then the equilibrium point  $E_3 = (0, I_3)$  is in  $D$ , where

$$I_3 = \frac{\beta - (\gamma + a + \alpha_0)}{\beta - (af + \alpha_0)}. \tag{7.5}$$

An equilibrium point in the interior of  $D$  must satisfy the equations

$$\begin{aligned} r(1 - N/K) - (af + \alpha_0)I + f\chi rIN/K &= 0, \\ \beta(1 - I) - (\gamma + a + \alpha_0) + (af + \alpha_0)I + \chi r(1 - fI)N/K &= 0. \end{aligned} \tag{7.6}$$

**Table 2.** Asymptotic behaviors for the SIS logistic model.

frequency-dependent incidence	$g = \beta XY/N \Rightarrow g^* = \beta(1 - I)I$
case 1: $1 \geq R_2 \geq R_1$	$N(0) > 0 \Rightarrow (N, I) \rightarrow E_2 = (K, 0)$
case 2: $R_2 > 1 \geq R_1$	$N(0) > 0, I(0) > 0 \Rightarrow (N, I) \rightarrow E_4 = (N_4, I_4)$
case 3: $R_1 > 1 \ \& \ \phi < 1$	$I(0) > 0 \Rightarrow (N, I) \rightarrow E_3 = (0, I_3)$
case 4: $R_1 > 1 \ \& \ \phi > 1$	$N(0) > 0, I(0) > 0 \Rightarrow (N, I) \rightarrow E_4 = (N_4, I_4)$
mass-action incidence	$g = \beta XY \Rightarrow g^* = \beta(1 - I)IN$
case 1: $R_3 \leq 1$	$N(0) > 0 \Rightarrow (N, I) \rightarrow E_2 = (K, 0)$
case 2: $R_3 > 1$	$N(0) > 0, I(0) > 0 \Rightarrow (N, I) \rightarrow E_3 = (N_3, I_3)$

Adding these equations yields the linear equation

$$\beta(1 - I) - (\gamma + b + \alpha_0) - r(1 - \chi)N/K = 0. \tag{7.7}$$

Solving (7.7) for  $rN/K$  and substituting into the first equation in (7.6) yields the quadratic equation  $Q_4(I) = f\chi\beta I^2 - cI + \beta - (\gamma + a + \alpha_0 - \chi r) = 0$ , where  $c = \beta(1 + f\chi) - (1 - \chi)(af + \alpha_0) - f\chi(\gamma + b + \chi_0)$ . Since  $Q_4(1)$  is always less than 0 and  $Q_4(0) > 0$  iff  $R_2 > 1$ , there is a unique positive solution  $I_4$  in the interval  $(0, 1)$  iff  $R_2 > 1$ . Solving (7.7) for  $I$  and substituting into the second equation in (7.6) yields a quadratic equation  $Q_5(N) = 0$  with  $Q_5(0) = r - (af + \alpha_0)[1 - (\gamma + b + \alpha_0)/\beta]$ , which is positive iff  $\phi > 1$ . Also  $Q_5(K) = -[f(a - r\chi) + \alpha_0](1 - 1/R_2)$ , which is negative iff  $R_2 > 1$ , so that there is a solution  $N_4$  in the interval  $(0, K)$  if  $\phi > 1$  and  $R_2 > 1$ . Hence we have an equilibrium point  $E_4 = (N_4, I_4)$  in the interior of  $D$  if  $R_2 > 1$  and  $\phi > 1$ .

The equilibrium point  $E_1 = (0, 0)$  is always repulsive in the  $N$  direction and is attractive in the  $I$  direction iff  $R_1 \leq 1$ . The equilibrium point  $E_2 = (K, 0)$  is always attractive in the  $N$  direction and is attractive in the  $I$  direction iff  $R_1 \leq 1$ . On the  $I = 0$  side of  $D$  with  $N(0) > 0$ ,  $N(t) \rightarrow K$  as  $t \rightarrow \infty$ . When the equilibrium point  $I_3$  is in  $D$ , it is always attractive in the  $I$  direction and is attractive in the  $N$  direction if  $\phi < 1$ .

There are four possible cases. Simple sketches in the  $NI$  plane of the equilibria and their local stabilities may help the reader understand these four cases. In case 1 with  $1 \geq R_2 \geq R_1$ , the only equilibria in  $D$  are the saddle  $E_1 = (0, 0)$  and the attractive equilibrium  $E_2 = (K, 0)$ . By the Poincare-Bendixson theory (Strogatz, 1994), all solutions in  $D$  with  $N(0) > 0$  approach the equilibrium  $E_2 = (K, 0)$  as  $t \rightarrow \infty$ .

Consider case 2 with  $R_2 > 1 \geq R_1$ . Epidemiologically, the average infectious period  $1/\gamma$  should be less than the low-population average lifetime  $1/a$ , so that  $\gamma > a > r = a - b$ . The assumption that  $\gamma > r$  and  $R_2 > 1$  imply that  $\beta > \gamma + a + \alpha_0 - \chi r > af + \alpha_0$ . Now  $1 \geq R_1$  implies that

$$\phi > \frac{r\beta}{(af + \alpha_0)[\gamma + a + \alpha_0 - (\gamma + b + \alpha_0)]} = \frac{\beta}{af + \alpha_0} > 1.$$

Thus the equilibria in  $D$  are the saddle  $E_1 = (0, 0)$ , the saddle  $E_2 = (K, 0)$  and the interior equilibrium  $E_4 = (N_4, I_4)$ . Using Dulac's criterion with multiplier  $1/(IN)$  in the system (7.3), we find that  $D$  has no periodic solutions (Strogatz, 1994). By the Poincare-Bendixson theory, all solutions in  $D$  with  $I(0) > 0$  and  $N(0) > 0$  approach the interior equilibrium  $E_4 = (I_4, N_4)$ . The intuitive explanation of case 2 is that the disease just barely remains endemic since  $R_2 > 1 \geq R_1$ , but the natural per capita growth rate  $r$  dominates the per capita infection-induced death rate given by  $af + \alpha_0$  since  $\phi > 1$ , so that the population size goes to a steady state  $N_4$  that is less than the carrying capacity  $K$ .

