

# THE ROLE OF COINFECTION IN MULTI-DISEASE DYNAMICS

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**Abstract.** We investigate an epidemic model of two diseases. The primary disease is assumed to be a slowly progressing disease and the density of individuals infected with it is structured by age since infection. Hosts that are already infected with the primary disease can become coinfecting with a secondary disease. We show that in addition to the disease-free equilibrium, there exists a unique dominance equilibrium corresponding to each disease. Without coinfection there are no coexistence equilibria, however, with coinfection the number of coexistence equilibria may vary. For some parameter values, there exist two coexistence equilibria. We also observe competitor mediated oscillatory coexistence. Furthermore, weakly subthreshold (which occur when exactly one of the reproduction numbers is below one) and strongly subthreshold (which occur when both reproduction numbers are below one) coexistence equilibria may exist. Some of those are a result of a two-parameter backward bifurcation. Bistability occurs in several regions of the parameter space. Despite the presence of coinfection, coexistence of the two diseases appears possible only for relatively small values of the reproduction numbers – for large values of the reproduction numbers the typical outcome of competition is the dominance of one of the diseases, including bistable dominance where the competition outcome is initial condition dependent.

**Key words.** coinfection, age-infection structure, subthreshold coexistence, backward bifurcation, Hopf bifurcation, oscillatory dominance, oscillatory coexistence, restricted pathogenic diversity

**AMS subject classifications.** 35B32, 35B35, 35B38, 35F25, 92D30

**1. Introduction.** Coinfection is a simultaneous infection of one host with multiple pathogens that may be the causative agents of different diseases or variants of the same parasite. Coinfections are common for individuals infected with the human immunodeficiency virus (HIV). Since HIV compromises the immune system, the carrier becomes vulnerable to other infections commonly called opportunistic infections [10]. For instance, the case of HIV-HSV (herpes simplex virus) coinfection has been well-documented. Such coinfection typically leads to reactivation of HSV that accelerates the progression of HIV disease towards AIDS. The HIV-HSV infected individuals are also more likely to unwittingly transmit HSV via an increased shedding common in HIV-infected patients. The treatment of HIV-HSV coinfecting patients may present additional challenges since the HSV is likely to be more resistant to antiviral therapy [22]. Coinfections may also occur when a patient is already infected with a slowly progressing disease which lasts for decades. In tuberculosis (TB), for example, coinfection even with a minor illness can trigger a reactivation of TB.

Many mathematical studies exist on a single disease, both general theoretic and treating a specific disease. At the same time, few studies exist that address the interaction of two or more diseases. On an epidemiological level, Courchamp *et al.* [7] studied a model of two feline retroviruses. Two recent articles - one by Allen *et al.* [1] and another by Gumel *et al.* [9] also consider two infections in a single host. On an immunological level, the interactions between *Mycobacterium tuberculosis* and HIV-1 are investigated in [11]. Statistical aspects of mapping two diseases are the focus of [8]. Coinfection has been studied from a general perspective in [14]. In [16],

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a connection between super-infection and coinfection with different strains and the impact of both on the coexistence and the evolution of virulence is discussed.

In this paper, we study an epidemic model with two diseases that can coinfect a single host. We include infection-age structure in the primary disease to account for slowly progressing and/or persistent disease that affect the immune status of individuals over time. Infection-age structure has been previously shown to cause qualitative changes, namely oscillatory behavior, in case of a single disease dynamics [19, 15, 12]. Although the model discussed here is relatively simple, we find complex dynamic behavior: Oscillatory dominance and coexistence, two-parameter backward bifurcation, multiple and subthreshold coexistence equilibria, and bistability. These phenomena have important epidemiological consequences for disease management. Most of them have been illustrated in the single-disease case. In particular, backward bifurcation which leads to multiple and subthreshold equilibria has been attracting significant attention in the literature (see [13] and the references there in). However, to the best of our knowledge, the backward bifurcations have not been studied in the context of multiple infectious agents.

This paper is organized as follows. In the next Section, we introduce the two-disease coinfection model. In Section 3, we introduce the reproduction numbers of the primary and secondary diseases  $\mathcal{R}_1$ ,  $\mathcal{R}_2$  and discuss the equilibria of the model. The values of the disease-free equilibrium and the two boundary equilibria are given explicitly. We also present sufficient conditions for the existence of a coexistence equilibrium. In Section 4, we consider scenarios for extinction of either disease or both. Section 5 focuses on the local stability of equilibria. We show that both the primary disease equilibrium and coexistence equilibria can lose stability leading to sustained oscillations. Section 6 is devoted to the derivation of necessary and sufficient conditions for the backward bifurcation in  $\mathcal{R}_1$  and  $\mathcal{R}_2$ . In Section 7, we present several numerical simulations to illustrate the various complex dynamic phenomena. In Section 8, we discuss the epidemiological implications of our model. Section 9 contains a summary of our results and it concludes the paper.

**2. A model of coinfection of two diseases.** Two diseases are spreading in a population of total size  $N(t)$ . They both compete for the same pool of susceptible individuals whose number at time  $t$  is denoted by  $S(t)$ . We assume that the first disease is a slowly progressing one and we structure the class of infected individuals with respect to the time since infection,  $a$ . The age-density is denoted by  $i(a, t)$ . The total number of individuals infected with the first disease is denoted by  $I_1(t)$ . Population members who eventually contract both diseases are assumed to be infected by the slowly progressing disease first. Consequently we call it the *primary disease*. A susceptible becomes infected with the primary disease at a rate  $\beta_1(a)$ . The number of individuals infected with the second disease is denoted by  $I_2(t)$ . The secondary disease is transmitted by the class  $I_2$  to susceptibles at a rate  $\beta_2$ . An individual already infected with the primary disease can be coinfecting with the secondary disease at a rate  $\delta(a)$  and thus become jointly infected with both diseases. We denote the number of jointly infected (coinfecting) individuals by  $J(t)$ . The individuals infected with both diseases can infect susceptibles with the primary disease at a rate  $\gamma_1$  and with the secondary diseases at a rate  $\gamma_2$ . Fig. 1.1 presents a schematic flow diagram

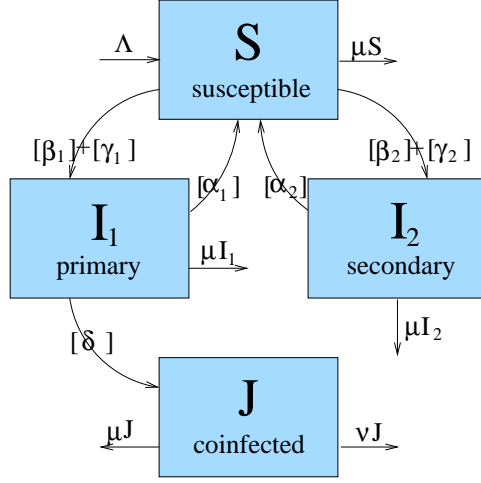


FIG. 1.1. The flow diagram of the model (2.1). The primary infection rate is shown as  $[\beta_1] + [\gamma_1]$  where  $[\beta_1] = \frac{S}{N} \int_0^\infty \beta_1(a)i(a) da$  and  $[\gamma_1] = \gamma_1 \frac{SJ}{N}$ . The secondary infection rate is shown as  $[\beta_2] + [\gamma_2]$  where  $[\beta_2] = \beta_2 \frac{SI_2}{N}$  and  $[\gamma_2] = \gamma_2 \frac{SJ}{N}$ . The coinfection rate is shown as  $[\delta] = \frac{I_2}{N} \int_0^\infty \delta(a)i(a) da$ . The primary and secondary recovery rates are shown as  $[\alpha_1] = \int_0^\infty \alpha_1(a)i(a) da$  and  $[\alpha_2] = \alpha_2 I_2$ . The parameters  $\Lambda$ ,  $\mu$ , and  $\nu$  represent the birth rate, the background mortality rate, and the disease induced mortality associated with coinfection respectively.

of the the mathematical model that takes the form:

$$\begin{aligned}
 S' &= \Lambda - \frac{S}{N} \int_0^\infty \beta_1(a)i(a, t) da - \beta_2 \frac{SI_2}{N} - (\gamma_1 + \gamma_2) \frac{SJ}{N} - \mu S \\
 &\quad + \int_0^\infty \alpha_1(a)i(a, t) da + \alpha_2 I_2, \\
 (\partial_t + \partial_a)i(a, t) &= -\alpha_1(a)i(a, t) - \delta(a) \frac{I_2}{N} i(a, t) - \mu i(a, t), \\
 i(0, t) &= \frac{S}{N} \int_0^\infty \beta_1(a)i(a, t) da + \gamma_1 \frac{SJ}{N}, \\
 I_2' &= \beta_2 \frac{SI_2}{N} + \gamma_2 \frac{SJ}{N} - (\mu + \alpha_2)I_2, \\
 J' &= \frac{I_2}{N} \int_0^\infty \delta(a)i(a, t) da - (\mu + \nu)J,
 \end{aligned} \tag{2.1}$$

where  $\mu$  is natural death rate. We assume that either disease by itself is not lethal but the two in combination can be. The biological motivation of this assumption is the case of HIV/AIDS where coinfections in late stages of the HIV (considered the primary disease) can be terminal. Specifically, we assume that jointly infected individuals do not recover and that coinfections cause the disease-induced mortality at a rate  $\nu$ . Individuals infected with either primary or secondary disease alone may be potentially treated and recover at rates  $\alpha_1(a)$ ,  $\alpha_2$  respectively. The functions  $\alpha_1(a)$ ,  $\beta_1(a)$  and  $\delta(a)$  are nonnegative and bounded. The parameters  $\beta_2$ ,  $\gamma_1$ ,  $\gamma_2$ ,  $\nu$ ,  $\alpha_2$  are nonnegative whereas  $\Lambda > 0$  and  $\mu > 0$ . A standard argument can be used to show that the model (2.1) is well-posed.

The total population size  $N(t)$  is the sum of all individuals in all classes

$$N(t) = S(t) + \int_0^\infty i(a, t) da + I_2(t) + J(t). \quad (2.2)$$

The total population size satisfies the equation  $N'(t) = \Lambda - \mu N - \nu J$ . We introduce the notation

$$\pi_1(a) = e^{-\int_0^a \alpha_1(s) ds}$$

To understand the biological meaning of the quantity  $\pi_1(a)$  we note that  $\pi_1(a)e^{-\mu a}$  is the probability to remain infected with the primary disease  $a$  time units after infection. In addition, we define the quantity

$$\Delta = \int_0^\infty \alpha_1(a) \pi_1(a) e^{-\mu a} da \quad (2.3)$$

which gives the probability of leaving the primary disease infectious period via recovery. Since individuals can only leave the primary infected class via recovery or death, the sum of the probabilities of recovery and death equals one, that is,

$$\int_0^\infty \alpha_1(a) \pi_1(a) e^{-\mu a} da + \mu \int_0^\infty \pi_1(a) e^{-\mu a} da = \int_0^\infty (\mu + \alpha_1(a)) e^{-\int_0^a (\mu + \alpha_1(s)) ds} da = 1.$$

It immediately follows that  $\Delta < 1$ .

**3. Equilibria of the model with coinfection.** We introduce the reproduction numbers of the two diseases. The reproduction number of the primary disease is

$$\mathcal{R}_1 = \int_0^\infty \beta_1(a) \pi_1(a) e^{-\mu a} da, \quad (3.1)$$

and the reproduction number of the secondary disease is

$$\mathcal{R}_2 = \frac{\beta_2}{\mu + \alpha_2}. \quad (3.2)$$

We note that the coinfection rate  $\delta(a)$  does not affect the reproduction numbers since coinfection does not lead to additional infections. We will adopt the notation  $s = S/N^*$ ,  $i_2 = I_2/N^*$ ,  $j = J/N^*$  and will use  $i(a)$  to denote the normalized version of  $i(a)$ . The quantity  $N^*$  is given by the sum (2.2) at an equilibrium. Let us define

$$\Gamma(a; i_2) = e^{-i_2 \int_0^a \delta(\sigma) d\sigma}. \quad (3.3)$$

Notice that  $\Gamma(a; 0) = 1$ . Setting the derivatives with respect to time to zero we obtain a system of algebraic equations and one ODE for the equilibria of (2.1). The ODE in the system can be solved to result

$$i(a) = i(0) \Gamma(a; i_2) \pi_1(a) e^{-\mu a}. \quad (3.4)$$

Substituting for  $i$  in the integrals, one obtains

$$\int_0^\infty \beta_1(a) i(a) da = i(0) \int_0^\infty \beta_1(a) \Gamma(a; i_2) \pi_1(a) e^{-\mu a} da = i(0) B(i_2),$$

and

$$\int_0^\infty \alpha_1(a)i(a) da = i(0) \int_0^\infty \alpha_1(a)\Gamma(a; i_2)\pi_1(a)e^{-\mu a} da = i(0)A(i_2).$$

Finally,

$$\int_0^\infty \delta(a)i(a) da = i(0) \int_0^\infty \delta(a)\Gamma(a; i_2)\pi_1(a)e^{-\mu a} da = i(0)D(i_2).$$

We notice that  $A(i_2) < 1$  and  $i_2D(i_2) + A(i_2) < 1$  because

$$\begin{aligned} i_2D(i_2) + A(i_2) &= \int_0^\infty (\alpha(a) + i_2\delta(a))e^{-\int_0^a (\alpha(\sigma) + i_2\delta(\sigma)) d\sigma} e^{-\mu a} da \\ &< \int_0^\infty (\alpha(a) + i_2\delta(a))e^{-\int_0^a (\alpha(\sigma) + i_2\delta(\sigma)) d\sigma} da = 1. \end{aligned}$$

With this notation the system for the equilibria becomes:

$$\begin{aligned} 0 &= \mu - si(0)B(i_2) - \beta_2si_2 - (\gamma_1 + \gamma_2)sj - \mu s + i(0)A(i_2) + \alpha_2i_2 + \nu j, \\ i(0) &= i(0)sB(i_2) + \gamma_1sj, \\ 0 &= \beta_2si_2 + \gamma_2sj - (\mu + \alpha_2)i_2, \\ 0 &= i(0)i_2D(i_2) - (\mu + \nu)j. \end{aligned} \tag{3.5}$$

This system has three boundary equilibria:

1. The disease-free equilibrium

$$\mathcal{E}_0 = (1, 0, 0, 0)$$

The disease-free equilibrium always exists.

