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Subthreshold and superthreshold coexistence of pathogen variants: The impact of host age-structure

Maia Martcheva [a,*], Sergei S. Pilyugin [a], Robert D. Holt [b]

[a] *Department of Mathematics, University of Florida, 358 Little Hall, PO Box 118105, Gainesville, FL 32611–8105, USA*
[b] *Department of Zoology, University of Florida, 620B Bartram Hall, PO Box 118525, Gainesville, FL 32611–8525, USA*

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Abstract

It is well known that in the most general epidemic models with multiple pathogen variants a competitive exclusion principle is valid, such that the variant with the highest reproduction number eliminates the rest. Mechanisms such as super-infection, coinfection, and cross-immunity can lead to pathogen polymorphism where multiple strains coexist. It is also known that variability of infectivity with host age can destabilize the endemic equilibrium and cause oscillations. In this article we show that the hosts' chronological age can itself lead to coexistence of microparasites in the most basic model where competitive exclusion will occur without the age structure. Moreover, the host age-structure leads to multiple subthreshold dominance equilibria, and both weakly and strongly subthreshold coexistence. We find that the two pathogens cannot cooperate to persist subthreshold if neither one of them can persist subthreshold by itself. If, however, one of them can persist subthreshold by itself, it can cause the two pathogens to coexist in a strongly subthreshold equilibrium. The second strain that persists subthreshold through the mediation of the first always has a lower virulence. Our results show that age structure in infectivity can permit the coexistence of competing pathogens when the incidence is of proportionate mixing type (frequency-dependent transmission) and at least one of the strains is virulent.

* Corresponding author. Tel.: +1 917 207 3931; fax: +1 352 392 8357.
E-mail addresses: maia@math.ufl.edu (M. Martcheva), pilyugin@math.ufl.edu (S.S. Pilyugin), rdholt@zoo.ufl.edu (R.D. Holt).

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1. Introduction

Identifying the factors that influence the coexistence of species has been a fundamental goal of the ecological sciences [24] since the early days of G.F. Gause's experiments on protozoan competition ([19, Chapter V]) to current concerns with the maintenance of biodiversity and the classification of coexistence mechanisms (e.g., [13]). Gause's experimental demonstration that in homogeneous, well-mixed systems similar species tended to show competitive exclusion led to the basic concept of competitive exclusion, which in effect says that for species to coexist stably and indefinitely, they must have distinct ecologies, and in particular be regulated by different limiting factors. In practice, what counts as a 'limiting factor' can often be quite difficult to identify. In simple cases, where there is single, unstructured resource of abundance R, the system is spatially closed, and the system settles down to an equilibrium, one can demonstrate simple rules of competitive dominance, such as the R^* rule ([44]; the asterisk denotes equilibrium). Basically, the dominant species in exploitative competition for a single limiting resource is the one that can persist at the lower resource level.

This same issue arises in infectious disease epidemiology, where one of the main questions is to identify the conditions that lead to the coexistence of alternative strains of a given disease agent. As noted in Holt and Dobson [25], there exist various mechanisms that can prevent competitive exclusion and permit coexistence of different pathogen species, corresponding to familiar ecological mechanisms such as keystone predation, niche partitioning [14], and competition-colonization trade-offs. One of the most interesting possible coexistence scenarios involves paying close attention to the detailed pattern of infection dynamics within single host species. Simple SI models in effect assume that all hosts are equivalent with respect to infection and recovery, but realistic populations may exhibit considerable variation in infectivity. The chronological age is a likely factor that may attribute to the differences in contact rates, and the vulnerability to infection via differential immunity ([2], Chapter 9). Differences between pathogen strains in age-specific patterns of infection could potentially permit a single host species to provide multiple limiting resources, permitting coexistence.

In this paper we use a mathematical model to show that the host heterogeneity in age allows for stable coexistence of two pathogen strains competing for a single host species. Such coexistence in some respect resembles niche partitioning, providing coexistence mechanism due to variability in transmission between alternative host species [25]. The variability in transmission, however, in our case is given by host age differentiation. To the best of our knowledge, the influence of the host age on strain coexistence has not been studied to date in mathematical models. An empirical motivation for such an analysis is that various recent studies report a link between the age of the infected individuals and the serotypes (strains) of infection. Host age was found to impact the proportion of certain strains of *Escherichia coli* isolated from individuals [21]. It is suggested that macroparasitic genetic diversity may explain the rise in prevalence and parasite burden with age in childhood with a peak around age of 11 [20]. Different serotypes of *Streptococcus pneumoniae* are viewed to cause infection in children and adults [41]. Finally, a study reports that some serotypes

of *S. pneumoniae* are never found in patients that belong to particular age groups [26]. These field observations provide evidence that the hosts' heterogeneities in age, perhaps through corresponding differences in exposure, infectivity, or immunity, can potentially be related to pathogen genetic diversity.