In case 3 with  $R_1 > 1$  and  $\phi < 1$ , the equilibria in  $D$  are the unstable node  $E_1 = (0, 0)$ , the saddle  $E_2 = (K, 0)$  (repulsive in the  $I$  direction) and the attractive node  $E_3 = (0, I_3)$ . Here  $R_1 > 1$  implies that  $\beta > af + \alpha_0$ , so the Dulac's criterion above still applies. By the Poincare-Bendixson theory, all solutions in  $D$

with  $I(0) > 0$  approach the equilibrium  $E_3 = (0, I_3)$ . The intuitive explanation of case 3 is that the disease remains endemic (i.e.  $\liminf_{t \rightarrow \infty} I(t) > 0$ ) since  $R_2 > 1$  and the per capita infection-induced death rate given by  $af + \alpha_0$  overpowers the per capita natural growth rate  $r$  since  $\phi < 1$ , so that the population is driven to extinction.

In case 4 with  $R_1 > 1$  and  $\phi > 1$ , the equilibria in  $D$  are the unstable node  $E_1 = (0, 0)$ , the saddle  $E_2 = (K, 0)$  (repulsive in the  $I$  direction), the saddle  $E_3 = (0, I_3)$  (repulsive in the  $N$  direction), and the equilibrium  $E_4 = (N_4, I_4)$ . By the Dulac's criterion above and the Poincare-Bendixson theory, all solutions in  $D$  with  $N(0) > 0$  and  $I(0) > 0$  approach the interior equilibrium  $E_4 = (N_4, I_4)$ . The intuitive explanation of case 4 is that the disease remains endemic since  $R_2 > 1$  and the per capita infection-induced death rate given by  $af + \alpha_0$  is dominated by the natural per capita growth rate  $r$  since  $\phi > 1$ , so that the population size goes to a steady state  $N_4$  that is less than the carrying capacity  $K$ .

Note that  $I_3$  is the same as  $I_e$  in the SIS model with exponential growth, so that  $r - (af + \alpha_0)I_3 = \rho$ , where  $\rho$  is given by (3.3). Thus for the SIS models with frequency-dependent incidence, and either exponential growth or logistic growth, the sign of  $\rho$  determines whether the population becomes extinct ( $\rho < 0 \Leftrightarrow \phi < 1$ ) or persists ( $\rho > 0 \Leftrightarrow \phi > 1$ ).

7.2. The SIS logistic model with mass-action incidence

For mass-action incidence the system (7.2) becomes

$$\begin{aligned} dN/dt &= [r(1 - N/K) - (af + \alpha_0)I + f\chi rIN/K]N, \\ dI/dt &= [\beta(1 - I)N - (\gamma + a + \alpha_0) + (af + \alpha_0)I + \chi r(1 - fI)N/K]I. \end{aligned} \tag{7.8}$$

The behavior of this system is governed by the threshold quantity

$$R_3 = \beta K / (\gamma + a + \alpha_0 - \chi r).$$

The system always has the equilibrium points  $E_1 = (0, 0)$  and  $E_2 = (K, 0)$ . An equilibrium point in the interior of  $D$  must satisfy equations similar to (7.6) and (7.7), but with  $\beta(1 - I)$  replaced by  $\beta(1 - I)N$ . Solving the analog of (7.7) for  $N/K$  and substituting into the first equation in (7.6) yields a quadratic equation  $Q_6(I) = 0$  with  $Q_6(1) < 0$  and  $Q_6(0) > 0$  iff  $R_3 > 1$ . Thus there is a positive solution  $I_3$  in the interval  $(0, 1)$  iff  $R_3 > 1$ . Solving the analog of (7.7) for  $I$  and substituting into the modified second equation in (7.6) yields a quadratic equation  $Q_7(N) = 0$  with  $Q_7(0) < 0$  and  $Q_7(K) < 0$  if  $R_3 > 1$ , so that there is a solution  $N_3$  in the interval  $(0, K)$  if  $R_3 > 1$ . Hence we have an equilibrium point  $E_3 = (N_3, I_3)$  in the interior of  $D$  if  $R_3 > 1$ .