2. The primary disease equilibrium exists if and only if  $\mathcal{R}_1 > 1$ . The steady distribution of infectives in the primary disease equilibrium is given by

$$i^*(a) = i(0)\pi_1(a)e^{-\mu a} \quad \text{where} \quad i(0) = \frac{\mu \left(1 - \frac{1}{\mathcal{R}_1}\right)}{1 - \Delta}$$

Thus, the equilibrium is

$$\mathcal{E}_1 = \left( \frac{1}{\mathcal{R}_1}, i^*(a), 0, 0 \right)$$

3. The secondary disease equilibrium exists if and only if  $\mathcal{R}_2 > 1$  and is given by

$$\mathcal{E}_2 = \left( \frac{1}{\mathcal{R}_2}, 0, \left(1 - \frac{1}{\mathcal{R}_2}\right), 0 \right)$$

Notice that the values of the two dominance equilibria do not depend on the coinfection. These exact same equilibria are present even if  $\delta(a) = 0$ .

We introduce the invasion reproduction numbers for each of the diseases. The invasion reproduction number of the first disease measures the ability of the primary disease to invade an equilibrium of the secondary disease. We define the invasion reproduction number of the primary disease as

$$\hat{\mathcal{R}}_1 = \frac{1}{\mathcal{R}_2}B(\hat{i}_2) + \frac{\gamma_1}{\mu + \nu} \frac{1}{\mathcal{R}_2} \left(1 - \frac{1}{\mathcal{R}_2}\right) D(\hat{i}_2), \quad \text{where } \hat{i}_2 = \left(1 - \frac{1}{\mathcal{R}_2}\right). \tag{3.6}$$

The invasion reproduction number of the secondary disease measures its ability to invade an equilibrium of the primary disease and it is defined as

$$\hat{\mathcal{R}}_2 = \frac{(\mathcal{R}_1 - 1)\mu\gamma_2 D(0)}{\mathcal{R}_1(\mu + \alpha_2)(\mu + \nu)(\mathcal{R}_1 - \mathcal{R}_2)(1 - \Delta)}, \text{ if } \mathcal{R}_1 > \mathcal{R}_2. \quad (3.7)$$

It is important to point out that due to the asymmetry of the model,  $\hat{\mathcal{R}}_1$  is defined if  $\mathcal{R}_2 > 1$ , and  $\hat{\mathcal{R}}_2$  is defined if  $\mathcal{R}_1 > \max(1, \mathcal{R}_2)$ . In addition, it is possible that  $\hat{\mathcal{R}}_1 > 1$  even if  $\mathcal{R}_1 < 1$ , that is, the dominance equilibrium  $\mathcal{E}_1$  of the primary disease does not exist and yet the primary disease can invade the dominance equilibrium of the secondary disease. It is also possible that  $\hat{\mathcal{R}}_2 > 1$  even if  $\mathcal{R}_2 < 1$ , that is, the dominance equilibrium  $\mathcal{E}_2$  of the secondary disease does not exist, but the secondary disease can invade the dominance equilibrium of the primary disease.

**LEMMA 3.1.** *The curves  $\mathcal{C}_1 = \{(\mathcal{R}_1, \mathcal{R}_2) | \hat{\mathcal{R}}_1 = 1\}$  and  $\mathcal{C}_2 = \{(\mathcal{R}_1, \mathcal{R}_2) | \hat{\mathcal{R}}_2 = 1\}$  enclose a nontrivial region in the positive  $(\mathcal{R}_1, \mathcal{R}_2)$  quadrant. The interior of this region always contains an unbounded component given by inequalities  $\hat{\mathcal{R}}_1, \hat{\mathcal{R}}_2 < 1$ .*

**Proof:** Using the fact that  $B(0) = \mathcal{R}_1$ , the curve  $\mathcal{C}_1 = \{(\mathcal{R}_1, \mathcal{R}_2) | \hat{\mathcal{R}}_1 = 1\}$  is given by the graph

$$\mathcal{R}_1 = \frac{B(0)}{B(\hat{i}_2)} \left( \mathcal{R}_2 - \frac{\gamma_1 \hat{i}_2 D(\hat{i}_2)}{\mu + \nu} \right) =: \mathcal{F}_1(\mathcal{R}_2),$$

where  $\mathcal{R}_2 \geq 1$  and  $\hat{i}_2 = 1 - 1/\mathcal{R}_2 \geq 0$ . The definition of  $\mathcal{F}_1$  implies that  $\mathcal{F}_1(1) = 1$ , and for large values of  $\mathcal{R}_2$ , the function

$$\mathcal{F}_1(\mathcal{R}_2) \approx \frac{B(0)}{B(1)} \mathcal{R}_2 + \frac{B(0)B'(1)}{B^2(1)} - \frac{\gamma_1 B(0)D(1)}{(\mu + \nu)B(1)}, \text{ for } \mathcal{R}_2 \gg 1,$$

is approximately linear in  $\mathcal{R}_2$  with a slope  $B(0)/B(1) > 1$ . On the other hand, the curve  $\mathcal{C}_2 = \{(\mathcal{R}_1, \mathcal{R}_2) | \hat{\mathcal{R}}_2 = 1\}$  is given by the graph

$$\mathcal{R}_2 = \mathcal{R}_1 - \left(1 - \frac{1}{\mathcal{R}_1}\right) \frac{\mu\gamma_2 D(0)}{(\mu + \alpha_2)(\mu + \nu)(1 - \Delta)} =: \mathcal{F}_2(\mathcal{R}_1),$$

where  $\mathcal{R}_1 \geq 1$ . It is easy to see that  $\mathcal{F}_2(1) = 1$ , and for large values of  $\mathcal{R}_1$ , the function

$$\mathcal{F}_2(\mathcal{R}_1) \approx \mathcal{R}_1 - \frac{\mu\gamma_2 D(0)}{(\mu + \alpha_2)(\mu + \nu)(1 - \Delta)}, \text{ for } \mathcal{R}_1 \gg 1,$$

is approximately linear in  $\mathcal{R}_1$  with a unit slope. Consequently, when both  $\mathcal{R}_1$  and  $\mathcal{R}_2$  are large, the curve  $\mathcal{C}_1$  lies below and to the right of the curve  $\mathcal{C}_2$ . The unbounded region enclosed by these curves is therefore given by the inequalities  $\mathcal{R}_2 < \mathcal{F}_2(\mathcal{R}_1)$  and  $\mathcal{R}_1 > \mathcal{F}_1(\mathcal{R}_2)$  that are equivalent to the inequalities  $\hat{\mathcal{R}}_1, \hat{\mathcal{R}}_2 < 1$ .  $\diamond$

In Figure 3.1, we present a simple diagram depicting the curves  $\mathcal{C}_1$  and  $\mathcal{C}_2$  and identify various parts of the region enclosed by these curves. The following theorem establishes the existence of at least one coexistence equilibrium for any point in the  $(\mathcal{R}_1, \mathcal{R}_2)$  plane that lies between the curves  $\mathcal{C}_1$  and  $\mathcal{C}_2$ . In what follows, we will refer to the region between the curves  $\mathcal{C}_1$  and  $\mathcal{C}_2$  as the *coexistence region*.

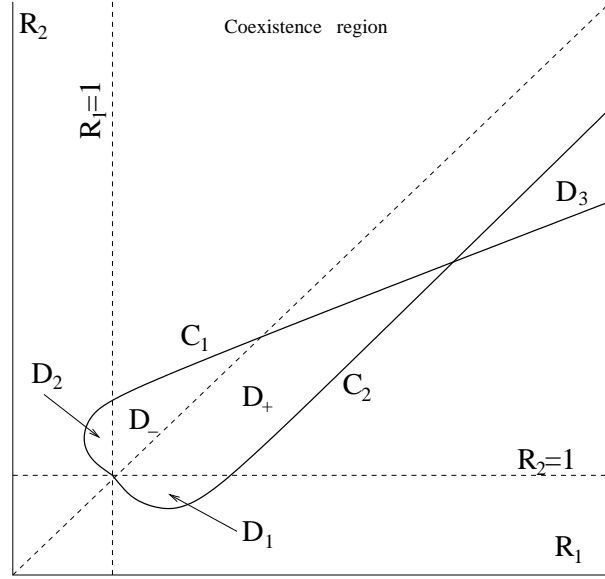


FIG. 3.1. A schematic diagram representing the coexistence region in the  $(\mathcal{R}_1, \mathcal{R}_2)$  plane. The boundary of the coexistence region is formed by the curves  $\mathcal{C}_1 : \hat{\mathcal{R}}_1 = 1$  and  $\mathcal{C}_2 : \hat{\mathcal{R}}_2 = 1$ . The coexistence region (as shown) consists of five components, namely:  $\mathcal{D}_-$  where  $1 < \mathcal{R}_1 < \mathcal{R}_2$  and  $\hat{\mathcal{R}}_1 > 1$ ;  $\mathcal{D}_+$  where  $1 < \mathcal{R}_2 < \mathcal{R}_1$  and  $\hat{\mathcal{R}}_1, \hat{\mathcal{R}}_2 > 1$ ;  $\mathcal{D}_1$  where  $\mathcal{R}_2 < 1 < \mathcal{R}_1$  and  $\hat{\mathcal{R}}_2 > 1$ ;  $\mathcal{D}_2$  where  $\mathcal{R}_1 < 1 < \mathcal{R}_2$  and  $\hat{\mathcal{R}}_1 > 1$ ; and finally,  $\mathcal{D}_3$  where  $1 < \mathcal{R}_2 < \mathcal{R}_1$  and  $\hat{\mathcal{R}}_1, \hat{\mathcal{R}}_2 < 1$ .  $\mathcal{D}_3$  is the only component of the coexistence region that is always nonempty, the other components may or may not exist depending on the parameter values.

THEOREM 3.2. *Let*

$$\begin{aligned} \mathcal{D}_- &= \{\mathcal{R}_1, \mathcal{R}_2 > 0 | 1 < \mathcal{R}_1 \leq \mathcal{R}_2, \hat{\mathcal{R}}_1 > 1\}, \\ \mathcal{D}_+ &= \{\mathcal{R}_1, \mathcal{R}_2 > 0 | 1 < \mathcal{R}_2 < \mathcal{R}_1, \hat{\mathcal{R}}_1 > 1, \hat{\mathcal{R}}_2 > 1\}, \\ \mathcal{D}_1 &= \{\mathcal{R}_1, \mathcal{R}_2 > 0 | \mathcal{R}_2 < 1 < \mathcal{R}_1, \hat{\mathcal{R}}_2 > 1\}, \\ \mathcal{D}_2 &= \{\mathcal{R}_1, \mathcal{R}_2 > 0 | \mathcal{R}_1 < 1 < \mathcal{R}_2, \hat{\mathcal{R}}_1 > 1\}, \\ \mathcal{D}_3 &= \{\mathcal{R}_1, \mathcal{R}_2 > 0 | 1 < \mathcal{R}_2 < \mathcal{R}_1, \hat{\mathcal{R}}_1 < 1, \hat{\mathcal{R}}_2 < 1\}, \end{aligned}$$

then for any  $(\mathcal{R}_1, \mathcal{R}_2)$  in the coexistence region  $\mathcal{D}_c = \mathcal{D}_- \cup \mathcal{D}_+ \cup \mathcal{D}_1 \cup \mathcal{D}_2 \cup \mathcal{D}_3$ , there exists at least one coexistence equilibrium for the two diseases.

**Proof:** The fourth equation in (3.5) implies that at a coexistence equilibrium,

$$j = \frac{i(0)i_2 D(i_2)}{\mu + \nu}.$$

Substituting this expression into the second equation in (3.5), we find that

$$s = \left( B(i_2) + \frac{\gamma_1 i_2 D(i_2)}{\mu + \nu} \right)^{-1} =: \mathcal{S}(i_2). \quad (3.8)$$

Now we substitute (3.8) into the third equation in (3.5) and solve for  $j$  to obtain the expressions

$$j = \frac{(\mu + \alpha_2)(1 - \mathcal{R}_2 \mathcal{S}(i_2))i_2}{\gamma_2 \mathcal{S}(i_2)}, \quad \mathcal{R}_2 = \frac{\beta_2}{\mu + \alpha_2},$$

and

$$i(0) = \frac{(\mu + \nu)j}{i_2 D(i_2)} = \frac{(\mu + \nu)(\mu + \alpha_2)(1 - \mathcal{R}_2 \mathcal{S}(i_2))}{\gamma_2 \mathcal{S}(i_2) D(i_2)}.$$

Finally, we express  $j$  and  $i_1$  as follows

$$j = \frac{i_2(\mu + \alpha_2)(1 - \mathcal{R}_2 \mathcal{S}(i_2))}{\gamma_2 \mathcal{S}(i_2)} =: \mathcal{J}(i_2), \quad (3.9)$$

and

$$i_1 = \int_0^\infty i(a) da = i(0)G(i_2) = \frac{(\mu + \nu)(\mu + \alpha_2)G(i_2)(1 - \mathcal{R}_2 \mathcal{S}(i_2))}{\gamma_2 \mathcal{S}(i_2) D(i_2)} =: \mathcal{I}(i_2), \quad (3.10)$$

where

$$G(i_2) = \int_0^\infty \Gamma(a; i_2) \pi_1(a) e^{-\mu a} da > 0, \quad G(0) = \frac{1 - \Delta}{\mu}.$$

Since we are working with rescaled variables, the relation  $s + i_1 + i_2 + j = 1$  implies that

$$\mathcal{M}(i_2) := i_2 + \mathcal{S}(i_2) + \mathcal{I}(i_2) + \mathcal{J}(i_2) = 1.$$

We note that the function  $\mathcal{S}(i_2)$  is positive for all  $i_2 \geq 0$ , and both functions  $\mathcal{I}(i_2), \mathcal{J}(i_2)$  are positive if  $i_2 > 0$  and  $\mathcal{R}_2 \mathcal{S}(i_2) < 1$ . To prove the existence of a coexistence equilibrium it suffices to show the existence of a positive root of the equation  $\mathcal{M}(i_2) = 1$  that satisfies  $\mathcal{R}_2 \mathcal{S}(i_2) < 1$ . We also note that the function  $\mathcal{M}(i_2)$  can be equivalently expressed as

$$\mathcal{M}(i_2) := i_2 + \mathcal{S}(i_2) + \frac{(\mu + \alpha_2)(1 - \mathcal{R}_2 \mathcal{S}(i_2))}{\gamma_2 \mathcal{S}(i_2)} \left( i_2 + \frac{G(i_2)(\mu + \nu)}{D(i_2)} \right).$$

We observe that  $\mathcal{S}(0) = 1/\mathcal{R}_1$  and therefore

$$\begin{aligned} \mathcal{M}(0) &= \frac{1}{\mathcal{R}_1} + \frac{(\mu + \nu)(\mu + \alpha_2)G(0)(1 - \mathcal{R}_2 \mathcal{S}(0))}{\gamma_2 \mathcal{S}(0) D(0)} \\ &= \frac{1}{\mathcal{R}_1} + \frac{(1 - \Delta)(\mu + \nu)(\mu + \alpha_2)(\mathcal{R}_1 - \mathcal{R}_2)}{\mu \gamma_2 D(0)}. \end{aligned}$$

Suppose that  $(\mathcal{R}_1, \mathcal{R}_2) \in \mathcal{D}_-$ , that is,  $1 < \mathcal{R}_1 \leq \mathcal{R}_2$ , and  $\hat{\mathcal{R}}_1 > 1$ . It follows that  $\mathcal{M}(0) \leq 1/\mathcal{R}_1 < 1$  because  $\mathcal{R}_1 \leq \mathcal{R}_2$ . Using the definition of  $\hat{\mathcal{R}}_1$ , we find that  $\hat{\mathcal{R}}_1 > 1$  implies that  $\mathcal{R}_2 \mathcal{S}(\hat{i}_2) < 1$ . Therefore, there exist the following three possibilities:

1. If  $\mathcal{M}(\hat{i}_2) = 1$ , then we are done because both  $\mathcal{I}(\hat{i}_2)$  and  $\mathcal{J}(\hat{i}_2)$  are positive.
2. If  $\mathcal{M}(\hat{i}_2) > 1$ , then one of the following holds
  - There exists  $i_2^* \in [0, \hat{i}_2)$  such that  $\mathcal{R}_2 \mathcal{S}(i_2^*) = 1$  and  $\mathcal{R}_2 \mathcal{S}(i_2) < 1$  for all  $i_2 \in (i_2^*, \hat{i}_2]$ . In this case, we have that

$$\mathcal{M}(i_2^*) = i_2^* + 1/\mathcal{R}_2 = 1 + i_2^* - \hat{i}_2 < 1,$$

and since  $\mathcal{M}(\hat{i}_2) > 1$ , there exists a number  $i_2 \in (i_2^*, \hat{i}_2)$  such that  $\mathcal{M}(i_2) = 1$  where both  $\mathcal{I}(i_2)$  and  $\mathcal{J}(i_2)$  are positive.