This paper is structured as follows. In the next section we introduce a two-strain ODE model with proportionate mixing incidence and show that a competitive exclusion principle holds. We then extend the model to include the host age structure by allowing the infectivity of infectious individuals to vary with age. In Section 3 we derive the trivial (disease-free) and semitrivial (dominance) equilibria of the age-structured model. In Section 4 we show that coexistence can occur in the form of a stable equilibrium. The coexistence discussed in Section 4 occurs when the reproduction numbers of both strains are above one, which we will call *superthreshold*. In Section 5 we show that dominance of each strain is possible in the age-structured case even when its corresponding reproduction number is below one (subthreshold). Furthermore we show that coexistence is also possible in the subthreshold case. In Section 6 we summarize our findings and conclusions.

2. A simple age-structured model with two pathogen variants

It is well-known that variability with time-since-infection in host infectivity can cause qualitative changes in the dynamics of infectious diseases [42,43,32] and destabilize the endemic equilibrium while leading to sustained oscillations. Moreover, theoretical studies have identified many mechanisms that lead to the polymorphism of pathogen variants. In this article we put these two themes together by investigating the impact that the host's chronological age heterogeneity has on the maintenance of microorganism genetic diversity. In the case when there is no coexistence, we elucidate the role of several mechanisms related to host age structure that determine which pathogen dominates.

To illustrate these points we consider a simple age-structured epidemiological model with two strains circulating in a population of size $N(t)$. The only interaction between the two pathogens is a purely exploitative competition for the common pool of susceptible individuals $S(t)$; co-infections or super-infections do not occur. The baseline model is of the standard SI type with two pathogen types. The number of hosts infected with the two strains are, respectively, $I(t)$ and $J(t)$. We also assume that an infection of type i is associated with an additional mortality rate of α_i added to a base mortality of $\mu > 0$. In the case when infectivity is constant the competition of the strains is governed by a system of ODEs:

$$\begin{aligned} S'(t) &= B - \lambda_1(t)S(t) - \lambda_2(t)S(t) - \mu S(t), \\ I'(t) &= \lambda_1(t)S(t) - (\mu + \alpha_1)I(t), \\ J'(t) &= \lambda_2(t)S(t) - (\mu + \alpha_2)J(t). \end{aligned} \tag{2.1}$$

In (2.1) we assume that the total birth rate of susceptibles is constant. There are many epidemiological and biological scenarios where this assumption is reasonable. Such constant recruitment is justified if the recruitment into the population is not internal but happens from an outside open source. For instance, constant recruitment is justified in the case of a population of school chil-

dren which are recruited from the general population with a fixed cohort size. Another biological example comes from intertidal marine systems, where recruitment into a local population is driven almost entirely by inputs from external source [15].

For the most of the paper we will assume that $\lambda_1(t) = \beta_1 I(t)/N(t)$ is the force of infection of the first type and $\lambda_2(t) = \beta_2 J(t)/N(t)$ is the force of infection of the second type. Thus, we assume proportionate mixing (sometimes called *'true' mass-action* [27]). The transmission rate of microorganism i is β_i The total population is the sum of all subgroups: $N(t) = S(t) + I(t) + J(t)$. We assume that all parameters are positive. The total population size is not constant and satisfies the following differential equation obtained by adding the three equations in the system (2.1):

$$N'(t) = B - \mu N(t) - \alpha_1 I(t) - \alpha_2 J(t). \tag{2.2}$$

The reproduction number of a pathogen is defined as the expected number of secondary infections one infectious individual can generate in a population of susceptible individuals during its lifetime. The reproduction numbers of the two strains are given by

$$\mathcal{R}_1 = \frac{\beta_1}{\mu + \alpha_1}, \quad \mathcal{R}_2 = \frac{\beta_2}{\mu + \alpha_2},$$

respectively. Bremermann and Thieme [7] showed that in a model of this form with mass-action [27] incidence (density dependent transmission), i.e. with $\lambda_1(t) = \beta_1 I$ and $\lambda_2(t) = \beta_2 J(t)$, the competitive exclusion is the ultimate outcome; the strain with the larger reproduction number persists, and the strain with the smaller reproduction number dies out. Similar techniques lead to the same result for model (2.1). In particular, if we consider the quantity $\xi = I^{\beta_2}/J^{\beta_1}$ it satisfies the simple differential equation $\xi'(t) = v\xi(t)$ where $v = (\mu + \alpha_1)(\mu + \alpha_2)[\mathcal{R}_1 - \mathcal{R}_2]$. The ratio $\xi(t)$ behaves as a time exponent e^{vt} where the sign of v determines the outcome of competition. For instance, if $v > 0$, that is if $\mathcal{R}_1 > \mathcal{R}_2$, then $\xi \to \infty$ and therefore $J(t) \to 0$ as $t \to \infty$ because $I(t)$ is bounded, since it is dominated by $N(t)$, whose limsup does not exceed B/μ. If $v < 0$, that is $\mathcal{R}_1 < \mathcal{R}_2$, then $\xi \to 0$ and necessarily $I(t) \to 0$ as $t \to \infty$ because $J(t)$ is bounded. The borderline case $v = 0$ is degenerate because it corresponds to a continuum of coexistence equilibria. We summarize this result in the following theorem:

Theorem 2.1. If $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$ then the disease-free equilibrium is locally and globally stable, that is $I(t) \to 0$ and $J(t) \to 0$ as $t \to \infty$. If at least one of the reproduction numbers is larger than one, then the pathogen type with the larger reproduction number persists and the other one dies out. Coexistence is not possible outside the degenerate case $\mathcal{R}_1 = \mathcal{R}_2$.