The equilibrium point  $E_1 = (0, 0)$  is a saddle that is repulsive in the  $N$  direction and attractive in the  $I$  direction. The equilibrium point  $E_2 = (K, 0)$  is always attractive in the  $N$  direction and is attractive in the  $I$  direction if  $R_3 < 1$ . On the

$I = 0$  side of  $D$  with  $N(0) > 0$ ,  $N(t) \rightarrow K$  as  $t \rightarrow \infty$ . Using the simultaneous equations for the equilibrium point  $E_3 = (N_3, I_3)$ , the Jacobian at  $E_3$  is

$$J = \begin{bmatrix} -[r - (af + \alpha_0)I_3] & -r \left(1 - \frac{N_3}{K}\right) \frac{N_3}{I_3} \\ \frac{[(\gamma + a + \alpha_0) + (af + \alpha_0)I_3]I_3}{N_3} & -\left[\beta N_3 - (\gamma + a + \alpha_0) + \frac{\chi r N_3}{K}\right] \end{bmatrix}.$$

Using  $Q_6(0) > 0$  if  $R_3 > 1$  and  $Q_6(r/(af + \alpha_0)) < 0$ , we see that  $I_3 < r/(af + \alpha_0)$  and Jacobian entry  $j_{11} < 0$ . Using  $Q_7(K) < 0$  if  $R_3 > 1$  and  $Q_7((\gamma + a + \alpha_0)/(\beta + \chi r/K)) > 0$ , we see that  $N_3 > (\gamma + a + \alpha_0)/(\beta + \chi r/K)$  and  $j_{22} < 0$ . Thus the Jacobian has a negative trace and positive determinant, so that the equilibrium point  $E_3 = (N_3, I_3)$  is always locally asymptotically stable if  $R_3 > 1$ .

There are two cases. In case 1 with  $R_3 < 1$ , the only equilibria in  $D$  are the saddle  $E_1 = (0, 0)$  and the attractive equilibrium  $E_2 = (K, 0)$ . By the Poincare-Bendixson theory, all solutions in  $D$  with  $N(0) > 0$  approach the equilibrium  $E_2 = (K, 0)$  as  $t \rightarrow \infty$ . In case 2 with  $R_3 > 1$ , the equilibria in  $D$  are the saddle  $E_1 = (0, 0)$ , the saddle  $E_2 = (K, 0)$  (repulsive in the  $I$  direction), and the locally attractive interior equilibrium  $E_3 = (N_3, I_3)$ . Using Dulac’s criterion with multiplier  $C = 1/[IN(1 - I)]$  in the system (7.8), we find that the region  $D$  has no periodic solutions. By the Poincare-Bendixson theory, all solutions in  $D$  with  $I(0) > 0$  and  $N(0) > 0$  approach the interior equilibrium  $E_3 = (I_3, N_3)$ .

**8. The logistic growth model with two hosts**

Now consider the generalization of the SIS model in the previous section to two host populations with density-dependent growth, which interact only through their transmission of infections to the other host population. For simplicity we assume that there is no infection-reduced reproduction.

$$\begin{aligned} dN_1/dt &= r_1(1 - N_1/K_1)N_1 - \alpha_{10}Y_1, \\ dX_1/dt &= \left(a_1 - \frac{\chi_1 r_1 N_1}{K_1}\right) N_1 - \left(b_1 + \frac{(1 - \chi_1)r_1 N_1}{K_1}\right) X_1 \\ &\quad - g_1(X_1, Y_1, N_1, X_2, Y_2, N_2) + \gamma_1 Y_1, \\ dY_1/dt &= g_1(X_1, Y_1, N_1, X_2, Y_2, N_2) - \left(\gamma_1 + b_1 + \frac{(1 - \chi_1)r_1 N_1}{K_1} + \alpha_{10}\right) Y_1, \\ dN_2/dt &= r_2(1 - N_2/K_2)N_2 - \alpha_{20}Y_2, \\ dX_2/dt &= \left(a_2 - \frac{\chi_2 r_2 N_2}{K_2}\right) N_2 - \left(b_2 + \frac{(1 - \chi_2)r_2 N_2}{K_2}\right) X_2 \\ &\quad - g_2(X_1, Y_1, N_1, X_2, Y_2, N_2) + \gamma_2 Y_2, \\ dY_2/dt &= g_2(X_1, Y_1, N_1, X_2, Y_2, N_2) - \left(\gamma_2 + b_2 + \frac{(1 - \chi_2)r_2 N_2}{K_2} + \alpha_{20}\right) Y_2. \end{aligned} \tag{8.1}$$

where the variables and parameter values are analogous to those in the one population model. As in the two host models with exponential growth, the incidence

$g_i(X_1, Y_1, N_1, X_2, Y_2, N_2)$  is either frequency-dependent incidence  $(\beta_{ii}Y_i/N_i + \beta_{ij}Y_j/N_j)X_i$  or mass-action incidence  $(\beta_{ii}Y_i + \beta_{ij}Y_j)X_i$ .

The system (8.1) can be reduced to the following system of four equations by using  $X_i = N_i - Y_i$  and  $I_i = Y_i/N_i$ .

$$\begin{aligned} dN_1/dt &= [r_1(1 - N_1/K_1) - \alpha_{10}I_1]N_1, \\ dI_1/dt &= g_1^*(I_1, N_1, I_2, N_2) - [d_1 - \alpha_{10}I_1 - \chi_1r_1N_1/K_1]I_1, \\ dN_2/dt &= [r_2(1 - N_2/K_2) - \alpha_{20}I_2]N_2, \\ dI_2/dt &= g_2^*(I_1, N_1, I_2, N_2) - [d_2 - \alpha_{20}I_2 - \chi_2r_2N_2/K_2]I_2, \end{aligned} \tag{8.2}$$

where  $r_i = a_i - b_i$ ,  $d_i = \gamma_i + a_i + \alpha_{i0}$ ,  $g_i^* = (\beta_{ii}I_i + \beta_{ij}I_j)(1 - I_i)$  for frequency-dependent incidence, and  $g_i^* = (\beta_{ii}I_iN_i + \beta_{ij}I_jN_i)(1 - I_i)$  for mass-action incidence. The system (8.2) is studied in the region

$$D = \{(N_1, I_1, N_2, I_2) : 0 \leq N_i \leq K_i, 0 \leq I_i \leq 1\}. \tag{8.3}$$