- $\mathcal{R}_2\mathcal{S}(i_2) < 1$  for all  $i_2 \in (0, \hat{i}_2]$ . Then since  $\mathcal{M}(0) < 1$  and  $\mathcal{M}(\hat{i}_2) > 1$ , there exists a number  $i_2 \in (0, \hat{i}_2)$  such that  $\mathcal{M}(i_2) = 1$  where both  $\mathcal{I}(i_2)$  and  $\mathcal{J}(i_2)$  are positive.
3. If  $\mathcal{M}(\hat{i}_2) < 1$ , then one of the following holds
- There exists  $i_2^* \in (\hat{i}_2, 1]$  such that  $\mathcal{R}_2\mathcal{S}(i_2^*) = 1$  and  $\mathcal{R}_2\mathcal{S}(i_2) < 1$  for all  $i_2 \in (\hat{i}_2, i_2^*)$ . In this case, we have that

$$\mathcal{M}(i_2^*) = i_2^* + 1/\mathcal{R}_2 = 1 + i_2^* - \hat{i}_2 > 1,$$

and since  $\mathcal{M}(\hat{i}_2) < 1$ , there exists a number  $i_2 \in (\hat{i}_2, i_2^*)$  such that  $\mathcal{M}(i_2) = 1$  where both  $\mathcal{I}(i_2)$  and  $\mathcal{J}(i_2)$  are positive.

- $\mathcal{R}_2\mathcal{S}(i_2) < 1$  for all  $i_2 \in [\hat{i}_2, 1)$ . Then we have that  $\mathcal{M}(1) \geq 1 + \mathcal{S}(1) > 1$ , and since  $\mathcal{M}(\hat{i}_2) < 1$ , there exists a number  $i_2 \in (\hat{i}_2, 1)$  such that  $\mathcal{M}(i_2) = 1$  where both  $\mathcal{I}(i_2)$  and  $\mathcal{J}(i_2)$  are positive.

Therefore, there exists a coexistence equilibrium for all  $(\mathcal{R}_1, \mathcal{R}_2) \in \mathcal{D}_-$ .

Now suppose that  $(\mathcal{R}_1, \mathcal{R}_2) \in \mathcal{D}_+$ , that is,  $1 < \mathcal{R}_2 < \mathcal{R}_1$ , and  $\hat{\mathcal{R}}_1, \hat{\mathcal{R}}_2 > 1$ . The inequality  $\hat{\mathcal{R}}_2 > 1$  implies that  $\mathcal{M}(0) < 1$ , and the inequality  $\hat{\mathcal{R}}_1 > 1$  implies that  $\mathcal{R}_2\mathcal{S}(\hat{i}_2) < 1$ . From this point forward, the proof of this case is analogous to the proof of the case  $(\mathcal{R}_1, \mathcal{R}_2) \in \mathcal{D}_-$ .

Suppose that  $(\mathcal{R}_1, \mathcal{R}_2) \in \mathcal{D}_2$ , that is,  $\mathcal{R}_1 < 1 < \mathcal{R}_2$ , and  $\hat{\mathcal{R}}_1 > 1$ . As before, the inequality  $\hat{\mathcal{R}}_1 > 1$  implies that  $\mathcal{R}_2\mathcal{S}(\hat{i}_2) < 1$ . On the other hand, we have that  $\mathcal{R}_2\mathcal{S}(0) = \mathcal{R}_2/\mathcal{R}_1 > 1$ . Now, if  $\mathcal{M}(\hat{i}_2) \leq 1$ , the proof is analogous to the proof of the case  $(\mathcal{R}_1, \mathcal{R}_2) \in \mathcal{D}_-$ . If  $\mathcal{M}(\hat{i}_2) > 1$ , then there exists  $i_2^* \in (0, \hat{i}_2)$  such that  $\mathcal{R}_2\mathcal{S}(i_2^*) = 1$  and  $\mathcal{R}_2\mathcal{S}(i_2) < 1$  for all  $i_2 \in (i_2^*, \hat{i}_2]$ . In addition, we have that  $\mathcal{M}(i_2^*) = i_2^* + 1/\mathcal{R}_2 = 1 + i_2^* - \hat{i}_2 < 1$ . Consequently, there exists a number  $i_2 \in (i_2^*, \hat{i}_2)$  such that  $\mathcal{M}(i_2) = 1$ . This concludes the proof of the case  $(\mathcal{R}_1, \mathcal{R}_2) \in \mathcal{D}_2$ .

Suppose that  $(\mathcal{R}_1, \mathcal{R}_2) \in \mathcal{D}_1$ , that is,  $\mathcal{R}_2 < 1 < \mathcal{R}_1$ , and  $\hat{\mathcal{R}}_2 > 1$ . As before, the inequality  $\hat{\mathcal{R}}_2 > 1$  implies that  $\mathcal{M}(0) < 1$ , but the value of  $\hat{i}_2 = 1 - 1/\mathcal{R}_2 < 0$  since  $\mathcal{R}_2 < 1$ . Instead, we have that  $\mathcal{R}_2\mathcal{S}(0) = \mathcal{R}_2/\mathcal{R}_1 < 1$ . Suppose that there exists  $i_2^* \in (0, 1)$  such that  $\mathcal{R}_2\mathcal{S}(i_2^*) = 1$  and  $\mathcal{R}_2\mathcal{S}(i_2) < 1$  for all  $i_2 \in (0, i_2^*)$ . Then we have that  $\mathcal{M}(i_2^*) = i_2^* + 1/\mathcal{R}_2 > 1/\mathcal{R}_2 > 1$  and there exists a number  $i_2 \in (0, i_2^*)$  such that  $\mathcal{M}(i_2) = 1$ . If no such  $i_2^*$  exists, we have that  $\mathcal{R}_2\mathcal{S}(i_2) < 1$  for all  $i_2 \in (0, 1)$ . Since  $\mathcal{M}(1) \geq 1 + \mathcal{S}(1) > 1$ , there exists a number  $i_2 \in (0, 1)$  such that  $\mathcal{M}(i_2) = 1$ . This concludes the proof of the case  $(\mathcal{R}_1, \mathcal{R}_2) \in \mathcal{D}_1$ .

Finally, suppose that  $(\mathcal{R}_1, \mathcal{R}_2) \in \mathcal{D}_3$ , that is,  $1 < \mathcal{R}_2 < \mathcal{R}_1$ , and  $\hat{\mathcal{R}}_1, \hat{\mathcal{R}}_2 < 1$ . The inequality  $\hat{\mathcal{R}}_2 < 1$  implies that  $\mathcal{M}(0) > 1$ , and the inequality  $\hat{\mathcal{R}}_1 < 1$  implies that  $\mathcal{R}_2\mathcal{S}(\hat{i}_2) > 1$ . In addition, since  $\mathcal{R}_1 > \mathcal{R}_2$ , we have that  $\mathcal{R}_2\mathcal{S}(0) < \mathcal{R}_1\mathcal{S}(0) = 1$ . Therefore, there exists  $i_2^* \in (0, \hat{i}_2)$  such that  $\mathcal{R}_2\mathcal{S}(i_2^*) = 1$  and  $\mathcal{R}_2\mathcal{S}(i_2) < 1$  for all  $i_2 \in [0, i_2^*)$ . Since  $\mathcal{M}(i_2^*) = 1 + i_2^* - \hat{i}_2 < 1$ , there exists a number  $i_2 \in (0, i_2^*)$  such that  $\mathcal{M}(i_2) = 1$ . This concludes the proof of the theorem.

◇

REMARK. Each of the subregions comprising the coexistence region  $\mathcal{D}_c$  has a clear epidemiological interpretation. These regions are presented in Fig. 3.1.

If  $(\mathcal{R}_1, \mathcal{R}_2) \in \mathcal{D}_- \cup \mathcal{D}_+$ , then both dominance equilibria  $\mathcal{E}_1$  and  $\mathcal{E}_2$  exist, and each disease can invade the equilibrium of the other disease. The difference between  $\mathcal{D}_-$  and  $\mathcal{D}_+$  is that  $\hat{\mathcal{R}}_2$  is only defined for  $(\mathcal{R}_1, \mathcal{R}_2) \in \mathcal{D}_+$ .

If  $(\mathcal{R}_1, \mathcal{R}_2) \in \mathcal{D}_1$ , then only the dominance equilibrium of the primary disease  $\mathcal{E}_1$  exists, and the secondary disease can invade the equilibrium of the primary disease. Although the secondary disease cannot persist in the absence of the primary disease, the presence of the primary disease mediates the coexistence.

If  $(\mathcal{R}_1, \mathcal{R}_2) \in \mathcal{D}_2$ , then only the dominance equilibrium of the secondary disease  $\mathcal{E}_2$  exists, and the primary disease can invade the equilibrium of the secondary disease. Although the primary disease cannot persist in the absence of the secondary disease, the presence of the secondary disease mediates the coexistence.

If  $(\mathcal{R}_1, \mathcal{R}_2) \in \mathcal{D}_3$ , then both dominance equilibria  $\mathcal{E}_1$  and  $\mathcal{E}_2$  exist, but neither disease can invade the equilibrium of the other disease.

**4. Extinction of one or both diseases.** In this section we provide the conditions that guarantee that one of the diseases or both of them will be eliminated from the population. These are global conditions in the sense that if they are satisfied extinction occurs for all other values of the parameters and all initial conditions. As we show in Section 6, there could be a backward bifurcation with respect to both  $\mathcal{R}_1$  and  $\mathcal{R}_2$  and therefore there could exist multiple coexistence equilibria even if  $\mathcal{R}_1 < 1$  and  $\mathcal{R}_2 < 1$ . Thus,  $\mathcal{R}_1 < 1$  and  $\mathcal{R}_2 < 1$  by itself do not necessarily imply extinction of one or both diseases. In what follows, we show that the diseases vanish if in addition  $\gamma_1 = 0$  or  $\gamma_2 = 0$ .

We denote the initial conditions by  $S(0) = S^0$ ,  $i(a, 0) = i_0(a)$ ,  $I_2(0) = I_2^0$  and  $J(0) = J^0$ .

**THEOREM 4.1.** *Assume  $i_0(a)$  is integrable. If  $\gamma_1 = 0$  or  $\gamma_2 = 0$  and  $\mathcal{R}_1 < 1$ ,  $\mathcal{R}_2 < 1$  then both diseases become extinct in the sense that  $\lim_{t \rightarrow \infty} i(a, t) = 0$  pointwise for every  $a$ ,  $I_2 \rightarrow 0$  as  $t \rightarrow \infty$  and  $J \rightarrow 0$  as  $t \rightarrow \infty$ .*

**Proof:** Assume  $\gamma_1 = 0$ . Let  $\mathcal{B}(t) = i(0, t)$ . Neglecting the term dependent on  $I_2$  we obtain a differential inequality for the primary disease. Integrating this inequality along the characteristic lines we have

$$i(a, t) \leq \begin{cases} i_0(a-t) \frac{\pi(a)}{\pi(a-t)} e^{-\mu t} & a \geq t \\ \mathcal{B}(t-a) \pi(a) e^{-\mu a} & a < t \end{cases} \quad (4.1)$$

Since  $\gamma_1 = 0$  we have

$$\mathcal{B}(t) \leq \int_0^t \beta_1(a) \mathcal{B}(t-a) \pi_1(a) e^{-\mu a} da + e^{-\mu t} \int_t^\infty \beta_1(a) i_0(a-t) da$$

Consequently, taking a limsup of both sides as  $t \rightarrow \infty$  we obtain  $\limsup_{t \rightarrow \infty} \mathcal{B} \leq \mathcal{R}_1 \limsup_{t \rightarrow \infty} \mathcal{B}(t)$ . Since  $\mathcal{R}_1 < 1$  and  $\limsup_{t \rightarrow \infty} \mathcal{B} < \infty$  this inequality can only be satisfied if  $\limsup_{t \rightarrow \infty} \mathcal{B}(t) = 0$ . This, in particular, implies that  $i(a, t)$  approaches zero as  $t \rightarrow \infty$  for every fixed  $a$ . From the equation for  $J$  we then have the following inequality

$$J(t) \leq e^{-(\mu+\nu)t} J_0 + \int_0^t e^{-(\mu+\nu)s} \int_0^\infty \delta(a) i(a, t-s) da ds$$

Since  $\delta(a)$  is bounded and the integral of  $i(a, t)$  goes to zero  $I_1(t) \rightarrow 0$  as  $t \rightarrow \infty$ , we get that  $\limsup_{t \rightarrow \infty} J(t) = 0$ . Consequently, the equality for  $I_2$  in (2.1) leads to the following differential inequality:  $I_2' \leq \beta_2 I_2 + \gamma_2 J(t) - (\mu + \alpha_2) I_2$ . Integrating this inequality we obtain

$$I_2(t) \leq e^{-(\mu+\alpha_2)t} I_2(0) + \beta_2 \int_0^t e^{-(\mu+\alpha_2)\tau} I_2(t-\tau) d\tau + \gamma_2 \int_0^t e^{-(\mu+\alpha_2)\tau} J(t-\tau) d\tau.$$

Taking a limsup as  $t \rightarrow \infty$  on both sides of this inequality, we obtain  $\limsup_{t \rightarrow \infty} I_2(t) \leq \mathcal{R}_2 \limsup_{t \rightarrow \infty} I_2(t)$ . Since  $\mathcal{R}_2 < 1$  this inequality implies  $\limsup_{t \rightarrow \infty} I_2(t) = 0$ .