Theorem 2.1 states that for the two strains in this ODE model a competitive exclusion principle is valid, and only the strain with the maximal reproduction number persists in the population [7]. The result of Theorem 2.1 illustrates the analogy between the infection dynamics and purely exploitative resource competition. Indeed, the basic reproduction number of each pathogen type $\mathcal{R}$ is related to the fraction of susceptible individuals at the corresponding endemic equilibrium as

$$\frac{S}{N} = \frac{1}{\mathcal{R}}.$$

Therefore, the pathogen type with the higher value of $\mathcal{R}$ is always a more efficient competitor because it can subsist at the lower level of 'resource', $\frac{S}{N}$.

We now consider the impact of the host chronological age structure on strain competition and coexistence. We start with the same model but introduce age-dependent heterogeneity in host infectivity by assuming that $\beta_1 = \beta_1(a)$ and $\beta_2 = \beta_2(a)$, where a is host chronological age. Thus the model equation (2.1) becomes:

$$\begin{aligned} s_t(a,t) + s_a(a,t) &= -\lambda_1(t)s(a,t) - \lambda_2(t)s(a,t) - \mu s(a,t), \quad s(0,t) = B, \\ i_t(a,t) + i_a(a,t) &= \lambda_1(t)s(a,t) - (\mu + \alpha_1)i(a,t), \quad i(0,t) = 0, \\ j_t(a,t) + j_a(a,t) &= \lambda_2(t)s(a,t) - (\mu + \alpha_2)j(a,t), \quad j(0,t) = 0, \end{aligned} \tag{2.3}$$

where $s(a,t)$ is the age-density of susceptible individuals, $i(a,t)$ and $j(a,t)$ are the age-densities of the individuals infected with the first and second strain, respectively. The force of infection terms are now given by

$$\lambda_1(t) = \frac{1}{N(t)} \int_0^\infty \beta_1(a) i(a,t) \mathrm{d}a, \quad \lambda_2(t) = \frac{1}{N(t)} \int_0^\infty \beta_2(a) j(a,t) \mathrm{d}a$$

and represent the total per capita infection rates of each microparasite strain. As before, we assume that all newborns are susceptible and both pathogens are horizontally transmitted. The equation for total population size $N(t)$ again is given by (2.2) with $I(t) = \int_0^\infty i(x,t)\,\mathrm{d}x$ and $J(t) = \int_0^\infty j(x,t)\,\mathrm{d}x$.

Several comments are in order regarding this age-structured model. First, the model assumes constant total 'birth' rate. This assumption is quite in contrast with most age-structured models. The assumption is necessary for two reasons. One of the reasons is that it provides necessary consistency with the corresponding ODE model (2.1) that allows the comparison of the two models. Another reason is that if the usual for age-structured models total birth rate is assumed, it must be given by

$$s(0,t) = \int_0^\infty b(a)[s(a,t) + i(a,t) + j(a,t)]\,\mathrm{d}a.$$

In this case the corresponding ODE model is obtained by assuming $b(a) = b$, that is, independent of age. Thus the recruitment term in the ODE model (2.1) becomes bN, so that both the ODE model and the PDE model are of homogeneous type, that is they do not have time-independent solutions. Moreover, for the ODE model with recruitment term given by bN (which applies to a closed host population without density-dependence) it is known that coexistence may occur [30]. This contrasts with model (2.1) where no such coexistence is possible. Our question is how age structure can impact pathogen coexistence in an open population with external recruitment. Second, our model is not designed to fit any particular realistic scenario. On the contrary, it is made intentionally as simple as possible to highlight the absolute minimal features necessary for coexistence to occur. As such it is closest to a model developed to describe the transmission dynamics of HIV-1 in a male homosexual population [22], which clearly is an open population sustained by recruitment from an external source. Our model is essentially the model in [22] but without the structure with respect to the new partners per unit of time and with a second strain introduced. Although behavioral variation plays the major role in HIV transmission, an individual's age is also an important factor primarily because it is correlated with behavior. For instance, Fig. 1 in [22] suggests that individuals (homosexual or heterosexual) age 40 or older are far more likely

to have a unique partner than multiple partners, while for younger individuals the likelihood of having unique vs. multiple partners is about the same. Another study considered the unsafe sexual behavior among HIV-infected individuals (homosexual or heterosexual) and found that individuals aged 41 or older are much less likely to report unsafe sex [45]. With the success of the antiretroviral therapy more infected individuals live to older ages and the importance of that age group is rising [8]. Through age-dependent transmission, our model captures some of these behavioral differences that covary with age.

Our model can be extended in various directions to be more realistic for other potential scenarios, while still exhibiting the behavior that we address in this article. For instance, a recovered class can be added to the model so that it becomes an SIR or an SIRS model. We believe our analysis can be extended to that scenario. The extended model can be used to model rotavirus infection in a school system that involves children of age up to six. Although rotavirus infections cause few deaths among young children in the US, they are a leading cause of death of children in developing countries [39].