8.1. *The Begon et al. model*

Consider the model (8.1) with mass-action incidence and density independent per capita death rate ( $\chi_i = 1$ ). With these conditions the model (8.1) becomes

$$\begin{aligned} dN_1/dt &= r_1(1 - N_1/K_1)N_1 - \alpha_{10}Y_1, \\ dX_1/dt &= (a_1 - \frac{r_1N_1}{K_1})N_1 - b_1X_1 - (\beta_{11}Y_1 + \beta_{12}Y_2)X_1 + \gamma_1Y_1, \\ dY_1/dt &= (\beta_{11}Y_1 + \beta_{12}Y_2)X_1 - (\gamma_1 + b_1 + \alpha_{10})Y_1, \\ dN_2/dt &= r_2(1 - N_2/K_2)N_2 - \alpha_{20}Y_2, \\ dX_2/dt &= (a_2 - \frac{r_2N_2}{K_2})N_2 - b_2X_2 - (\beta_{21}Y_1 + \beta_{22}Y_2)X_2 + \gamma_2Y_2, \\ dY_2/dt &= (\beta_{21}Y_1 + \beta_{22}Y_2)X_2 - (\gamma_2 + b_2 + \alpha_{20})Y_2. \end{aligned} \tag{8.4}$$

This model is equivalent to the model with density variables studied by Begon et al. (1992), which uses equations for  $N_1, N_2, Y_1,$  and  $Y_2$ . However, they did not include the equations for  $X_1$  and  $X_2$ , and they did not state explicitly that they were assuming density-independent death rates in the logistic growth. In terms of the populations sizes and infective fractions, this model (8.4) becomes

$$\begin{aligned} dN_1/dt &= [r_1(1 - N_1/K_1) - \alpha_{10}I_1]N_1, \\ dI_1/dt &= (\beta_{11}I_1N_1 + \beta_{12}I_2N_2)(1 - I_1) - [d_1 - \alpha_{10}I_1 - r_1N_1/K_1]I_1, \\ dN_2/dt &= [r_2(1 - N_2/K_2) - \alpha_{20}I_2]N_2, \\ dI_2/dt &= (\beta_{21}I_1N_1 + \beta_{22}I_2N_2)(1 - I_2) - [d_2 - \alpha_{20}I_2 - r_2N_2/K_2]I_2. \end{aligned} \tag{8.5}$$

In this model the equations for the infected fractions  $I_1$  and  $I_2$  are not independent of the population sizes  $N_1$  and  $N_2$ , so that there is no uncoupling of the four dimensional system.

Relevant coexistence equilibria for the model (8.4) correspond to intersection points of two third order polynomial curves, so there can be up to three relevant infected coexistence equilibria. After a numerical investigation, Begon et al. (1992) conjectured that if all of the boundary equilibria were unstable, then at most one infected coexistence equilibrium would be stable, and if at least one boundary equilibrium were stable, then no relevant infected coexistence equilibrium would be stable. The conditions under which contingent elimination, species  $i$  elimination, and infected coexistence occur are given in tables in the survey paper of Begon and Bowers (1995).

When Greenman and Hudson (1997) continued the analysis of this model, they found several counterexamples to some of the Begon et al. conjectures. In one case they found that when there are no relevant one host equilibria and the uninfected coexistence equilibrium is unstable, then for some parameter values (example B1 in their Table 1), there are three unstable infected coexistence equilibria. In another case with a stable infected one host equilibrium, they found a parameter set (example C1 in their Table 1) for which there are two stable infected coexistence equilibria. In a third case in which all uninfected one host equilibria are unstable and both one host infected equilibria are unstable, they found a parameter set (example D1 in their Table 1) for which the infected coexistence equilibrium is also unstable. They also found examples with no relevant stable equilibria, so that solutions approached limit cycles (stable periodic solutions).

As with the Holt Pickering model, it is possible to extend the results of Greenman and Hudson by doing a Hopf bifurcation analysis on the existence of periodic solutions and obtaining a Hopf bifurcation surface in parameter space. We do not include details of this analysis here, since our main purpose is to give a different formulation using frequency-dependent incidence in the next section.

### 8.2. A similar model with frequency-dependent incidence

Consider the model (8.2) with frequency-dependent incidence and density independent per capita birth rate ( $\chi_i = 0$ ), so that (8.2) reduces to

$$\begin{aligned} dN_1/dt &= [r_1(1 - N_1/K_1) - \alpha_1 I_1]N_1, \\ dI_1/dt &= (\beta_{11}I_1 + \beta_{12}I_2)(1 - I_1) - [d_1 - \alpha_1 I_1]I_1, \\ dN_2/dt &= [r_2(1 - N_2/K_2) - \alpha_2 I_2]N_2, \\ dI_2/dt &= (\beta_{21}I_1 + \beta_{22}I_2)(1 - I_2) - [d_2 - \alpha_2 I_2]I_2. \end{aligned} \tag{8.6}$$

For this model with frequency-dependent incidence, the system (8.6) uncouples, since the differential equations for the infective fractions  $I_i$  are independent of the  $N_i$  variables. Indeed, the  $I_1 I_2$  system is exactly the same as the system (6.2), so that the results on the asymptotic behavior of that  $I_1 I_2$  system hold for this model.