If  $\gamma_2 = 0$  then the proof is symmetrical and somewhat analogous. Thus, it will be omitted. That concludes the proof of this theorem.  $\diamond$

As a special case of the theorem above we have the following results on extinction of one of the diseases.

**COROLLARY 4.2.** *Assume  $i_0(a)$  is integrable. If  $\gamma_1 = 0$  and  $\mathcal{R}_1 < 1$  then the primary disease becomes extinct in the sense that  $\lim_{t \rightarrow \infty} i(a, t) = 0$  pointwise for every  $a$ . As a consequence,  $J(t) \rightarrow 0$  as  $t \rightarrow \infty$ .*

A similar result for the secondary disease is also valid.

**COROLLARY 4.3.** *If  $\gamma_2 = 0$  and  $\mathcal{R}_2 < 1$  then the secondary disease becomes extinct, that is,  $I_2(t) \rightarrow 0$  as  $t \rightarrow \infty$ . As a consequence,  $J(t) \rightarrow 0$  as  $t \rightarrow \infty$ .*

A special instance which deserves consideration is the one with  $\delta(a) = 0$ . In this case there is no coinfection and the jointly infected class  $J$  vanishes. Only three equilibria are possible - the coexistence equilibrium does not exist. The main question is: does the competitive exclusion principle hold for the two diseases with no coinfection? This question can be answered positively in the case when all coefficients are constant and the model (2.1) consists of ODEs only. Then, with  $\delta = 0$ , it becomes a particular case of a more general model considered in [4]. The results there imply that the competitive exclusion holds and only the disease with higher reproduction number persists in the population, the other one becomes extinct.

We have not been able to establish whether competitive exclusion for the model (2.1) with  $\delta(a) = 0$  is the only possible outcome in the strictly age-structured case. Although there is no coexistence equilibrium, coexistence might still be possible in the form of, say, stable oscillatory solution. Such situation has been found to occur in model ecosystems such as the chemostat [3, 5, 18]. This option is even more plausible here given that the dominance equilibrium of the primary disease can lose stability due to the age-structure, and oscillatory solutions are present (see Section 5.2 for more detailed discussion). Despite the oscillatory solutions simulations lead to extinction of the disease with lower reproduction number. Thus, we conjecture that competitive exclusion is still the norm. The rigorous justification, however, remains an open problem.

**5. Local stability of equilibria.** In this section we investigate the local stability of the equilibria. In particular, we derive conditions for the stability of the disease-free equilibrium, and of the secondary disease dominance equilibrium. We also show that Hopf bifurcation occurs in the coexistence equilibrium. The stability of equilibria determines conditions under which the ultimate outcome will be elimination of both diseases, dominance of the primary disease, dominance of the secondary disease, or endemic presence of both of them.

To investigate the stability of the equilibria, we linearize the model (2.1). In particular, let  $x(t)$ ,  $y(a, t)$ ,  $z(t)$  and  $w(t)$  be the perturbations respectively of  $S^*$ ,  $i^*(a)$ ,  $I_2^*$ ,  $J^*$ . That is,  $S = S^* + x$ ,  $i = i^* + y$ ,  $I_2 = I_2^* + z$ ,  $J = J^* + w$ . Thus the perturbations satisfy a linear system. Further we consider the eigenvalue problem for the linearized system. We will denote the eigenvector again with  $x$ ,  $y(a)$ ,  $z$ , and  $w$ . These satisfy the following linear eigenvalue problem (here  $s$ ,  $i$ ,  $i_2$  and  $j$  are the

proportions in the corresponding equilibrium).

$$\begin{aligned}
\lambda x &= -s \int_0^\infty \beta_1(a)y(a)da - xi(0)B(i_2) - \beta_2sz - \beta_2xi_2 + \int_0^\infty \alpha_1(a)y(a)da, \\
&\quad -(\gamma_1 + \gamma_2)sw - (\gamma_1 + \gamma_2)xj - \mu x + \alpha_2z, \\
y'(a) &= -\lambda y - \alpha_1(a)y - \delta(a)i_2y - \delta(a)i(a)z - \mu y, \\
y(0) &= s \int_0^\infty \beta_1(a)y(a)da + xi(0)B(i_2) + \gamma_1sw + \gamma_1xj, \\
\lambda z &= \beta_2sz + \beta_2i_2x + \gamma_2sw + \gamma_2jx - (\mu + \alpha_2)z, \\
\lambda w &= i_2 \int_0^\infty \delta(a)y(a)da + zi(0)D(i_2) - (\mu + \nu)w.
\end{aligned} \tag{5.1}$$

**5.1. Stability of the disease-free equilibrium.** For the disease-free equilibrium we have  $i(0) = 0$ ,  $i_2 = 0$  and  $j = 0$  and  $s = 1$ . Thus the system above simplifies to the following system:

$$\begin{aligned}
\lambda x &= - \int_0^\infty \beta_1(a)y(a)da - \beta_2z - (\gamma_1 + \gamma_2)w - \mu x + \int_0^\infty \alpha_1(a)y(a)da + \alpha_2z, \\
y'(a) &= -\lambda y - \alpha_1(a)y - \mu y, \\
y(0) &= \int_0^\infty \beta_1(a)y(a)da + \gamma_1w, \\
\lambda z &= \beta_2z + \gamma_2w - (\mu + \alpha_2)z, \\
\lambda w &= -(\mu + \nu)w.
\end{aligned} \tag{5.2}$$

From this system we will establish the following result regarding the local stability of the disease-free equilibrium  $\mathcal{E}_0$ .

**PROPOSITION 5.1.** *If  $\mathcal{R}_1 < 1$  and  $\mathcal{R}_2 < 1$  then the disease-free equilibrium  $\mathcal{E}_0$  is locally asymptotically stable. If  $\mathcal{R}_1 > 1$  or  $\mathcal{R}_2 > 1$  then the disease-free equilibrium  $\mathcal{E}_0$  is unstable.*

**Proof:** To see this, first notice that from the last equation we have either  $\lambda = -(\mu + \nu)$  which is the first eigenvalue, or  $w = 0$ . From the second to last equation we have  $\lambda z = \beta_2z - (\mu + \alpha_2)z$  where either  $\lambda = \beta_2 - (\mu + \alpha_2)$  or  $z = 0$ . This eigenvalue  $\lambda = \beta_2 - (\mu + \alpha_2) < 0$  if and only if  $\mathcal{R}_2 < 1$ . Thus, if  $\mathcal{R}_2 > 1$  the disease-free equilibrium  $\mathcal{E}_0$  is unstable because this eigenvalue is positive. Further, from the second equation we have that the remaining eigenvalues satisfy the equation, also referred to as the characteristic equation

$$\int_0^\infty \beta_1(a)e^{-(\lambda+\mu)a}\pi_1(a)da = 1 \tag{5.3}$$

Denoting the left hand side of the equation above by  $\mathcal{G}(\lambda)$  where  $\lambda$  is in general a complex number. Assume  $\Re \lambda \geq 0$ . For such  $\lambda$  we have  $|\mathcal{G}(\lambda)| \leq \mathcal{G}(\Re \lambda)$ . Furthermore  $\mathcal{G}(\Re \lambda)$  is a decreasing function of  $\Re \lambda$ . Consequently,

$$|\mathcal{G}(\lambda)| \leq \mathcal{G}(\Re \lambda) \leq \mathcal{G}(0) = \mathcal{R}_1 < 1$$

Thus, if both  $\mathcal{R}_1 < 1$  and  $\mathcal{R}_2 < 1$  all eigenvalues have negative real part and the disease-free equilibrium  $\mathcal{E}_0$  is locally asymptotically stable. If only  $\mathcal{R}_1 > 1$  then if we consider  $\mathcal{G}(\lambda)$  for  $\lambda$  real, we see that  $\mathcal{G}(\lambda)$  is a decreasing function of  $\lambda$  approaching zero as  $\lambda$  approaches infinity. Since  $\mathcal{G}(0) = \mathcal{R}_1 > 1$  that implies that there is a positive eigenvalue  $\lambda^* > 0$  and the disease-free equilibrium  $\mathcal{E}_0$  is unstable. This concludes the proof.

◇

**5.2. Stability of the primary disease equilibrium.** In this subsection we discuss the local stability of the equilibrium  $\mathcal{E}_1$  and derive conditions for domination of the primary disease. We show that the equilibrium  $\mathcal{E}_1$  can lose stability and dominance of the first disease is possible in the form of sustained oscillation. In this case  $i_2 = 0$ ,  $j = 0$ ,  $s = \frac{1}{\mathcal{R}_1}$  and  $i(a) = i(0)\pi_1(a)e^{-\mu a}$  where

$$i(0) = \frac{\mu \left(1 - \frac{1}{\mathcal{R}_1}\right)}{1 - \Delta} \quad (5.4)$$

The eigenvalue problem takes the form

$$\begin{aligned} \lambda x &= -s \int_0^\infty \beta_1(a)y(a)da - xi(0)B(0) - \beta_2 s z \\ &\quad - (\gamma_1 + \gamma_2)sw - \mu x + \int_0^\infty \alpha_1(a)y(a)da + \alpha_2 z, \\ y'(a) &= -\lambda y - \alpha_1(a)y - \delta(a)i(a)z - \mu y, \\ y(0) &= s \int_0^\infty \beta_1(a)y(a)da + xi(0)B(0) + \gamma_1 s w, \\ \lambda z &= \beta_2 s z + \gamma_2 s w - (\mu + \alpha_2)z, \\ \lambda w &= zi(0)D(0) - (\mu + \nu)w. \end{aligned} \quad (5.5)$$

From the last equation we have

$$w = \frac{zi(0)D(0)}{\lambda + \mu + \nu}.$$

Substituting in the equation for  $z$ , assuming  $z$  is nonzero and cancelling  $w$ , we arrive at the following characteristic equation

$$\frac{\gamma_2 si(0)D(0)}{(\lambda + \mu + \nu)(\lambda + \mu + \alpha_2 - \beta_2 s)} = 1 \quad (5.6)$$

We are ready to establish the first result.

**PROPOSITION 5.2.** *Let  $\mathcal{R}_1 > 1$  and  $\mathcal{R}_1 > \mathcal{R}_2$ . Then, the equilibrium  $\mathcal{E}_1$  is unstable if the secondary disease can invade the equilibrium of the primary disease, that is,  $\hat{\mathcal{R}}_2 > 1$ . If  $\hat{\mathcal{R}}_2 < 1$  then all solutions to the characteristic equation (5.6) have negative real part.*

**Proof:** To see these results, denote by  $\mathcal{G}(\lambda)$  the left hand side of the characteristic equation (5.6). First, we notice that using the values of  $s$  and  $i(0)$  we have

$$\mathcal{G}(0) = \frac{\gamma_2 si(0)D(0)}{(\mu + \nu)(\mu + \alpha_2 - \beta_2 s)} = \frac{\mu \gamma_2 \left(1 - \frac{1}{\mathcal{R}_1}\right) D(0)}{(1 - \Delta)(\mu + \alpha_2)(\mu + \nu)(\mathcal{R}_1 - \mathcal{R}_2)} = \hat{\mathcal{R}}_2 \quad (5.7)$$

First, in the case  $\hat{\mathcal{R}}_2 > 1$  we have that  $\mathcal{G}(0) > 1$ . In addition, if  $\mathcal{G}(\lambda)$  is considered as a function of a real variable, we see that  $\mathcal{G}(\lambda) \rightarrow 0$  as  $\lambda \rightarrow \infty$ . Since  $\mathcal{R}_1 > \mathcal{R}_2$ ,  $\mathcal{G}(\lambda)$  is also a continuous function of  $\lambda$  for  $\lambda \geq 0$ . Consequently, there exists  $\lambda^* > 0$  such that  $\mathcal{G}(\lambda^*) = 1$ . Thus,  $\mathcal{E}_1$  is unstable.

In the case when  $\hat{\mathcal{R}}_2 < 1$  we have for  $\lambda$ 's with  $\Re \lambda \geq 0$

$$\begin{aligned} |\mathcal{G}(\lambda)| &= \frac{\gamma_2 si(0)D(0)}{|\lambda + \mu + \nu||\lambda + \mu + \alpha_2 - \beta_2 s|} \\ &\leq \frac{\gamma_2 si(0)D(0)}{(\Re \lambda + \mu + \nu)(\Re \lambda + \mu + \alpha_2 - \beta_2 s)} \leq \mathcal{G}(0) = \hat{\mathcal{R}}_2 < 1. \end{aligned}$$

Consequently, the equation  $\mathcal{G}(\lambda) = 1$  has no solutions with nonnegative real parts. This concludes the proof of the proposition.  $\diamond$

We note that the fact that all solutions to the characteristic equation (5.6) have negative real part does not yet imply that  $\mathcal{E}_1$  is stable since there is a second characteristic equation associated with this case. For stability both characteristic equations must have only roots with negative real parts.