3. Equilibria of the age-structured model

In this section we investigate the trivial (disease-free) equilibrium and the semitrivial (dominance) equilibria of the age-structured model (2.3). The question of existence of non-trivial (coexistence) equilibria is postponed till the next section. Equilibria are time-independent but age-dependent solutions of the system (2.3). Setting the time derivatives equal to zero we obtain a system of ordinary differential equations:

$$\begin{aligned} s_a(a) &= -\lambda_1 s(a) - \lambda_2 s(a) - \mu s(a), \quad s(0) = B,\\ i_a(a) &= \lambda_1 s(a) - (\mu + \alpha_1) i(a), \quad i(0) = 0,\\ j_a(a) &= \lambda_2 s(a) - (\mu + \alpha_2) j(a), \quad j(0) = 0. \end{aligned} \tag{3.1}$$

If we treat λ_1 and λ_2 as known, the above equations can be explicitly solved. We first find the expression for s,

$$s(a) = B\mathrm{e}^{-(\lambda+\mu)a}, \tag{3.2}$$

where $\lambda = \lambda_1 + \lambda_2$. This expression upon substitution into the second and third equation of (3.1) yields the following expressions for i and j,

$$i(a) = \lambda_1 B \mathrm{e}^{-(\mu+\alpha_1)a} \frac{1 - \mathrm{e}^{-(\lambda-\alpha_1)a}}{\lambda - \alpha_1}, \tag{3.3}$$

$$j(a) = \lambda_2 B \mathrm{e}^{-(\mu+\alpha_2)a} \frac{1 - \mathrm{e}^{-(\lambda-\alpha_2)a}}{\lambda - \alpha_2}. \tag{3.4}$$

Integrating (3.3) and (3.4) over $a \in [0, +\infty)$, we find

$$I = \frac{\lambda_1 B}{(\mu + \alpha_1)(\mu + \lambda)}, \quad J = \frac{\lambda_2 B}{(\mu + \alpha_2)(\mu + \lambda)}. \tag{3.5}$$

Substituting these values into (2.2), we can express N in terms of λ_1 and λ_2 as

$$N = \frac{B}{\mu}\left(1 - \frac{1}{\mu+\lambda}\left(\frac{\alpha_1\lambda_1}{\mu+\alpha_1} + \frac{\alpha_2\lambda_2}{\mu+\alpha_2}\right)\right). \tag{3.6}$$

Finally, combining (3.3) and (3.4) and the definitions of λ_i, we obtain the following equations for λ_1 and λ_2.

$$\lambda_1 = \lambda_1 \frac{B}{N}\int_0^\infty \beta_1(a)\mathrm{e}^{-(\mu+\alpha_1)a}\frac{1-\mathrm{e}^{-(\lambda-\alpha_1)a}}{\lambda-\alpha_1}\,\mathrm{d}a, \tag{3.7}$$

$$\lambda_2 = \lambda_2 \frac{B}{N}\int_0^\infty \beta_2(a)\mathrm{e}^{-(\mu+\alpha_2)a}\frac{1-\mathrm{e}^{-(\lambda-\alpha_2)a}}{\lambda-\alpha_2}\,\mathrm{d}a. \tag{3.8}$$

Replacing the value of N in (3.6) and rearranging the terms we obtain the following equations for λ_1 and λ_2,

$$\lambda_1\left(1 - \frac{1}{\mu+\lambda}\left(\frac{\alpha_1\lambda_1}{\mu+\alpha_1} + \frac{\alpha_2\lambda_2}{\mu+\alpha_2}\right)\right) = \lambda_1\,\mu\int_0^\infty \beta_1(a)e^{-(\mu+\alpha_1)a}\frac{1-\mathrm{e}^{-(\lambda-\alpha_1)a}}{\lambda-\alpha_1}\,\mathrm{d}a, \tag{3.9}$$

$$\lambda_2\left(1 - \frac{1}{\mu+\lambda}\left(\frac{\alpha_1\lambda_1}{\mu+\alpha_1} + \frac{\alpha_2\lambda_2}{\mu+\alpha_2}\right)\right) = \lambda_2\,\mu\int_0^\infty \beta_2(a)\mathrm{e}^{-(\mu+\alpha_2)a}\frac{1-\mathrm{e}^{-(\lambda-\alpha_2)a}}{\lambda-\alpha_2}\,\mathrm{d}a. \tag{3.10}$$

We distinguish three types of equilibria: First, the trivial or disease-free equilibrium ($\lambda_1 = \lambda_2 = 0$), given by $\mathcal{E}_0 = (0,0)$. In the disease-free equilibrium we have $i(a) = j(a) = 0$. This equilibrium clearly always exists. The conditions for stability and loss of stability of the disease-free equilibrium lead to the definition of the reproduction numbers of the two strains. These stability conditions for each strain can be obtained much along the lines in [9]. Following the procedure there leads to

$$\mathcal{R}_1 = \frac{B}{N^*}\int_0^\infty \beta_1(a)\mathrm{e}^{-\mu a}\frac{1-\mathrm{e}^{-\alpha_1 a}}{\alpha_1}\,\mathrm{d}a, \qquad \mathcal{R}_2 = \frac{B}{N^*}\int_0^\infty \beta_2(a)\mathrm{e}^{-\mu a}\frac{1-\mathrm{e}^{-\alpha_2 a}}{\alpha_2}\,\mathrm{d}a, \tag{3.11}$$

where N^* is the total population size at the disease free equilibrium, that is, $N^* = B/\mu$. The coefficient in front of the integrals can be simplified to $B/N^* = \mu$ but we will retain it as B/N^* so that the reproduction numbers and the invasion reproduction numbers introduced in the next section have the same form.