Recall that the modified reproduction number  $R_1$  is given by equation (6.3). If  $R_1 \leq 1$ , then  $\hat{E}_1 = (0, 0)$  is the only equilibrium in  $\hat{D}$  and all solution paths in  $\hat{D}$  must approach  $\hat{E}_1$ . If  $R_1 > 1$ , then there is a unique endemic equilibrium  $\hat{E}_2 = (I_1^e, I_2^e)$  satisfying the equations (6.5) in the unit square  $\hat{D}$ , and all solution

paths starting in  $\hat{D} - \{(0, 0)\}$  approach this  $\hat{E}_2$  equilibrium. An intuitive justification is that if a disease would remain endemic in one isolated population but die out in the other isolated population, it remains endemic in both populations because there are always some contacts between the populations. Of course, if the disease would die out in both isolated populations, then it would also die out in both even though there are contacts between the populations.

For the system (8.6), the limiting differential equations for  $N_i(t)$  when  $R_1 \leq 1$  are  $N_i' = r_i(1 - N_i/K_1)N_i$ , and by Corollary 4 on limiting systems in Hethcote et al. (2004),  $N_i(t)$  approaches the carrying capacity  $K_i$  if  $N_i(0) > 0$ . If  $R_1 > 1$ , then Corollary 4 in Hethcote et al. (2004) implies that the asymptotic behavior is given by the logistic-like, limiting differential equations  $N_i' = [r_i - \alpha_i I_i^e - r_i N_i/K_1]N_i$ . Thus if  $r_i \leq \alpha_i I_i^e$ , then  $N_i(t)$  approaches 0. Intuitively, the  $i$ th population becomes extinct, because the net per capita growth rate  $r_i$  at low population size is weaker than the infection-induced death rate  $\alpha_i$ . If  $r_i > \alpha_i I_i^e$ , then  $N_i(t)$  approaches  $(1 - \alpha_i I_i^e/r_i)K_i$ . An intuitive explanation of this situation is that the net per capita growth rate  $r_i$  at low population size is stronger than the infection-induced death rate  $\alpha_i$ , so that the population persists, but the endemicity of the disease drives the population size to a new equilibrium below the original carrying capacity  $K_i$ .

Now consider solutions of the 4 dimensional system (8.6) in the region  $D$  given by (8.3). If  $R_1 \leq 1$ , then the results in the previous paragraph imply that the disease dies out and solution paths starting in the interior of  $D$  approach the equilibrium  $E_1 = (K_1, 0, K_2, 0)$  with the population sizes at their original carrying capacities. The equilibria  $(0, 0, 0, 0)$ ,  $(K_1, 0, 0, 0)$ , and  $(0, 0, K_2, 0)$  are always unstable. If  $R_1 > 1$ , then the disease always remains endemic in both populations and there are 4 possible cases. If  $r_1 \leq \alpha_1 I_1^e$  and  $r_2 \leq \alpha_2 I_2^e$ , then solutions starting in the interior of the region  $D$  approach the boundary equilibrium  $E_2 = (0, I_1^e, 0, I_2^e)$ , at which both populations are extinct. If  $r_1 \leq \alpha_1 I_1^e$  and  $r_2 > \alpha_2 I_2^e$ , then solutions approach the boundary equilibrium  $E_3 = (0, I_1^e, (1 - \alpha_2 I_2^e/r_2)K_2, I_2^e)$ , in which case population 1 becomes extinct, but population 2 persists. In the analogous symmetric situation with  $r_1 > \alpha_1 I_1^e$  and  $r_2 \leq \alpha_2 I_2^e$ , solutions approach  $E_4 = ((1 - \alpha_1 I_1^e/r_1)K_1, I_1^e, 0, I_2^e)$ . In the fourth endemic case with  $r_1 > \alpha_1 I_1^e$  and  $r_2 > \alpha_2 I_2^e$ , solutions starting in the interior of the region  $D$  approach the interior equilibrium

$$E_5 = ((1 - \alpha_1 I_1^e/r_1)K_1, I_1^e, (1 - \alpha_2 I_2^e/r_2)K_2, I_2^e),$$

so that both populations persist and approach new equilibrium values below their original carrying capacities.

In contrast with the Begon et al. system (8.5), the system (8.6) never has contingent elimination of a species, in which the winner of the competition for pathogen-free space depends on the initial values of the variables. When the endemic, coexistence equilibrium  $E_5$  of system (8.6) is in the interior of  $D$ , this unique endemic equilibrium is globally attractive, so that periodic solutions never arise by Hopf bifurcation. So for this model (8.6) formulated with frequency-dependent incidence, the coexistence equilibrium  $E_5$  is globally asymptotically stable whenever it exists in  $D$ . Hence this new model has the simple, desired behavior sought by Greenman and Hudson (1997).

## 9. Discussion

The goal of this paper is to raise awareness that different forms of the disease incidence term in infectious disease models often lead to significantly different thresholds and asymptotic behaviors of the models. As described in Section 2, these differences have been noted previously for both single and multiple populations (Hethcote, 1976, 1996; Hethcote and Van Ark, 1987; Gao and Hethcote, 1992; Mena-Lorca and Hethcote, 1992; De Jong et al., 1995, Diekmann et al., 1995, Begon et al. 1999, 2002, 2003; Turner et al., 2003). Different forms of the incidence also led to different asymptotic behaviors in SEI endemic models related to a fox rabies model of Anderson et al. (1981). Specifically, Gao et al. (1995, 1996) found that SEI models with mass-action incidence could have periodic solutions, but analogous models with frequency-dependent incidence did not have periodic solutions.