Next, we extend the result above to the case  $\mathcal{R}_1 < \mathcal{R}_2$ . In particular, we have

**PROPOSITION 5.3.** *Let  $\mathcal{R}_1 > 1$ . If  $\mathcal{R}_1 < \mathcal{R}_2$  then the equilibrium  $\mathcal{E}_1$  is unstable.*

**Proof:** To see that we rewrite the characteristic equation (5.6) in the form

$$\frac{\gamma_2 s i(0) D(0)}{\lambda + \mu + \nu} = \lambda + \mu + \alpha_2 - \beta_2 s \quad (5.8)$$

We notice that  $\mu + \alpha_2 - \beta_2 s = (\mu + \alpha_2) \left(1 - \frac{\mathcal{R}_2}{\mathcal{R}_1}\right)$  which is negative. Let  $\lambda^* = -(\mu + \alpha_2 - \beta_2 s) > 0$ . Thus for  $\lambda \geq \lambda^*$  the expression  $\lambda + \mu + \alpha_2 - \beta_2 s$  considered as a function of the real variable  $\lambda$  is increasing from zero to infinity. On the other hand for  $\lambda \geq \lambda^*$  the expression

$$\frac{\gamma_2 s i(0) D(0)}{\lambda + \mu + \nu}$$

is decreasing from some positive value to zero. Thus, there is a unique positive (actually larger than  $\lambda^*$ ) solution of the equation (5.8). Consequently,  $\mathcal{E}_1$  is unstable. This completes the proof.  $\diamond$

We continue with the consideration of the system (5.5). If we assume that  $z = 0$  that implies  $w = 0$ . In this case the remaining two equations become

$$\begin{aligned} \lambda x &= -s \int_0^\infty \beta_1(a) y(a) da - x i(0) B(0) - \mu x + \int_0^\infty \alpha_1(a) y(a) da \\ y'(a) &= -\lambda y - \alpha_1(a) y - \mu y \\ y(0) &= s \int_0^\infty \beta_1(a) y(a) da + x i(0) B(0) \end{aligned} \quad (5.9)$$

Solving the differential equation, substituting in the equation for  $x$  and the initial condition, we obtain a system in  $x$  and  $y(0)$  which has a nontrivial solution if and only if the following characteristic equation is satisfied:

$$(\lambda + \mu) s B_2(\lambda) = \lambda + \mu + i(0) B(0) (1 - A_2(\lambda)) \quad (5.10)$$

where the following notation has been used

$$B_2(\lambda) = \int_0^\infty \beta_1(a) \pi_1(a) e^{-(\lambda + \mu)a} da, \quad A_2(\lambda) = \int_0^\infty \alpha_1(a) \pi_1(a) e^{-(\lambda + \mu)a} da.$$

If we denote by

$$E_2(\lambda) = \int_0^\infty \pi_1(a) e^{-(\lambda + \mu)a} da$$

we can notice that integration by parts leads to the equality  $1 - A_2(\lambda) = (\lambda + \mu) E_2(\lambda)$ . Consequently the characteristic equation (5.10) has one eigenvalue equal to  $-\mu$ . The remaining eigenvalues satisfy the following reduced characteristic equation

$$s B_2(\lambda) = 1 + i(0) B(0) E_2(\lambda) \quad (5.11)$$

This equation clearly does not have real nonnegative solutions since for  $\lambda$  real and nonnegative the left hand side is smaller than one while the right hand side is larger than one. However, the dominant eigenvalue is not necessarily real - it may be complex with nonnegative real part. Thus, the dominance equilibrium of the primary disease may lose stability and oscillations are possible. We include an example and results of simulations later in this Section. First, we show that the mechanism responsible for the instability of the primary disease equilibrium is the presence of infection-age structure and variable infectivity. Indeed, if  $\beta_1(a) = \beta_1$  and  $\alpha_1(a) = \alpha_1$  are constants then  $i(0)B(0) = \beta_1 i$  where  $i$  is the proportion infected with primary disease. In addition,  $B_2(\lambda) = \beta_1 E_2(\lambda)$  and  $E_2(\lambda) = (\lambda + \mu + \alpha_1)^{-1}$ . Hence, in the constant coefficient case the characteristic equation (5.11) becomes  $\lambda + \mu + \alpha_1 + \beta_1 i - \beta_1 s = 0$ . Since,  $\beta_1 s = \mu + \alpha_1$  the only eigenvalue is  $-\beta_1 i$  and is clearly negative. We formulate this result in the following proposition:

**PROPOSITION 5.4.** *Let  $\beta_1(a) = \beta_1$  and  $\alpha_1(a) = \alpha_1$  be constants. Let  $\mathcal{R}_1 > 1$ . Assume that  $\mathcal{R}_1 > \mathcal{R}_2$  and the secondary disease cannot invade the equilibrium of the primary disease, that is,  $\hat{\mathcal{R}}_2 < 1$ . Then the equilibrium  $\mathcal{E}_1$  is locally asymptotically stable. If  $\hat{\mathcal{R}}_2 > 1$  the equilibrium  $\mathcal{E}_1$  is unstable.*

We conclude this section with an example that the presence of infection-age structure may lead to loss of stability of the dominance equilibrium of the primary disease and oscillations. For this specific example the characteristic equation (5.11) has a complex root with a positive real part. Simulations show the presence of a stable oscillatory solution with persistence of the primary disease only.

Consider the following values for the parameters:  $\delta(a) = 0$ ,  $\mu = 0.05$ ,  $\gamma_1 = 0.1$ ,  $\nu = 0$ . The recovery rate for the primary disease is:

$$\alpha_1(a) = \begin{cases} 0 & 0 \leq a < 3 \\ 1.58259 & a \geq 3. \end{cases} \quad (5.12)$$

The transmission coefficient for the primary disease is

$$\beta_1(a) = \begin{cases} 2.33193e^{2a} & 0 \leq a < 1 \\ 0 & a \geq 1. \end{cases} \quad (5.13)$$

The parameters related to the secondary disease are not relevant as  $I_2 \rightarrow 0$  and  $J \rightarrow 0$  but they were chosen as follows:  $\beta_2 = 0.2$ ,  $\alpha_2 = 0.1$ ,  $\gamma_2 = 8$ . The recruitment rate  $\Lambda = 1$ . With these parameters the reproduction numbers are  $\mathcal{R}_1 = 7.207464746$  and  $\mathcal{R}_2 = 1.3333$ . The characteristic equation (5.11) has a root  $0.05 + i\frac{\pi}{2}$ . The initial conditions for the primary disease are chosen close to the equilibrium:  $S_0 = 2.77$ ,  $I_2(0) = 0$ ,  $J_0 = 0$ ,

$$i_0(a) = \begin{cases} 5.2e^{-0.05a} & 0 \leq a < 3 \\ 5.2e^{-1.58259(a-3)}e^{-0.05a} & a \geq 3. \end{cases} \quad (5.14)$$

The results of the simulations are given in Figure 5.1. The step-size is 0.01 and the integration in age is for up to 100 units. Both figures give the dynamics of the proportion of all cases of the primary disease in the total population as a function of time, that is  $\frac{I_1}{N}$  where  $I_1$  is the integral in age of  $i(a, t)$ .

In the first figure all oscillations are presented. They are so dense that the space they occupy looks like a solid. The oscillations grow in magnitude up to time unit 1000 and then they stabilize in magnitude. The solution takes long to stabilize into

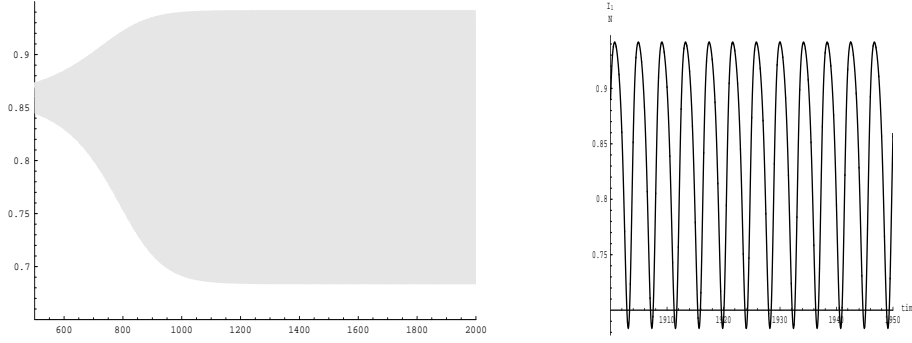


FIG. 5.1. The left figure shows the proportion of individuals infected with the primary disease  $\frac{I_1}{N}$  where  $I_1$  is the integral in age of  $i(a, t)$  for up to 2000 time units. The horizontal axis shows the time. The right figure presents a sample of the solution between the time units 1900 and 1950. The numerical solution exhibits sustained oscillations.

sustained oscillations because the real part of the eigenvalue with positive real part is relatively small  $-0.05$ . In the second figure a zoomed in picture is presented for the oscillations between time units 1900 and 1950.

**5.3. Stability of the secondary disease equilibrium.** In this subsection we establish that the equilibrium  $\mathcal{E}_2$  is locally stable whenever it exists. Thus, unlike  $\mathcal{E}_1$ , the presence of host age-structure does not lead to oscillations in the dominance equilibrium of the secondary disease. In this case  $i(0) = 0$ ,  $j = 0$ ,  $s = \frac{1}{\mathcal{R}_2}$  and  $i_2 = \hat{i}_2 = 1 - \frac{1}{\mathcal{R}_2}$ . The linear eigenvalue problem becomes:

$$\begin{aligned}
 \lambda x &= -s \int_0^\infty \beta_1(a)y(a)da - \beta_2sz - \beta_2xi_2 \\
 &\quad - (\gamma_1 + \gamma_2)sw - \mu x + \int_0^\infty \alpha_1(a)y(a)da + \alpha_2z \\
 y'(a) &= -\lambda y - \alpha_1(a)y - \delta(a)i_2y - \mu y \\
 y(0) &= s \int_0^\infty \beta_1(a)y(a)da + \gamma_1sw \\
 \lambda z &= \beta_2sz + \beta_2i_2x + \gamma_2sw - (\mu + \alpha_2)z \\
 \lambda w &= i_2 \int_0^\infty \delta(a)y(a)da - (\mu + \nu)w
 \end{aligned} \tag{5.15}$$

From the last equation we have

$$w = \frac{i_2}{\lambda + \mu + \nu} \int_0^\infty \delta(a)y(a)da$$

From the equation for  $y(a)$  we have

$$y(a) = y(0)\Gamma(a; i_2)\pi_1(a)e^{-(\lambda+\mu)a}$$

Substituting in the equation for the initial condition  $y(0)$  and assuming that  $y(0) \neq 0$  we obtain the following characteristic equation:

$$sB_1(\lambda) + \frac{\gamma_1si_2}{\lambda + \mu + \nu}D_1(\lambda) = 1 \tag{5.16}$$



where we have used the notation:

$$B_1(\lambda) = \int_0^\infty \beta_1(a)\Gamma(a; i_2)\pi_1(a)e^{-(\lambda+\mu)a} da,$$

$$D_1(\lambda) = \int_0^\infty \delta(a)\Gamma(a; i_2)\pi_1(a)e^{-(\lambda+\mu)a} da.$$

Clearly,  $B_1(0) = B(i_2)$  and  $D_1(0) = D(i_2)$ . Now, we are ready to prove the main result in this subsection.

**THEOREM 5.5.** *Let  $\mathcal{R}_2 > 1$ . Assume that the primary disease cannot invade the equilibrium of the secondary disease, that is,  $\hat{\mathcal{R}}_1 < 1$ . Then the equilibrium  $\mathcal{E}_2$  is locally asymptotically stable and the secondary disease dominates in the population. If  $\hat{\mathcal{R}}_1 > 1$  the equilibrium  $\mathcal{E}_2$  is unstable.*

**Proof:** Denote by  $\mathcal{G}(\lambda)$  the left-hand side of the characteristic equation (5.16). We notice that

$$\mathcal{G}(0) = \hat{\mathcal{R}}_1$$

First we assume that  $\hat{\mathcal{R}}_1 > 1$ . We consider  $\mathcal{G}(\lambda)$  as a function of a real variable. We have  $\mathcal{G}(0) = \hat{\mathcal{R}}_1 > 1$ . In addition  $\mathcal{G}(\lambda) \rightarrow 0$  as  $\lambda \rightarrow \infty$ . Consequently, there exists  $\lambda^* > 0$  such that  $\mathcal{G}(\lambda^*) = 1$  and the equilibrium  $\mathcal{E}_2$  is unstable.

Next, we assume  $\hat{\mathcal{R}}_1 < 1$ . For  $\lambda$ 's with real part  $\Re \lambda \geq 0$  we have

$$\begin{aligned} |\mathcal{G}(\lambda)| &\leq s|B_1(\lambda)| + \frac{\gamma_1 s i_2}{|\lambda + \mu + \nu|} |D_1(\lambda)| \\ &\leq sB_1(\Re \lambda) + \frac{\gamma_1 s i_2}{\Re \lambda + \mu + \nu} D_1(\Re \lambda) \\ &\leq sB(i_2) + \frac{\gamma_1 s i_2}{\mu + \nu} D(i_2) = \hat{\mathcal{R}}_1 < 1 \end{aligned}$$

Thus, the characteristic equation (5.16) has no solution with nonnegative real part. Furthermore, for  $y(0) = 0$  we have that  $y(a) = 0$  and  $w = 0$ . The remaining two equations become

$$\begin{aligned} \lambda x &= -\beta_2 s z - \beta_2 x i_2 - \mu x + \alpha_2 z \\ \lambda z &= \beta_2 s z + \beta_2 i_2 x - (\mu + \alpha_2) z \end{aligned} \tag{5.17}$$

We express  $x$  from the first equation

$$x = \frac{(-\beta_2 s + \alpha_2)z}{\lambda + \mu + \beta_2 i_2}$$

and substitute in the equation for  $z$ . Assuming that  $z$  is nonzero, we cancel it to obtain the following characteristic equation

$$(\lambda + \mu)(\lambda + \mu + \alpha_2 + \beta_2 i_2 - \beta_2 s) = 0$$

Noticing that  $\beta_2 s = \mu + \alpha_2$  we obtain the following eigenvalues  $-\mu$  and  $-\beta_2 i_2$  which are both negative. Consequently, the equilibrium  $\mathcal{E}_2$  is locally asymptotically stable. This concludes the proof.  $\diamond$

**5.4. Loss of stability of a coexistence equilibrium - oscillatory coexistence.** The stability of the coexistence equilibria depends on the analysis of the perturbation equations (5.1). For the general case, however, it is difficult to derive the corresponding characteristic equation, let alone analyze the positions of its roots. Since the main thrust is that a characteristic equation of this complexity is likely to have roots with positive real part, we address the more interesting and tractable question of whether a Hopf bifurcation of a coexistence equilibrium can occur in the absence of age structure, that is, in the case when  $\beta_1(a) = \beta_1$ ,  $\alpha_1(a) = \alpha_1$  and  $\delta(a) = \delta$ . We established that in the constant coefficient case the two dominance equilibria are locally stable. Some additional but simple argument shows that in the absence of the second disease, the solutions converge to the dominance equilibrium, provided the reproduction number is larger than one and no oscillations are possible. Thus, if a Hopf bifurcation occurs, the loss of stability of the coexistence equilibrium is due to the presence of the competitor.