Second, we consider the boundary or dominance equilibria for which only one of λ_i is zero. The dominance equilibrium of the first strain is denoted by $\mathcal{E}_1 = (\lambda_1^*, 0)$ and the dominance equilibrium of the second strain is denoted by $\mathcal{E}_2 = (0, \lambda_2^*)$. Finally, the non-trivial or coexistence equilibria where both infectious classes are positive ($\lambda_1, \lambda_2 > 0$), are given by $\mathcal{E}^{**} = (\lambda_1^{**}, \lambda_2^{**})$.

To study semitrivial and non-trivial equilibria, we first divide both sides of Eq. (3.9) above by λ_1 and both sides of Eq. (3.10) by λ_2. Furthermore, for convenience, we rewrite Eqs. (3.9) and (3.10) in the form

$$\gamma_1\lambda_1 + \gamma_2\lambda_2 = (\mu+\lambda)\left(1 - \mu\int_0^\infty \beta_1(a)\mathrm{e}^{-(\mu+\alpha_1)a}\frac{1-\mathrm{e}^{-(\lambda-\alpha_1)a}}{\lambda-\alpha_1}\,\mathrm{d}a\right) =: F_1(\lambda), \tag{3.12}$$

$$\gamma_1\lambda_1 + \gamma_2\lambda_2 = (\mu+\lambda)\left(1 - \mu\int_0^\infty \beta_2(a)\mathrm{e}^{-(\mu+\alpha_2)a}\frac{1-\mathrm{e}^{-(\lambda-\alpha_2)a}}{\lambda-\alpha_2}\,\mathrm{d}a\right) =: F_2(\lambda), \tag{3.13}$$

where we have introduced the quantities $\gamma_i = \frac{\alpha_i}{\mu+\alpha_i}$ which represent the fraction of hosts infected with strain i that die due to infection. For instance, Eq. (3.12) alone can be used to find the semitrivial equilibria $\mathcal{E}_1 = (\lambda_1^*, 0)$ which correspond to the positive roots λ_1^* of

$$\gamma_1 = \left(1+\frac{\mu}{\lambda_1}\right)\left(1 - \mu\int_0^\infty \beta_1(a)\mathrm{e}^{-(\mu+\alpha_1)a}\frac{1-\mathrm{e}^{-(\lambda_1-\alpha_1)a}}{\lambda_1-\alpha_1}\,\mathrm{d}a\right) =: \frac{F_1(\lambda_1)}{\lambda_1}. \tag{3.14}$$

With a minimal amount of analysis, one can see that the function $F_1(\lambda_1)$ is monotonically increasing with $\lim_{\lambda_1\to\infty}\frac{F_1(\lambda_1)}{\lambda_1} = 1$ and that the sign of $F_1(0) = \mu(1-\mathcal{R}_1)$ is determined by the magnitude of the reproduction number of the first strain (3.11). If $\mathcal{R}_1 > 1$, then Eq. (3.14) must have at least one positive root. Indeed, in this case the set of all possible values for $F_1(\lambda_1)/\lambda_1$ for $\lambda_1 > 0$ contains the interval $(-\infty,1)$, while the left hand side of (3.14) is a constant $\gamma_1 < 1$. Existence of at least one positive root λ_1^* follows from continuity of both sides of (3.14).

We summarize this result in the following theorem.

Theorem 3.1. If $\mathcal{R}_1 > 1$ then there exists at least one dominance equilibrium of strain one at $\mathcal{E}_1 = (\lambda_1^*, 0)$. Analogously, if $\mathcal{R}_2 > 1$ then there exists at least one dominance equilibrium of strain two at $\mathcal{E}_2 = (0, \lambda_2^*)$.

We remark that λ_i^* (for $i = 1,2$) is the time-independent value of $\lambda_i(t)$ at an equilibrium; both are assumed non-zero.

4. Coexistence

Coexistence depends not so much on the reproduction numbers but on the *invasion reproduction numbers*. The invasion reproduction number of, say, the first strain $\hat{\mathcal{R}}_1$ gives the number of secondary infections that one individual infected with the first strain can produce in a population where the second strain is already present and at equilibrium during the infected period. Technically, this number is computed the same way as the reproduction number but instead of being evaluated at the disease-free equilibrium, it is evaluated at the equilibrium abundance of strain two [40]. We say that the first strain can invade the equilibrium of the second strain if $\hat{\mathcal{R}}_1 > 1$, because in this case the growth rate of the first strain in the population where the second strain is at equilibrium is positive. The invasion reproduction number of the second strain $\hat{\mathcal{R}}_2$ is defined analogously; the second strain can invade the equilibrium of the first if $\hat{\mathcal{R}}_2 > 1$. Coexistence, and in particular stable coexistence, occurs when each strain can invade the equilibrium of the other, that is, when $\hat{\mathcal{R}}_1 > 1$ and $\hat{\mathcal{R}}_2 > 1$.