For the model for an infectious disease pathogen in one host population without self-regulation, but with infection-reduced reproduction, infection-related deaths, and frequency-dependent incidence, there is a reproduction number that determines the asymptotic behavior. For the analogous model with mass-action incidence, the asymptotic behavior is determined by the values of the maximum growth rate and the infection-related death rate (see Table 1), so there is no reproduction number threshold. When Holt and Pickering (1985) formulated the analogous host-pathogen model for two host populations with a shared pathogen and mass-action incidence, they expected their two host model to behave like the one host model and like a competing species model. Their analyses confirmed many of their expectations and all of their numerical simulations were consistent with their very plausible conjecture that the endemic (coexistence) equilibrium is relevant and stable when no other equilibrium is relevant and stable.

In their numerical explorations of the Holt-Pickering model, Greenman and Hudson (1997) found unusual, but plausible parameter values for which the coexistence equilibrium is unstable and solution paths approach periodic solutions, so that the Holt-Pickering conjecture is not true for these parameter values. At the end of their paper, Greenman and Hudson (1997) state, “given the complexities that have been revealed in this paper, it would make sense to search for reformulations of the Holt-Pickering model that might give a simpler and biologically intuitive dynamic structure.” In this paper we present a reformulation that gives “a simpler and biologically intuitive dynamic structure.” This reformulation of the two host model with frequency-dependent incidence instead of mass-action incidence has the intuitive behavior that Holt and Pickering sought and expected. Namely, if the modified reproduction number is below the threshold, then the disease dies out, but if the modified reproduction number is above the threshold, then the disease remains endemic in both hosts and the infective fractions approach endemic equilibrium values. Moreover, the two host populations grow or decay at their usual per capita rates when the disease dies out, and at infection-reduced per capita rates when the disease remains endemic.

The survey paper of Begon and Bowers (1995) explains how the competition between the species is not for shared resources, but for pathogen-free space. This

indirect competition was called apparent competition by Holt (1977). Bonsall and Hassell (1997) conducted laboratory experiments with two moth species that could each persist alone in the presence of a parasitic wasp population. In the experiments the moths did not compete, since they were separated by a nylon mesh through which only the shared parasitic wasp population could pass. They found that the shared wasp population drove one moth species to extinction while the other moth species persisted. Thus the apparent competition due to the wasp parasitoid changed the outcome.

The asymptotic behaviors are different when the exponential population dynamics (i.e. without self-regulation) are replaced by logistic population dynamics (i.e. with self-regulation). For an SIS disease in one host population with logistic growth and frequency-dependent incidence, two threshold quantities determine whether 1) the disease dies out and the population size approaches its carrying capacity, 2) the disease remains endemic and the population size approaches a new equilibrium value below the carrying capacity, or 3) the disease remains endemic, but the infection-reduced deaths are stronger than the maximum population growth rate, so that the population is driven to extinction. This third possibility is plausible, but it does not occur in the one host model with mass-action incidence (see Table 2).

An SIS model with self-regulation (logistic growth) in two host populations and mass-action incidence was considered by Begon et al. (1992), who obtained some results on the number and stability of the equilibria. Based on their numerical simulations, they conjectured that if all boundary equilibria were unstable, then at most one infected coexistence equilibrium was stable, and if at least one boundary equilibrium was stable, then no relevant infected coexistence equilibrium was stable. In their analyses and numerical simulations of this model, Greenman and Hudson (1997) found unusual behaviors including counterexamples to some of the Begon et al. conjectures. One counterexample had a stable periodic solution, but had no relevant stable equilibria. Another counterexample had no relevant one host equilibria, an unstable uninfected coexistence equilibrium, and three unstable infected coexistence equilibria.

In a model with frequency-dependent incidence similar to that of Begon et al. (1992), we have obtained the classic endemic model result. Namely, below the threshold, the disease dies out in both populations and the population sizes approach their carrying capacities, but above the threshold, the disease remains endemic in both populations and drives the two population sizes to either zero or new equilibrium sizes below their carrying capacities. Thus this two host SIS model with logistic growth and frequency-dependent incidence has the property that whenever there is a relevant coexistence equilibrium, it is globally attractive.

We have shown that two host SIS models with frequency-dependent incidence have three advantages. First, frequency-dependent incidence is often consistent with available data. Second, the parameter values  $\beta_{ij}$  have precise epidemiological interpretations as contact rates. Third, the behaviors of these models are consistent with the epidemiological concept that below the threshold, the disease dies out, and about the threshold, the disease remains endemic.

*Acknowledgements.* The research of Wendi Wang is supported by the National Natural Science Fund of China (No. 10271096).

The research of Yi Li is supported in part by the Xiao-Xiang Grant at the Hunan Normal University, and by the National Natural Science Fund of China (No. 10471052).

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### Appendix A. Global stability in Section 3

For the SIS model with exponential growth and mass-action incidence in Section 3, if  $\psi = r/(af + \alpha_0) < 1$ , then all solutions in the region  $D$  of the system (3.2) with mass-action incidence and  $I(0) > 0$  and  $N(0) > 0$  approach the endemic equilibrium  $(N_e, I_e)$ . Consider the Liapunov function given by

$$V(I, N) = (af + \alpha_0) \int_{I_e}^I \frac{I' - I_e}{I'(1 - I')} dI' + \int_{N_e}^N \frac{F(N')}{N'} dN',$$

where  $F(N') = \beta N' - af - \alpha_0 - [\gamma + a(1 - f)]/(1 - I_e)$  is a non-decreasing function of  $N'$  that is 0 at  $N' = N_e$ . Thus  $V(N_e, I_e) = 0$  and  $V(N, I) \geq 0$  in  $D$ . The Liapunov derivative is

$$\begin{aligned}
 V' &= (af + \alpha_0)(I - I_e) \left[ \beta N - af - \alpha_0 - \frac{\gamma + a(1 - f)}{1 - I} \right] \\
 &\quad + F(N)[r - (af + \alpha_0)I] \\
 &= (af + \alpha_0)(I - I_e) \left[ F(N) - \frac{[\gamma + a(1 - f)](I - I_e)}{(1 - I_e)(1 - I)} \right] \\
 &\quad - (af + \alpha_0)F(N)(I - I_e) \\
 &= -\frac{(af + \alpha_0)[\gamma + a(1 - f)](I - I_e)^2}{(1 - I_e)(1 - I)} \leq 0,
 \end{aligned}$$