It turns out that a Hopf bifurcation of the coexistence equilibrium occurs for a limiting and much simpler form of the original system (2.1) taken with constant coefficients corresponding to  $\alpha_1 = \alpha_2 = \gamma_1 = \nu = 0$ . Since  $\nu = 0$ , the total population size is asymptotically constant  $N(t) \rightarrow \frac{\Lambda}{\mu} = N^*$ . We will restrict our analysis to this invariant subspace [21]. We further rescale all state variables by  $1/N^*$  and consider the system:

$$\begin{aligned} i_1' &= \beta_1 s i_1 - \mu i_1 - \delta i_1 i_2, \\ i_2' &= \beta_2 s i_2 + \gamma_2 s j - \mu i_2, \\ j' &= \delta i_1 i_2 - \mu j, \end{aligned} \quad (5.18)$$

where  $s \equiv 1 - i_1 - i_2 - j$ . We establish the existence of Hopf bifurcation for values of the parameters satisfying the inequalities:  $\beta_2 < \mu < \beta_1 < \gamma_2$ . In this case, we have that

$$\mathcal{R}_1 = \frac{\beta_1}{\mu} > 1 > \frac{\beta_2}{\mu} = \mathcal{R}_2,$$

which implies that  $\mathcal{E}_2$  does not exist, and the secondary disease alone is always eliminated. Hence, the coexistence of both diseases must be mediated by the presence of the competitor, that is, the primary disease.

It is convenient to fix the parameters  $\mu$ ,  $\beta_1$ ,  $\beta_2$  and  $\gamma_2$  and treat  $\delta$  as a bifurcation parameter. Solving for positive coexistence equilibria we find:

$$s = \frac{\mu\gamma_2 + \gamma_2\delta - \beta_1\mu}{\gamma_2(\delta + \beta_1) - \beta_1\beta_2} \quad i_1 = \frac{\mu^2 - \beta_2\mu s}{\gamma_2\delta s} \quad i_2 = \frac{\beta_1 s - \mu}{\delta} \quad j = \frac{\delta i_1 i_2}{\mu}$$

Under the above conditions  $s$  and  $i_1$  are automatically positive. The value of  $i_2$  is positive if and only if  $\delta > \delta^*$  where

$$\delta^* = \frac{\mu\beta_1(\beta_1 - \beta_2)}{\gamma_2(\beta_1 - \mu)}$$

Since we consider  $\delta$  as a bifurcation parameter, we view the values of the positive equilibrium as functions of delta:  $s = s(\delta)$ ,  $i_1 = i_1(\delta)$ ,  $i_2 = i_2(\delta)$ ,  $j = j(\delta)$ . The variational matrix of the system (5.18) at the positive equilibrium  $(i_1, i_2, j)$  is given by

$$A(\delta) = \begin{pmatrix} -\beta_1 i_1 & -(\beta_1 + \delta) i_1 & -\beta_1 i_1 \\ -\beta_2 i_2 - \gamma_2 j & \beta_2 s - \mu - \beta_2 i_2 - \gamma_2 j & \gamma_2(s - j) - \beta_2 i_2 \\ \delta i_1 & \delta i_1 & -\mu \end{pmatrix}. \quad (5.19)$$

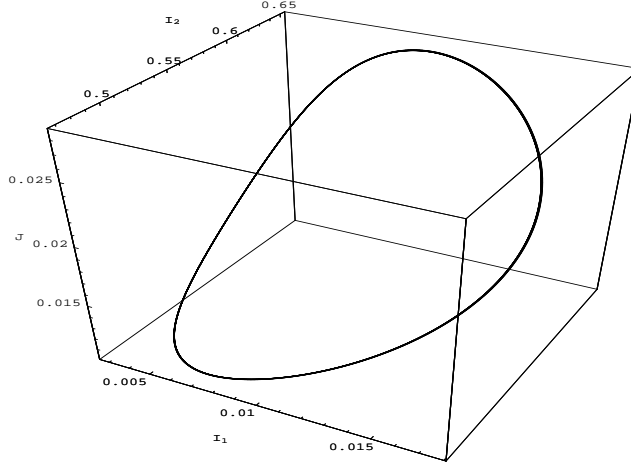


FIG. 5.2. *Existence of periodic orbit for the age-independent case. Values of parameters as in the text.*

Calculating the determinant of  $A(\delta)$  we find that  $\det A(\delta) = \delta i_1 i_2 [\beta_1 \mu - \gamma_2 (\mu + \delta)]$ . Hence,  $\det A(\delta) < 0$  whenever  $\delta > \delta^*$  (since then  $i_2 > 0$ ). Since  $s(\delta^*) = \frac{\mu}{\beta_1}$ ,  $i_1(\delta^*) = 1 - \frac{\mu}{\beta_1}$ , and  $i_2(\delta^*) = j(\delta^*) = 0$ , we have that

$$A(\delta^*) = \begin{pmatrix} \mu - \beta_1 & (\beta_1 + \delta) \frac{\mu - \beta_1}{\beta_1} & \mu - \beta_1 \\ 0 & \left( \frac{\beta_2}{\beta_1} - 1 \right) \mu & \frac{\gamma_2 \mu}{\beta_1} \\ 0 & \delta^* \frac{\beta_1 - \mu}{\beta_1} & -\mu \end{pmatrix}.$$

The eigenvalues of  $A(\delta^*)$  are given by  $\lambda_1 = \mu - \beta_1 < 0$ ,  $\lambda_2 = \left( \frac{\beta_2}{\beta_1} - 2 \right) \mu < 0$ ,  $\lambda_3 = 0$ . Using the continuity of eigenvalues with respect to  $\delta$ , we conclude that  $A(\delta)$  has three negative eigenvalues when  $\delta$  is slightly greater than  $\delta^*$ . Hence, the positive equilibrium is stable for "small"  $\delta > \delta^*$ .

Next we argue that the positive equilibrium is unstable for sufficiently large values of  $\delta$ . First we notice that  $\lim_{\delta \rightarrow \infty} s(\delta) = 1$ . Furthermore,

$$\lim_{\delta \rightarrow \infty} \delta i_1(\delta) = \frac{\mu^2 - \beta_2 \mu}{\gamma_2}, \quad \lim_{\delta \rightarrow \infty} \delta i_2(\delta) = \beta_1 - \mu, \quad \lim_{\delta \rightarrow \infty} j(\delta) = 0.$$

Thus, we have that

$$\lim_{\delta \rightarrow \infty} A(\delta) = A_\infty = \begin{pmatrix} 0 & -\frac{\mu^2 - \beta_2 \mu}{\gamma_2} & 0 \\ 0 & \beta_2 - \mu & \gamma_2 \\ \beta_1 - \mu & \frac{\mu^2 - \beta_2 \mu}{\gamma_2} & -\mu \end{pmatrix}.$$

The characteristic polynomial of  $A_\infty$  has the form

$$p_\infty(\lambda) = \lambda^3 + (2\mu - \beta_2)\lambda^2 + (\beta_1 - \mu)(\mu^2 - \beta_2 \mu).$$

Since  $2\mu - \beta_2 > 0$  and  $(\beta_1 - \mu)(\mu^2 - \beta_2 \mu) > 0$ ,  $p_\infty(\lambda)$  has one real negative and two complex roots with positive real parts. We conclude that the positive equilibrium

changes stability as we increase  $\delta$ . Since the determinant of the variational matrix remains negative for all  $\delta > \delta^*$ , the change of stability corresponds to a Hopf bifurcation. The rigorous analysis of this bifurcation is outside of the scope of this paper.

A continuation argument can establish that this bifurcation must also occur when the parameters  $\alpha_1, \alpha_2, \gamma_1$  and  $\nu$  are small and positive. In Figure 5.2 we demonstrate the presence of oscillatory coexistence when  $\alpha_1, \alpha_2$  and  $\gamma_1$  are small and positive. The figure shows a periodic orbit in the three dimensional space of the variables  $I_1(t), I_2(t)$  and  $J(t)$ . In this example the parameter values are taken as  $\beta_1 = 10, \beta_2 = 0.2, \alpha_1 = 1, \alpha_2 = 0.1, \mu = 1, \delta = 4, \nu = 0, \gamma_1 = 0.1, \gamma_2 = 80, \Lambda = 1$ . Since  $\frac{\Delta}{\mu} = 1$  the values of  $I_1, I_2$  and  $J$  are also the values of the proportions. The reproduction number of the primary disease is  $\mathcal{R}_1 = 5$  while the reproduction number of the secondary disease is below one  $\mathcal{R}_2 = 0.18182$ . Despite the fact that  $\mathcal{R}_1 \gg \mathcal{R}_2$  the prevalence for the secondary disease  $I_2$  is much higher than that of the primary disease  $I_1$  – a result of the very high rate at which the jointly infected individuals can infect with the secondary disease  $\gamma_2 = 80$ .

**6. Backward bifurcation.** In this section we analyze the existence of backward bifurcations in the system (2.1). In the single disease case, a backward bifurcation occurs when the equilibrium number (or proportion) of infectives bifurcates at the critical value of the reproduction number  $\mathcal{R} = 1$  not forward but backward and there are nontrivial equilibria when the reproduction number is below one.

In the case of two diseases, an analogous phenomenon occurs when the equilibrium number (or proportion) of infectives with each disease  $i_1$  and  $i_2$  bifurcates backward in both parameters  $\mathcal{R}_1$  and  $\mathcal{R}_2$ , and nontrivial equilibria exist for values of both reproduction numbers below one. We will call this phenomenon *a two-parameter backward bifurcation*. In what follows we derive necessary and sufficient conditions for two-parameter backward bifurcation.

We treat  $\beta_1(a)$  and  $\beta_2$  (equivalently  $\mathcal{R}_1$  and  $\mathcal{R}_2$ ) as bifurcation parameters and assume that all other parameters are fixed. Specifically, we define

$$\beta_1(a, \varepsilon_1) = \tilde{\beta}_1(a)(1 + \varepsilon_1 \tilde{v}_1(a)), \quad \beta_2(\varepsilon_2) = \tilde{\beta}_2(1 + \varepsilon_2),$$

so that  $\tilde{\beta}_2 = \alpha_2 + \mu$  and the functions  $\tilde{\beta}_1(a)$  and  $\tilde{v}_1(a)$  are normalized as follows,

$$\int_0^\infty \tilde{\beta}_1(a) \pi_1(a) e^{-\mu a} da = \int_0^\infty \tilde{\beta}_1(a) \tilde{v}_1(a) \pi_1(a) e^{-\mu a} da = 1.$$

In this setting, the choice  $\varepsilon_1 = \varepsilon_2 = 0$  corresponds to the basic reproduction numbers of both strains being equal to unity, that is,  $\mathcal{R}_1 = \mathcal{R}_2 = 1$ . We also introduce the auxiliary functions

$$B(i_2, \varepsilon_1) = \int_0^\infty \tilde{\beta}_1(a)(1 + \varepsilon_1 \tilde{v}_1(a)) \Gamma(a; i_2) \pi_1(a) e^{-\mu a} da, \quad (6.1)$$

$$G(i_2) = \int_0^\infty \Gamma(a; i_2) \pi_1(a) e^{-\mu a} da. \quad (6.2)$$

where  $\Gamma(a; i_2)$  is given by (3.3). Previously, we have shown that the fraction of susceptible individuals at the coexistence equilibrium must equal

$$s = \left( B(i_2, \varepsilon_1) + \frac{\gamma_1 i_2 D(i_2)}{\mu + \nu} \right)^{-1} = S(i_2, \varepsilon_1),$$

where  $i_2$  is the fraction of individuals infected by secondary infection. Solving for  $i(0)$ , we find that

$$i(0) = (\mu + \nu)(\mu + \alpha_2) \frac{1 - (1 + \varepsilon_2)S(i_2, \varepsilon_1)}{\gamma_2 S(i_2, \varepsilon_1) D(i_2)} = T(i_2, \varepsilon_1, \varepsilon_2),$$

and thus the total fraction of individuals infected by primary infection is given by  $i_1 = G(i_2)T(i_2, \varepsilon_1, \varepsilon_2)$ . The fraction of individuals carrying both infections can be expressed as

$$j = \frac{i_2 D(i_2) T(i_2, \varepsilon_1, \varepsilon_2)}{\mu + \nu}.$$

The relation  $s + i_1 + i_2 + j = 1$  now can be written as

$$M(i_2, \varepsilon_1, \varepsilon_2) = i_2 + S(i_2, \varepsilon_1) + G(i_2)T(i_2, \varepsilon_1, \varepsilon_2) + \frac{i_2 D(i_2) T(i_2, \varepsilon_1, \varepsilon_2)}{\mu + \nu} = 1.$$

Since

$$S(0, 0) = \frac{1}{B(0, 0)} = \left( \int_0^\infty \tilde{\beta}_1(a) \pi_1(a) e^{-\mu a} da \right)^{-1} = 1,$$

we find that  $T(0, 0, 0) = 0$  and  $M(0, 0, 0) = 1$ . For a given pair  $(\varepsilon_1, \varepsilon_2)$ , we define the equilibrium values of  $i_2(\varepsilon_1, \varepsilon_2)$  as an implicit solution of the equation  $M(i_2, \varepsilon_1, \varepsilon_2) = 1$ . The corresponding equilibrium values  $i_1(\varepsilon_1, \varepsilon_2)$  are obtained from  $i_1 = G(i_2)T(i_2, \varepsilon_1, \varepsilon_2)$ . The backward bifurcation occurs whenever both functions  $i_1(\varepsilon_1, \varepsilon_2)$  and  $i_2(\varepsilon_1, \varepsilon_2)$  have positive values for (perhaps some)  $\varepsilon_1, \varepsilon_2 < 0$ . To pose the conditions for backward bifurcation we need all partial derivatives  $\frac{\partial i_m}{\partial \varepsilon_n}(0, 0)$ , where  $m, n = 1, 2$ .

We compute the required partial derivatives. First, we have

$$\frac{\partial B}{\partial i_2}(0, 0) = - \int_0^\infty \tilde{\beta}_1(a) \pi_1(a) e^{-\mu a} \left( \int_0^a \delta(s) ds \right) da = -\hat{\delta} < 0,$$

Next, if we define

$$\sigma = \hat{\delta} - \frac{\gamma_1 D(0)}{\mu + \nu}, \quad \tau = \frac{(\mu + \nu)(\mu + \alpha_2)}{\gamma_2 D(0)},$$

then the remaining partial derivatives are given by

$$\begin{aligned} \frac{\partial S}{\partial \varepsilon_1}(0, 0) &= -1, \quad \frac{\partial S}{\partial i_2}(0, 0) = \sigma, \quad \frac{\partial T}{\partial \varepsilon_1}(0, 0, 0) = \tau, \\ \frac{\partial T}{\partial \varepsilon_2}(0, 0, 0) &= -\tau, \quad \frac{\partial T}{\partial i_2}(0, 0, 0) = -\tau\sigma. \end{aligned}$$

Finally, we have that

$$\begin{aligned} \frac{\partial M}{\partial i_2}(0, 0, 0) &= 1 + (1 - G(0)\tau)\sigma, \\ \frac{\partial M}{\partial \varepsilon_1}(0, 0, 0) &= -1 + G(0)\tau, \quad \frac{\partial M}{\partial \varepsilon_2}(0, 0, 0) = -G(0)\tau. \end{aligned} \tag{6.3}$$

Using the Implicit Function Theorem, we find the derivatives of  $i_2$  and as a result – those of  $i_1$

$$\frac{\partial i_2}{\partial \varepsilon_1}(0, 0) = \frac{1 - G(0)\tau}{1 + (1 - G(0)\tau)\sigma}, \quad \frac{\partial i_1}{\partial \varepsilon_1}(0, 0) = \frac{G(0)\tau}{1 + (1 - G(0)\tau)\sigma}, \tag{6.4}$$

$$\frac{\partial i_2}{\partial \varepsilon_2}(0, 0) = \frac{G(0)\tau}{1 + (1 - G(0)\tau)\sigma}, \quad \frac{\partial i_1}{\partial \varepsilon_2}(0, 0) = \frac{-G(0)\tau(1 + \sigma)}{1 + (1 - G(0)\tau)\sigma}. \tag{6.5}$$

Since  $G(0)\tau > 0$ , all of these partial derivatives are negative if and only if

$$1 + (1 - G(0)\tau)\sigma < 0, \text{ and } 1 - G(0)\tau > 0. \quad (6.6)$$

Note that (6.6) enforces  $\sigma < -1$ .