The invasion reproduction numbers of the system (2.1) without age-structure are given by $\hat{\mathcal{R}}_1 = \mathcal{R}_1/\mathcal{R}_2$ and $\hat{\mathcal{R}}_2 = \mathcal{R}_2/\mathcal{R}_1$. Thus, $\hat{\mathcal{R}}_1 > 1$ if and only if $\hat{\mathcal{R}}_2 < 1$, hence coexistence does not occur. With age-structure, the invasion reproduction numbers of the system (2.3) depend on the corresponding dominance equilibria.

The invasion reproduction number of the first strain at the equilibrium of the second strain $\mathcal{E}_2 = (0, \lambda_2^*)$ is given by

$$\hat{\mathcal{R}}_1 = \frac{B}{N_2^*}\int_0^\infty \beta_1(a)\mathrm{e}^{-(\mu+\alpha_1)a}\frac{1-\mathrm{e}^{-(\lambda_2^*-\alpha_1)a}}{\lambda_2^*-\alpha_1}\,\mathrm{d}a, \tag{4.1}$$

where N_2^* is the equilibrium value of the total population when the second strain is at equilibrium (see Eq. (3.6) with $\lambda_1 = 0$ and λ_2^*. This quantity is obtained from (3.7) after cancelling λ_1 from both sides and taking $\lambda_1 = 0$ and $\lambda_2 = \lambda_2^*$. Analogously, the invasion reproduction number of the second strain at the equilibrium of the first strain $\mathcal{E}_1 = (\lambda_1^*, 0)$ is given by

$$\hat{\mathcal{R}}_2 = \frac{B}{N_1^*}\int_0^\infty \beta_2(a)\mathrm{e}^{-(\mu+\alpha_2)a}\frac{1-\mathrm{e}^{-(\lambda_1^*-\alpha_2)a}}{\lambda_1^*-\alpha_2}\,\mathrm{d}a, \tag{4.2}$$

where N_1^* is the equilibrium value of the total population when the first strain is at equilibrium. Again, this is obtained from (3.8) after cancelling λ_2 from both sides and taking $\lambda_1 = \lambda_1^*$ and $\lambda_2 = 0$.

To investigate the existence of the non-trivial equilibria, $\mathcal{E}^{**} = (\lambda_1^{**}, \lambda_2^{**})$, we observe that $\lambda_1^{**} > 0$ and $\lambda_2^{**} > 0$ must satisfy the system of equations (3.9) and (3.10), which can be rewritten in the following concise form:

$$\gamma_1\lambda_1 + \gamma_2\lambda_2 = F_1(\lambda) = F_2(\lambda), \quad \lambda_1 + \lambda_2 = \lambda, \tag{4.3}$$

where $\gamma_1 = \alpha_1/(\mu+\alpha_1) < 1$, $\gamma_2 = \alpha_2/(\mu+\alpha_2) < 1$ and $F_1(\lambda)$ and $F_2(\lambda)$ are two functions defined in (3.12) and (3.13). Dividing all sides of this equation by λ we see that its left-hand side is a convex combination of the values γ_1 and γ_2 and as such takes any value in the interval between the minimum of γ_1 and γ_2 and the maximum of γ_1 and γ_2. Consequently, Eq. (4.3) are consistent if and only if there exists a positive number λ^{**} such that

$$\frac{F_1(\lambda^{**})}{\lambda^{**}} = \frac{F_2(\lambda^{**})}{\lambda^{**}} \in (\min\{\gamma_1,\gamma_2\}, \max\{\gamma_1,\gamma_2\}),$$

that is if the two curves $F_1(\lambda)/\lambda$ and $F_2(\lambda)/\lambda$ intersect between the lines $\Gamma_1{:}y = \gamma_1$ and $\Gamma_2{:}y = \gamma_2$ (see Fig. 1). To demonstrate that this observation implies coexistence, let us consider without loss of generality the case $\gamma_1 > \gamma_2$, as is the case in Fig. 1.