The set where  $V' = 0$  is  $I = I_e$ , which has the equilibrium  $(N_e, I_e)$  as the largest invariant subset, since  $I' \neq 0$  when  $N \neq N_e$ . By the Liapunov-Lasalle theorem (Hale, 1969, pp.296-7), all solutions in  $D$  approach  $(N_e, I_e)$ .

**Appendix B. The characteristic equation in Section 5**

The characteristic equation for the eigenvalues of the Jacobian at the equilibrium  $E_3$  of system (5.5) is a fourth degree polynomial  $P_4(\lambda) = \lambda^4 + c_1\lambda^3 + c_2\lambda^2 + c_3\lambda + c_4 = 0$ , where the coefficients are

$$\begin{aligned}
 c_1 &= \frac{(\beta_1 - 1)d_1^* + (\beta_2 - 1)d_2^*}{\beta_1\beta_2 - 1} + g_1 + g_2, \\
 c_2 &= \frac{(\beta_2 - 1)(\beta_1 d_1^* r_1 + g_1 d_2^*) + (\beta_1 - 1)(\beta_2 d_2^* r_2 + g_2 d_1^*)}{\beta_1\beta_2 - 1} + g_1 g_2, \\
 c_3 &= \frac{(\beta_2 - 1)r_1 d_1^* (d_2^* + g_2 \beta_1) + (\beta_1 - 1)r_2 d_2^* (d_1^* + g_1 \beta_2)}{\beta_1\beta_2 - 1}, \\
 c_4 &= \frac{r_1 r_2 d_1^* d_2^* (\beta_2 - 1)(\beta_1 - 1)}{\beta_1\beta_2 - 1}.
 \end{aligned} \tag{B.1}$$

In case 3 with  $\beta_1 < 1$  and  $\beta_2 < 1$ , we have  $c_1, c_2, c_3 > 0$  but  $c_4 < 0$ . By Descartes' rule of signs, the characteristic equation at  $E_3$  always has one positive real root  $\lambda^+$ . Since  $dP_4/d\lambda = 4\lambda^3 + 3c_1\lambda^2 + 2c_2\lambda + c_3 > 0$  for all  $\lambda > 0$ , there is only one positive real eigenvalue. If  $P_4(\lambda)$  has another eigenvalue  $\lambda$  with positive real part, then there must be a complex conjugate pair with nonzero imaginary parts. Substituting  $\lambda = y + zi$ , with  $y, z > 0$  into  $P_4(\lambda) = 0$  and separating the real part from the imaginary part leads to

$$\begin{aligned}
 y^4 + c_1 y^3 + (-6z^2 + c_2)y^2 + (c_3 - 3c_1 z^2)y + c_4 + z^4 - c_2 z^2 &= 0, \\
 (-c_1 - 4y)z^2 + 4y^3 + c_3 + 3c_1 y^2 + 2c_2 y &= 0.
 \end{aligned} \tag{B.2}$$

Solving  $z^2$  from the second equation of (B.2), we obtain that

$$z^2 = (4y^3 + c_3 + 3c_1 y^2 + 2c_2 y)/(c_1 + 4y).$$

Substituting this into the first equation of (B.2), we have after some simplification that

$$\begin{aligned}
 0 = & 64y^6 + 96c_1y^5 + (48c_1^2 + 32c_2)y^4 \\
 & + 8c_1(4c_2 + c_1^2)y^3 + (4c_3c_1 + 8c_2c_1^2 + 4c_2^2 - 16c_4)y^2 \\
 & + 2c_1(c_3c_1 + c_2^2 - 4c_4)y + c_1c_2c_3 - c_3^2 - c_1^2c_4. \tag{B.3}
 \end{aligned}$$

Since  $c_4 < 0$ , all the coefficients of  $y$  in (B.3) are positive if  $c_1c_2c_3 - c_3^2 - c_1^2c_4 > 0$ , so that there is no nonnegative solution  $y$  and hence no complex roots of  $P_4(\lambda) = 0$  with nonnegative real parts. By rewriting the coefficients in terms of  $r_1$  and  $r_2$ , it is possible to show that there is always a non-empty region in the parameter space where the condition  $c_1c_2c_3 - c_3^2 - c_1^2c_4 > 0$  is satisfied. If  $c_1c_2c_3 - c_3^2 - c_1^2c_4 < 0$ , then Descartes' rule of signs implies that (B.3) has a positive solution  $y$ , so that  $P_4(\lambda) = 0$  has a complex conjugate pair of roots with positive real part.