Since we consider a two-parameter bifurcation it may occur for all pairs  $(\varepsilon_1, \varepsilon_2)$  or only for some pairs  $(\varepsilon_1, \varepsilon_2)$ . We will call a backward bifurcation *total* if the positive equilibrium exists for *all* pairs  $(\varepsilon_1, \varepsilon_2)$  with sufficiently small  $\varepsilon_k < 0$ ,  $k = 1, 2$ . We will call a backward bifurcation *partial* if the positive equilibrium exists for *some* pairs  $(\varepsilon_1, \varepsilon_2)$  with sufficiently small  $\varepsilon_k < 0$ ,  $k = 1, 2$ . In what follows, we argue that the model (2.1) admits only total backward bifurcations.

Indeed, a partial backward bifurcation occurs if and only if there exist pairs of positive numbers  $(\omega_1, \omega_2)$  such that

$$\begin{aligned} \omega_1 \frac{\partial i_1}{\partial \varepsilon_1}(0, 0) + \omega_2 \frac{\partial i_1}{\partial \varepsilon_2}(0, 0) &< 0, \\ \omega_1 \frac{\partial i_2}{\partial \varepsilon_1}(0, 0) + \omega_2 \frac{\partial i_2}{\partial \varepsilon_2}(0, 0) &< 0. \end{aligned}$$

In contrast, total backward bifurcation occurs if the above inequalities are valid for all pairs of nonnegative numbers  $(\omega_1, \omega_2)$ . These inequalities are equivalent to

$$\frac{(1 - G(0)\tau) + \omega G(0)\tau}{1 + (1 - G(0)\tau)\sigma} < 0, \quad (6.7)$$

$$\frac{G(0)\tau(1 - \omega(1 + \sigma))}{1 + (1 - G(0)\tau)\sigma} < 0, \quad (6.8)$$

where  $\omega = \omega_2/\omega_1 > 0$  (we assume  $\omega_1 > 0$ ). We also note that  $G(0)\tau > 0$ .

Suppose that  $1 + (1 - G(0)\tau)\sigma > 0$ . Then (6.7-6.8) imply that  $\sigma > -1$  and

$$\frac{1}{1 + \sigma} < \omega < \frac{G(0)\tau - 1}{G(0)\tau},$$

and thus  $G(0)\tau < (G(0)\tau - 1)(1 + \sigma)$ . The last inequality clearly contradicts  $1 + (1 - G(0)\tau)\sigma > 0$ . No backward bifurcations occur in this case.

Now suppose that  $1 + (1 - G(0)\tau)\sigma < 0$ . Then (6.7-6.8) imply that

$$\omega > \frac{G(0)\tau - 1}{G(0)\tau}, \quad 1 - \omega(1 + \sigma) > 0.$$

If  $1 + \sigma > 0$ , then the second inequality implies that

$$\frac{G(0)\tau - 1}{G(0)\tau} < \omega < \frac{1}{1 + \sigma},$$

and thus  $G(0)\tau > (G(0)\tau - 1)(1 + \sigma)$  which is a contradiction. If  $1 + \sigma < 0$ , then  $1 - \omega(1 + \sigma) > 0$  holds for all  $\omega > 0$ . On the other hand, we must have that  $\sigma < 0$  and

$$G(0)\tau < \frac{1 + \sigma}{\sigma} < 1.$$

Therefore,  $(1 - G(0)\tau) + \omega G(0)\tau > 0$  also holds for all  $\omega \geq 0$ . In this case, the backward bifurcation is total. We conclude that only total backward bifurcations

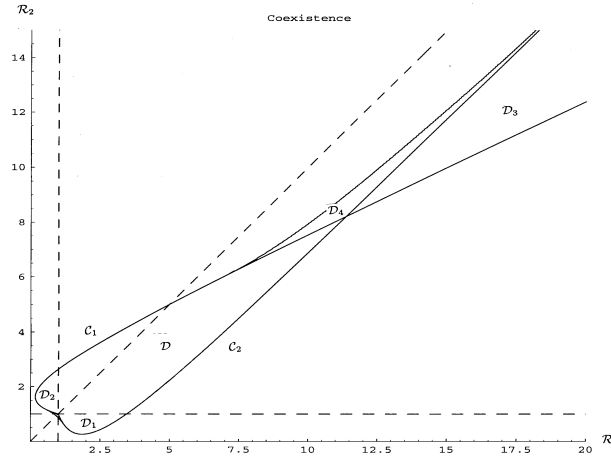


FIG. 7.1. Boundaries of coexistence and stability of dominance equilibria. Parameters as in text.

may occur in this model and the criterion is given by (6.6). We summarize this result in the following Proposition.

**PROPOSITION 6.1.** *The model (2.1) exhibits the backward bifurcation if and only if*

$$1 + (1 - G(0)\tau)\sigma < 0, \text{ and } 1 - G(0)\tau > 0. \quad (6.9)$$

*If at least one of the inequalities in (6.9) does not hold, then the model (2.1) does not admit any nontrivial equilibria with  $\mathcal{R}_1, \mathcal{R}_2 < 1$ . If both inequalities in (6.9) hold, then the backward bifurcation is total, that is, there exists a sufficiently small  $0 < \varepsilon_0 < 1$  such that the model (2.1) admits nontrivial equilibria for all pairs of the reproduction numbers  $(\mathcal{R}_1, \mathcal{R}_2)$  such that  $1 - \varepsilon_0 < \mathcal{R}_1, \mathcal{R}_2 < 1$ .*

**7. Numerical results.** In this section we consider several types of complex behavior which stem largely from the presence of coinfection. These regimes have important consequences for the development and eradication of one or both diseases.

We consider the following phenomena: subthreshold coexistence equilibria, multiple coexistence equilibria and bistable dominance. Subthreshold coexistence equilibria may be generated by two-parameter backward bifurcation. These are multiple coexistence equilibria (two in our case), but multiple coexistence equilibria may also exist superthreshold. Finally we consider the bistability of the dominance equilibria which is defined as dominance of one of the diseases depending on the initial conditions. All these are illustrated in Figure 7.1. The Figure is generated with the following values of the parameters:  $\alpha_1 = 14$ ,  $\alpha_2 = 25$ ,  $\mu = 3.9$ ,  $\nu = 0.1$ ,  $\delta = 20$ ,  $\gamma_1 = 20$ ,  $\gamma_2 = 20$ . The values of  $\mathcal{R}_1$  and  $\mathcal{R}_2$  are treated as operating parameters that are directly related to the values of  $\beta_1$  and  $\beta_2$ . In this section, we only consider the case where  $\beta_1(a) \equiv \beta_1$  is age-independent. The values of  $\mathcal{R}_1$  and  $\mathcal{R}_2$  are plotted on the  $x$  and  $y$  axis, respectively. The upper of the two curves that originate at  $(1,1)$  is obtained from the equation  $\hat{\mathcal{R}}_1 = 1$  while the lower is obtained from the equation  $\hat{\mathcal{R}}_2 = 1$ . We denote these curves by  $\mathcal{C}_1$  and  $\mathcal{C}_2$ , respectively. The geometry of these curves was analyzed in Lemma 3.1.

**7.1. Backward bifurcation and subthreshold equilibria.** The presence of subthreshold equilibria has important implications for the control of a single disease. It means that the disease might not be eradicated by reducing its reproduction number slightly below one. Instead, it is necessary to reduce the reproduction number below the minimal transition value  $\mathcal{R}^*$  such that there are no nontrivial equilibria for values of the reproduction number below  $\mathcal{R}^*$ .

When multiple diseases are present the situation is more complex. We call a coexistence equilibrium *subthreshold* if it occurs when at least one of the reproduction numbers is below one. Furthermore, there are two distinct cases with different consequences for the control of the diseases. In the first scenario, coexistence equilibria occur when exactly one of the reproduction number is below one. We will call those *weakly subthreshold* equilibria. In the Figure 7.1 weakly subthreshold coexistence equilibria occur both in the case  $\mathcal{R}_1 < 1$ ,  $\mathcal{R}_2 > 1$  and in the case  $\mathcal{R}_1 > 1$ ,  $\mathcal{R}_2 < 1$ . Those are to be found to the right of the curve  $\mathcal{C}_1$  but to the left of the line  $\mathcal{R}_1 = 1$  (Figure 7.1, region  $\mathcal{D}_2$ ) and above the curve  $\mathcal{C}_2$  but below the line  $\mathcal{R}_2 = 1$  correspondingly (Figure 7.1, region  $\mathcal{D}_1$ ). Given coinfection  $\delta \neq 0$ , a necessary condition for the first area to be non-empty is that  $\gamma_1 \neq 0$ ; similarly, the second area can be nonempty only if  $\gamma_2 \neq 0$ . In both of these areas there is a unique coexistence equilibrium not obtained as a result of a backward bifurcation. In terms of disease control the presence of weakly subthreshold equilibria leads to the fact that reducing only one of the reproduction numbers below unity does not necessarily lead to the disappearance of the corresponding disease. Thus, eradicating only one of the two diseases may be difficult particularly as the curves  $\mathcal{C}_1$  and  $\mathcal{C}_2$  pass very close to the corresponding axes. However, if both reproduction numbers are brought slightly below unity both diseases will be eliminated. We note here that we may only have weakly subthreshold coexistence equilibria with  $\mathcal{R}_1 < 1$ ,  $\mathcal{R}_2 > 1$  without having such with  $\mathcal{R}_1 > 1$ ,  $\mathcal{R}_2 < 1$  or vice versa (not shown). In this case only the primary disease cannot be eliminated by reducing  $\mathcal{R}_1$  below one while the secondary will be if  $\mathcal{R}_2$  is reduced below one. Weakly subthreshold equilibria also appear as a consequence of backward bifurcation (see Figure 7.2) and are discussed more in the next subsection.

In the second scenario, coexistence equilibria occur when both of the reproduction numbers are below one. We call those *strongly subthreshold* coexistence equilibria. Strongly subthreshold equilibria in our model are a result of a backward bifurcation in two parameters, namely  $\mathcal{R}_1$  and  $\mathcal{R}_2$ . We established necessary and sufficient conditions for the two-parameter backward bifurcation in the previous section. If we consider  $J^*$  as the coexistence variable and we view it as a function of  $\mathcal{R}_1$  and  $\mathcal{R}_2$ , then the surface  $J^* = f(\mathcal{R}_1, \mathcal{R}_2)$  bifurcates backwards along the curves  $\mathcal{C}_1$  and  $\mathcal{C}_2$  near the critical point  $(1, 1)$  and then turns around and heads in the direction of increasing values of  $\mathcal{R}_1$  and  $\mathcal{R}_2$ . The projection of the turning curve on the plane  $(\mathcal{R}_1, \mathcal{R}_2)$  is the curve that connects  $\mathcal{C}_1$  and  $\mathcal{C}_2$  (see Figure 7.2, region  $\mathcal{S} = \mathcal{S}_1 \cup \mathcal{S}_2 \cup \mathcal{S}_3$ ). In analogy with the single disease case, we will call this curve *minimal transition curve*. In Figure 7.2 the area enclosed by the curves  $\mathcal{C}_1$ ,  $\mathcal{C}_2$  and the minimal transition curve,  $\mathcal{S}$ , is the projection of the overlapping branches of the surface  $J^* = f(\mathcal{R}_1, \mathcal{R}_2)$ . Thus, in this area there are two distinct coexistence equilibria. Figure 7.2 is a zoom in of the part of Figure 7.1 near the critical point  $(1, 1)$ .

Next, we show that backward bifurcation occurs if and only if the angle between the tangent lines to the curves  $\mathcal{C}_1$  and  $\mathcal{C}_2$  (see Figure 7.1) at the point  $(1, 1)$  is sufficiently small - smaller than  $180^\circ$ . Let  $l_1$  be the tangent to  $\mathcal{C}_1$  with slope  $m_1$  and  $l_2$  be the tangent to the curve  $\mathcal{C}_2$  with slope  $m_2$ . Along the curve  $\mathcal{C}_1$  we have



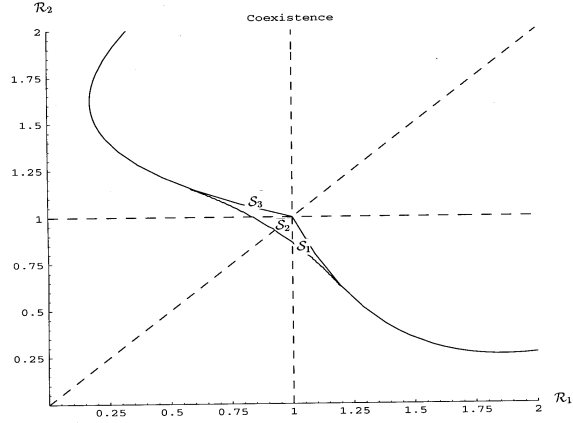


FIG. 7.2. This is a zoom in of the area from Figure 7.1 near the critical point where both reproduction numbers are near one.

$i_1(\varepsilon_1, \varepsilon_2) = 0$ . Along the curve  $\mathcal{C}_2$  we have  $i_2(\varepsilon_1, \varepsilon_2) = 0$ . The slopes of  $l_1$  and  $l_2$  are given by  $\frac{d\varepsilon_2}{d\varepsilon_1}$  which is obtained for each curve by differentiating implicitly. Thus,

$$m_1 = \frac{1}{1 + \sigma} \quad m_2 = -\frac{1 - G(0)\tau}{G(0)\tau}.$$

The angle between the tangents is obtuse if  $m_2 < m_1 < 0$ . The angle between the tangents is larger than  $180^\circ$  and backward bifurcation does not occur if  $m_1 < m_2 < 0$ . Consequently, the conditions for the angle to be obtuse is

$$\frac{G(0)\tau - 1}{G(0)\tau} < \frac{1}{1 + \sigma} < 0.$$

It is easy to see that these inequalities are equivalent to the inequalities (6.9).