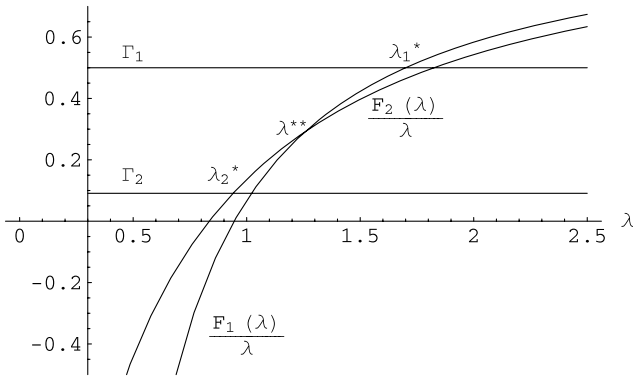

Fig. 1. The graphs of the functions $F_1(\lambda)/\lambda$ and $F_2(\lambda)/\lambda$ in case when $\gamma_1 > \gamma_2$ and both semitrivial equilibria are unique. The particular disposition of the curves corresponds to the case when $F_1(\lambda_2^*)/\lambda_2^* < \gamma_2$ (that is, $\hat{\mathcal{R}}_1 > 1$) and $F_2(\lambda_1^*)/\lambda_1^* < \gamma_1$ (that is, $\hat{\mathcal{R}}_2 > 1$). Existence of the appropriate intersection is evident. Parameter values used in the figure are as follows: $\mu = 0.1$, $\alpha_1 = 0.1$, $\alpha_2 = 0.01$, and the two transmission rates are set by $\beta_1(a) = \mathrm{e}^{0.15a}(a-10)(15-a)/1.32261$ if $10 \leqslant a \leqslant 15$ (and zero otherwise) and $\beta_2(a) = \mathrm{e}^{-a}(a-1)(10-a)/0.196222$ if $1 \leqslant a \leqslant 10$ (and zero otherwise).

In this section we assume that $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 > 1$ and that both dominance equilibria that exist are unique. Fig. 1 gives the graphs of the functions $F_1(\lambda)/\lambda$ and $F_2(\lambda)/\lambda$. The first key observation following from Eq. (3.14) is that the equilibrium value λ_1^* at the dominance equilibrium $\mathcal{E}_1$ satisfies the equation

$$\frac{F_1(\lambda_1^*)}{\lambda_1^*} = \gamma_1$$

and is therefore obtained from the intersection of the graph of $F_1(\lambda)/\lambda$ with the horizontal line Γ_1 (see Fig. 1). Similarly, the equilibrium value λ_2^* in the dominance equilibrium $\mathcal{E}_2$ satisfies the equation

$$\frac{F_2(\lambda_2^*)}{\lambda_2^*} = \gamma_2$$

and is obtained from the intersection of the graph of $F_2(\lambda)/\lambda$ with the horizontal line Γ_2. We consider two separate groups of assumptions that can each lead to coexistence:

(1) Assume first that $\hat{\mathcal{R}}_1 > 1$ and $\hat{\mathcal{R}}_2 > 1$. The conditions that both invasion reproduction numbers are larger than one are equivalent correspondingly to

$$\frac{F_1(\lambda_2^*)}{\lambda_2^*} < \gamma_2 \qquad \text{and} \qquad \frac{F_2(\lambda_1^*)}{\lambda_1^*} < \gamma_1.$$

These inequalities in turn imply that $\lambda_2^* < \lambda_1^*$ because if the reversed inequality holds, the function $F_1(\lambda)/\lambda$ would cross the line Γ_1 at λ_1^* and become larger than γ_1. In order for this function to be smaller than γ_2 later at λ_2^*, it would have to cross the line Γ_1 again, which contradicts the assumption that this crossing is unique. Furthermore, since at λ_2^* the value of $F_1(\lambda)/\lambda$ is smaller than the value of the function $F_2(\lambda)/\lambda$ (which is equal to γ_2), while at λ_1^* the value of $F_2(\lambda)/\lambda$ is smaller than the value of the function $F_1(\lambda)/\lambda$ (which is equal to γ_1), the graphs of these two functions must intersect for some λ^{**} in the interval $(\lambda_2^*, \lambda_1^*)$. Their common value lies somewhere in the interval (γ_2, γ_1). This implies that λ^{**} satisfies all conditions, that is, coexistence occurs (see Fig. 1).

(2) Assume next that $\hat{\mathcal{R}}_1 < 1$ and $\hat{\mathcal{R}}_2 < 1$. The conditions that both invasion reproduction numbers are smaller than one are equivalent correspondingly to

$$\frac{F_1(\lambda_2^*)}{\lambda_2^*} > \gamma_2 \qquad \text{and} \qquad \frac{F_2(\lambda_1^*)}{\lambda_1^*} > \gamma_1.$$

Similar arguments as in the previous paragraph show that the curves $F_1(\lambda)/\lambda$ and $F_2(\lambda)/\lambda$ must intersect so that their common value is somewhere in the interval (γ_2, γ_1). Therefore, a coexistence equilibrium also exists in this case.

We summarize these findings in the following theorem:

Theorem 4.1. Assume $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 > 1$ and that both semitrivial equilibria $\mathcal{E}_1$ and $\mathcal{E}_2$ are unique. Then there is a coexistence equilibrium if and only if either both invasion reproduction numbers are larger than one or both invasion reproduction numbers are smaller than one.