### Appendix C. Hopf bifurcation in Section 5

We prove the results on the Hopf bifurcation at the coexistence equilibrium  $E_3$  in case 4 in Section 5. Let  $\mu_0$  be the bifurcation point and  $H_n(\mu)$  be the  $n$  dimensional Hurwitz determinant. If  $H_3(\mu_0) = 0$ ,  $H_2(\mu_0) \neq 0$ ,  $H_1(\mu_0) \neq 0$ ,  $c_j(\mu_0) > 0$ , for  $j = 1, \dots, 4$ , and  $H_3'(\mu_0) \neq 0$ , then the real part of a complex conjugate pair of eigenvalues changes sign at  $\mu = \mu_0$  (Shen and Jing, 1993). It is clear from (B.1) that  $c_i > 0$  for all  $i$ . The Hurwitz determinants are  $H_1 = c_1$ ,  $H_2 = c_1c_2 - c_3$ ,  $H_3 = c_1c_2c_3 - c_3^2 - c_1^2c_4$ , and  $H_4 = c_4H_3$ . Thus we look for Hopf bifurcation by seeking a surface in parameter space where  $H_3 = 0$ , so that the complex conjugate pair of eigenvalues are pure imaginary. This Hopf surface lies in the ten dimensional space of the parameters in the original system (5.1), or in the eight dimensional space of the parameters in the rescaled system (5.5). Rewriting the coefficients in terms of  $r_1$  and  $r_2$  leads to  $H_1 = c_1 > 0$ ,

$$\begin{aligned}
 H_2 &= (c_1c_{21} - c_{31})r_1 + (c_1c_{22} - c_{32})r_2 + c_1c_{23}, \\
 H_3 &= c_{31}(c_1c_{21} - c_{31})r_1^2 + (c_1c_{22}c_{31} + c_1c_{21}c_{32} - 2c_{32}c_{31} - c_{41}c_1^2)r_2r_1 \\
 &\quad + c_{32}(c_1c_{22} - c_{32})r_2^2 + c_1c_{23}c_{31}r_1 + c_1c_{23}c_{32}r_2, \tag{C.1}
 \end{aligned}$$

and

$$\begin{aligned}
 \frac{\partial H_3}{\partial r_1} &= 2c_{31}(c_1c_{21} - c_{31})r_1 + Cr_2 + c_1c_{23}c_{31}, \\
 \frac{\partial H_3}{\partial r_2} &= Cr_1 + 2c_{32}(c_1c_{22} - c_{32})r_2 + c_1c_{23}c_{32},
 \end{aligned}$$

where  $C = c_1c_{22}c_{31} + c_1c_{21}c_{32} - 2c_{32}c_{31} - c_{41}c_1^2$ .

In order to show that  $\nabla_{(r_1,r_2)} H_3 \neq 0$  whenever  $H_3 = 0$ , suppose the contrary, i.e. that  $\nabla_{(r_1,r_2)} H_3 = 0$  and  $H_3 = 0$ . From  $\nabla_{(r_1,r_2)} H_3 = 0$ , Gaussian elimination leads to

$$\begin{aligned}
 Dr_1 &= (c_{41}c_1 - c_{21}c_{32} + c_{31}c_{22})c_{32}c_{23}, \\
 Dr_2 &= (c_{41}c_1 + c_{21}c_{32} - c_{31}c_{22})c_{23}c_{31}, \tag{C.2}
 \end{aligned}$$

where

$$D = c_{22}^2 c_{31}^2 + c_{21}^2 c_{32}^2 + c_{41}^2 c_1^2 + 4c_{32}c_{31}c_{41} - 2c_{41}c_1c_{22}c_{31} - 2c_{41}c_1c_{21}c_{32} - 2c_{22}c_{31}c_{21}c_{32}$$

Note that if the right hand sides of (C.2) were both zero, then adding up the terms inside the parentheses leads to  $2c_{41}c_1 = 0$ , which contradicts the positivity of the constants. Otherwise, solve (C.2) for  $r_1$  and  $r_2$  and substitute them into  $H_3 = 0$  to obtain  $c_{31}c_{32}c_{23}^2c_{41}c_1^2/D = 0$ , which again contradicts the positivity of the constants. Thus the transversality condition holds with respect to  $(r_1, r_2)$  on the set where  $H_3 = 0$ .

Suppose that  $H_2 = 0$  and  $H_3 = 0$ . Thus either  $c_1c_{21} - c_{31} < 0$  or  $c_1c_{22} - c_{32} < 0$ . Without loss of generality we assume that  $c_1c_{21} - c_{31} < 0$ . Solving  $H_2 = 0$  for  $r_1$ , we obtain

$$r_1 = -\frac{c_1c_{22} - c_{32}}{c_1c_{21} - c_{31}}r_2 - \frac{c_1c_{23}}{c_1c_{21} - c_{31}}, \quad (\text{C.3})$$

Substituting this back into  $H_3 = 0$ , we obtain

$$\frac{c_{41}r_2c_1^2(r_2c_1c_{22} - c_{32}r_2 + c_1c_{23})}{c_1c_{21} - c_{31}} = 0,$$

so that the only valid solution is  $r_2 = -c_1c_{23}/(c_1c_{22} - c_{32})$ . When we substitute this expression for  $r_2$  into (C.3), we obtain  $r_1 = 0$ , which is a contradiction. Thus  $H_2 \neq 0$  whenever  $H_3 = 0$ . Also  $H_1 = c_1 > 0$  on the Hopf surface. Zero is not a root and the pure imaginary roots  $\pm i\omega$  are not repeated roots, since  $P_4'(i\omega) = 0$  leads to a contradiction when the expressions for the coefficients are substituted. Thus all conditions for Hopf bifurcation have been established (Guckenheimer and Holmes, 1983).