The fact that backward bifurcation occurs only if the angle between the tangent lines of the curves  $\mathcal{C}_1$  and  $\mathcal{C}_2$  at the point  $(1, 1)$  is obtuse implies that strongly subthreshold coexistence equilibria are present only in conjunction with both types of weakly subthreshold coexistence equilibria. Thus, the existence of strongly subthreshold coexistence equilibria through two-parameter backward bifurcation is the analogue of the backward bifurcation in the single-disease case. It has the same implication for the disease control - reducing both reproduction numbers slightly below one does not lead to the eradication of either disease. It is necessary to reduce both reproduction numbers in the square  $[0, 1] \times [0, 1]$  below the minimal transition curve.

**7.2. Multiple coexistence equilibria. Bistability.** The presence of multiple equilibria, and particularly, of multiple stable equilibria can have significant impact on the outcome of the disease as for a fixed set of parameters this outcome depends on the initial status of the population. For the present model and parameter values as in Figure 7.1 results in previous sections and simulations suggested the presence of multiple coexistence equilibria in two areas.

The first one is the subthreshold area  $\mathcal{S}$  illustrated also in Figure 7.2. As we discussed above the multiple equilibria there are obtained from backward bifurcation.

In this case there are two coexistence equilibria. If they are ordered in increasing order of  $J^*$ , simulations suggest that the lower one is unstable while the upper one is locally stable. In the subregion  $\mathcal{S}_2$  there is also the disease-free equilibrium which is locally stable. Thus, in that part the two diseases might coexist or they might both disappear depending on the initial conditions. Looking at Figure 7.2 we see that the area of backward bifurcation overlaps also with the regions  $\mathcal{R}_1 > 1$ ,  $\mathcal{R}_2 < 1$  forming region  $\mathcal{S}_1$  and  $\mathcal{R}_1 < 1$ ,  $\mathcal{R}_2 > 1$  forming region  $\mathcal{S}_3$ . Consequently we have multiple weakly subthreshold coexistence equilibria. In those regions the disease-free equilibrium is unstable. However, in addition to the locally stable coexistence equilibrium, in the region  $\mathcal{S}_1$  the equilibrium  $\mathcal{E}_1$  is also locally stable while in the second region  $\mathcal{S}_3$  the equilibrium  $\mathcal{E}_2$  is also locally stable. Thus, the ultimate outcome is either dominance of one of the diseases or coexistence depending on the initial conditions.

The second area where multiple coexistence equilibria exist is the superthreshold area in Figure 7.1 where the curves  $\mathcal{C}_1$  and  $\mathcal{C}_2$  cross and a third curve that touches both of them forming a curvilinear triangle, denoted by  $\mathcal{D}_4$ . There are two coexistence equilibria in that area, the lower one there is stable while the upper one is unstable. The disease-free equilibrium is again unstable. Both dominance equilibria  $\mathcal{E}_1$  and  $\mathcal{E}_2$  exist; however,  $\mathcal{E}_1$  is unstable and  $\mathcal{E}_2$  is locally stable. Consequently, if the combination of the reproduction numbers forms a point in that area, there are two possible outcomes for the long-term dynamics of the diseases - dominance of the secondary disease or coexistence. Which of the two will materialize depends on the initial status of the population.

A unique coexistence equilibrium exists in the area  $\mathcal{D}$  between the curves  $\mathcal{C}_1$  and  $\mathcal{C}_2$  which for most parameter values is locally stable. When it loses stability oscillatory coexistence occurs.

**7.3. Bistable dominance.** One of distinctive features of this model is that the two curves that define the boundaries of stability of the dominance equilibria  $\mathcal{E}_1$  and  $\mathcal{E}_2$  always intersect (see Lemma 3.1 for details).

In the constant coefficient case, there is a unique intersection of the curves  $\mathcal{C}_1$  and  $\mathcal{C}_2$  that occurs at the point  $(\mathcal{R}_1^*, \mathcal{R}_2^*)$  where  $\mathcal{R}_1^* > 1$  and  $\mathcal{R}_2^* > 1$ . This intersection creates a region between the curves  $\mathcal{C}_1$  and  $\mathcal{C}_2$  with  $\mathcal{R}_1 > \mathcal{R}_1^*$  and  $\mathcal{R}_2 > \mathcal{R}_2^*$  (see Figure 7.1, area  $\mathcal{D}_3$ ) where both dominance equilibria  $\mathcal{E}_1$  and  $\mathcal{E}_2$  are locally stable and the outcome of the competition between the diseases depends on the initial conditions. In other words, based only on the parameters values we cannot predict which disease will persist in the population. Figures 7.3 and 8.1 show the possible outcomes with two sets of initial conditions which differ only in the value of  $J_0$ . In the first figure  $J_0 = 0.05$ , while in the second  $J_0 = 0.04$ .

The curve  $\mathcal{C}_1$  will not cross below the diagonal if  $\gamma_1 = 0$ , given there is coinfection ( $\delta \neq 0$ ). Thus the bistable dominance occurs as a result of the possibility that the jointly infected individuals can infect with the primary disease  $\gamma_1 \neq 0$ .

**8. Discussion.** At any given time thousands of diseases cocirculate in a population. Many of them participate in joint infections of a single host. New diseases like SARS appear, others fade only to re-emerge later with strains that are more difficult to treat. The complexity of interactions of the diseases through the host population can have a significant impact on the dynamics and management of each disease.

In this paper we introduce and investigate a simple epidemiological model with two diseases that can coinfect a single host. We compute the reproduction numbers and the invasion reproduction numbers of both diseases. We observe a variety of complex dynamic phenomena with significant consequences for disease control.

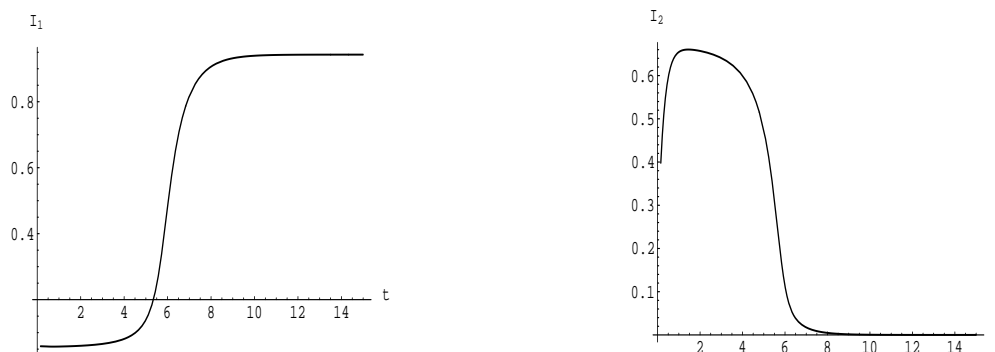


FIG. 7.3. *Primary disease persists, secondary disease dies out. Parameters are as in Figure 7.1 with  $\mathcal{R}_1 = 17.5$  and  $\mathcal{R}_2 = 12$  (from region  $\mathcal{D}_3$ ). Initial conditions are  $S_0 = 0.2$ ,  $I_1(0) = 0.01$ ,  $I_2(0) = 0.05$ ,  $J_0 = 0.05$ .*

**1. Cooperative subthreshold coexistence.** First, we establish that the dominance equilibria  $\mathcal{E}_1$  and  $\mathcal{E}_2$  are present only if  $\mathcal{R}_1 > 1$  and  $\mathcal{R}_2 > 1$  correspondingly. That implies that neither disease can exist by itself when its reproduction number is below one. However, the “cooperation” of the two leads to subthreshold coexistence. Consequently, both diseases can persist concurrently for values of the reproduction numbers below one. We call this phenomenon *cooperative subthreshold coexistence*. We show two types of cooperative subthreshold coexistence - weakly subthreshold coexistence (occurs when exactly one of the reproduction numbers is below one) and strongly subthreshold coexistence (occurs when both reproduction numbers are below one). The strongly subthreshold coexistence is a result of backward bifurcation in both  $\mathcal{R}_1$  and  $\mathcal{R}_2$ . Weakly subthreshold coexistence can result from the backward bifurcation or from expansion of the coexistence region between the curves  $\mathcal{C}_1$  and  $\mathcal{C}_2$  to the below threshold areas. We derive necessary and sufficient conditions for existence of backward bifurcation. We show that the bifurcation is always *total*, that is, it occurs for all pairs of  $(\mathcal{R}_1, \mathcal{R}_2)$  which are close to  $(1, 1)$ . A sufficient condition for backward bifurcation is that the angle between the tangents to those curves at the critical point  $(1, 1)$  is obtuse which occurs if both  $\gamma_1$  and  $\gamma_2$  are large. We establish that  $\gamma_1 = 0$  leads to extinction of the primary disease if  $\mathcal{R}_1 < 1$  and  $\gamma_2 = 0$  with  $\mathcal{R}_2 < 1$  leads to extinction of the secondary disease. No backward bifurcation occurs in this case. One consequence of the observation is that public health mechanisms that lead to reduction of spread of either disease by the jointly infected individuals - like isolating those who are infected with both diseases - can have very dramatic effect on the eradication of one or both diseases. Furthermore, disease induced mortality in the jointly infected class  $\nu$  is a mechanism that impedes the backward bifurcation. This suggests that diseases which are more lethal in a combination, are easier to manage from an epidemiological perspective.

**2. Restricted pathogenic diversity. Bistable dominance.** The dynamics of two diseases is reminiscent of the dynamics of two variants of the same pathogen. In many instances coexistence in stable form occurs in unbounded domains of the parameter space [17]. This is not the case here. The curves  $\mathcal{C}_1$  and  $\mathcal{C}_2$  intersect thus making the region  $\hat{\mathcal{R}}_1 > 1$ ,  $\hat{\mathcal{R}}_2 > 1$  finite (Figure 7.1). We find coexistence in domains outside that one - namely, the area of backward bifurcation (Figure 7.2) and the area of two coexistence equilibria adjacent to the cross-point of  $\mathcal{C}_1$  and  $\mathcal{C}_2$ . It appears from the simulations that these two areas are also finite. Consequently, stable coexistence is

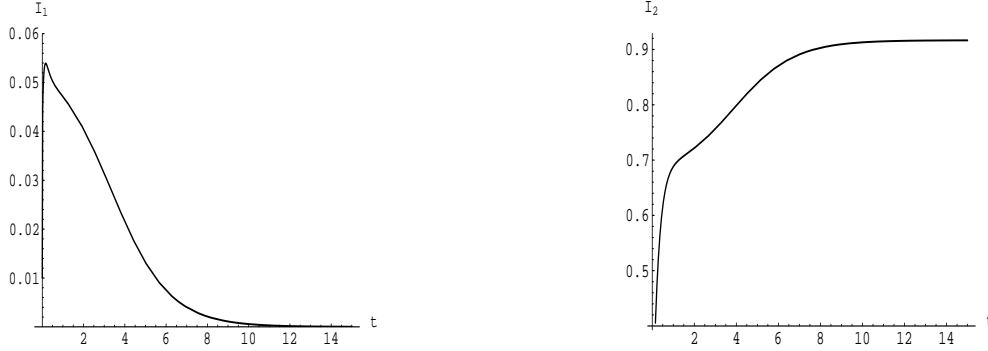


FIG. 8.1. *Primary disease dies out, secondary disease persists. Parameters as in Figure 7.1 with  $\mathcal{R}_1 = 17.5$  and  $\mathcal{R}_2 = 12$  (from region  $\mathcal{D}_3$ ). Initial conditions are  $S_0 = 0.2$ ,  $I_1(0) = 0.01$ ,  $I_2(0) = 0.05$ ,  $J_0 = 0.04$ .*

limited to finite regions in the  $(\mathcal{R}_1, \mathcal{R}_2)$  plane and does not occur if the reproduction numbers are sufficiently large. We call this *restricted pathogenic diversity*. In other words, if evolution maximizes the reproduction numbers, then under this scenario it works against pathogenic diversity. It is interesting to know what mechanisms would lead to such an effect. In our case this is the ability of the jointly infected individuals to spread the primary diseases,  $\gamma_1 \neq 0$ . The intersection of the curves  $\mathcal{C}_1$  and  $\mathcal{C}_2$  also leads to emergence of a region between them where  $\hat{\mathcal{R}}_1 < 1$ ,  $\hat{\mathcal{R}}_2 < 1$ . Simulations suggest that in this region there is still a unique coexistence equilibrium which is unstable. At the same time the two boundary equilibria are both locally stable. A situation like this has been described to occur from a two-sex two-strain model of STD [6]. The result is bistable dominance - which disease persists and which dies out depends on the initial conditions and the outcome can be very sensitive (Figures 7.3 and 8.1). In fact, bistability is somewhat common for the model (2.1). We find it in several regions of the  $(\mathcal{R}_1, \mathcal{R}_2)$  plane, particularly where multiple coexistence equilibria exist. In all remaining cases, however, one of the possible outcomes is stable coexistence, the other is either dominance of one of the diseases or extinction.

**9. Summary.** In this paper, we have analyzed an epidemic model of two diseases with age-since-infection structure in the primary disease. We have obtained the expressions for the basic reproduction numbers  $\mathcal{R}_i$  for both diseases, and showed that the unique primary (resp., secondary) single disease equilibrium exists if and only if  $\mathcal{R}_1 > 1$  (resp.,  $\mathcal{R}_2 > 1$ ). We have also shown that the disease-free equilibrium is locally stable if  $\mathcal{R}_1, \mathcal{R}_2 < 1$ , and unstable if  $\mathcal{R}_i > 1$  for some  $i = 1, 2$  (Proposition 5.1), and obtained sufficient conditions for the extinction of one or both diseases (Section 4).

We have computed the invasion reproduction numbers  $\hat{\mathcal{R}}_i$  for both single disease equilibria. We presented the necessary condition for the local stability of the primary disease equilibrium in Propositions 5.2 and 5.3. In the case of the secondary disease equilibrium, we presented the necessary and sufficient condition for the local stability in Proposition 5.5. In Theorem 3.2, we presented sufficient conditions for the presence of coexistence equilibria. In Proposition 6.1, we showed that multiple coexistence equilibria may exist via the backward bifurcation. In the absence of the age structure, we showed that a coexistence equilibrium can lose stability via a Hopf bifurcation (Section 5.4). In general, the stability of coexistence equilibria remains an open

problem. Finally, we presented results of numerical simulations that illustrate different dynamic outcomes of the interactions between the two diseases.

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