This theorem states that the age-structured model (2.3) has a coexistence equilibrium, while the corresponding age-independent model (2.1) does not. Thus host age-structure plays the role of a

trade-off mechanism that permits the two strains to coexist. It is interesting to know what other features of the model (2.3) allow for that coexistence. One feature that is absolutely necessary is the frequency-dependent force of infection. If the force of infection in the model (2.3) were replaced by

$$\tilde{\lambda}_1(t) = \int_0^\infty \beta_1(a) i(a,t)\,\mathrm{d}a, \quad \tilde{\lambda}_2(t) = \int_0^\infty \beta_2(a) j(a,t)\,\mathrm{d}a$$

then coexistence cannot occur regardless of the magnitude of virulence. One can see this by examining Eqs. (3.7) and (3.8). After canceling λ_1 in Eq. (3.7) and λ_2 in Eq. (3.8) we have that their right-hand sides have to be equal to one. Both resulting equations have a unique solution, say λ_1^* and λ_2^* which in general are different. Thus they cannot be satisfied for a unique value of λ, and are inconsistent as a system. Coexistence cannot occur except in the degenerate case $\lambda_1^* = \lambda_2^*$.

One other constraint on coexistence is that if there is no virulence in the original system (2.3), that is if $\alpha_1 = 0$ and $\alpha_2 = 0$, there will be no coexistence. In the case of non-virulent strains the total population size is asymptotically constant, and the system behaves as if it were a constant. A similar argument as given before shows that there is no coexistence. (In these cases when we say that there is no coexistence, we mean that there is no coexistence equilibrium outside of the case $\mathcal{R}_1 = \mathcal{R}_2$.)

In the example of Fig. 1 the transmission rates of the two strains have disjoint support, that is the two strains are transmitted for different ages of the host, so there is a complete niche partitioning by age. Is such complete partitioning necessary for coexistence to occur? In fact, coexistence is possible under a great variety of functions describing age-dependent transmission rates of the two strains. One particular case that is of interest is when one of the strains is transmitted better at all host ages, say the transmission rate of the first strain is higher than the transmission rate of the second strain: $\beta_1(a) \geqslant \beta_2(a)$. Can coexistence still occur? It turns out that the answer depends on the virulence of the strains. From Eq. (3.11) it can be seen that if the transmission rate decreases, while virulence stays fixed, the reproduction number of the strain decreases. The reproduction number also decreases when transmission rate decreases and virulence increases. In this case, we say that transmission and virulence act *synergistically* on the reproduction number. On the other hand, when transmission rate decreases and virulence decreases, then the impact on the reproduction number is not clear, and, in particular, the reproduction number may remain unchanged. In this case we say that transmission and virulence act as *trade-offs*. These changes in transmission rates and virulence have similar impact (actually exactly opposite in direction) on the functions $F_1(\lambda)$ and $F_2(\lambda)$. Consequently, if transmission and virulence act synergistically, that is, $\beta_1(a) \geqslant \beta_2(a)$ and $\alpha_1 < \alpha_2$, then $F_1(\lambda) < F_2(\lambda)$ for all λ. This, in particular means that the two functions cannot intersect and there is no coexistence. On the other hand, when transmission and virulence experience a trade-off, that is, $\beta_1(a) \geqslant \beta_2(a)$ and $\alpha_1 > \alpha_2$, then the impact on the functions F_1 and F_2 is unclear and coexistence may occur. We illustrate this scenario with an example in Fig. 2 where we have also taken $\beta_1(a)$ to be constant. We summarize these observations in the following proposition.

Proposition 4.2. Suppose for all host's ages the first pathogen has a higher transmission rate than the second: $\beta_1(a) \geqslant \beta_2(a)$.

(1) If $\alpha_1 > \alpha_2$ then coexistence is possible.
(2) If $\alpha_1 < \alpha_2$ then coexistence is not possible.

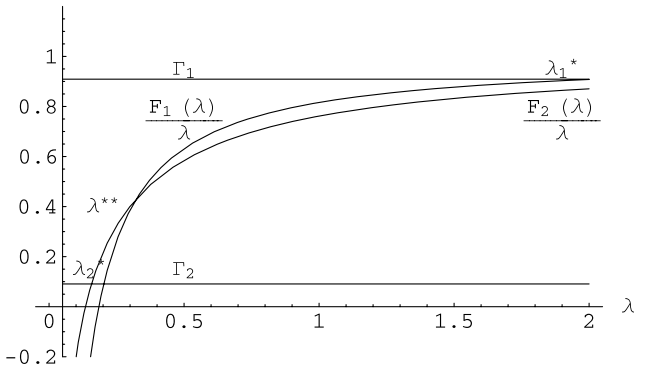

Fig. 2. The graphs of the functions $F_1(\lambda)/\lambda$ and $F_2(\lambda)/\lambda$ in case when $\gamma_1 > \gamma_2$ and both semitrivial equilibria are unique. In this case as in Figure 1 we have $\hat{\mathcal{R}}_1 > 1$ and $\hat{\mathcal{R}}_2 > 1$. The two curves intersect at $\lambda^{**} = (\lambda_1^{**}, \lambda_2^{**})$ and between the lines Γ_2 and Γ_1. Coexistence occurs when transmission and virulence are in trade-off: $\beta_1(a) > \beta_2(a)$ and $\alpha_1 > \alpha_2$ even though $\beta_1(a)$ is age-independent. Parameter values used are as follows: $\mu = 0.1$, $\alpha_1 = 1.0$, $\alpha_2 = 0.01$. The transmission rate of the first strain is constant $\beta_1(a) = 3.125$ while the transmission rate of the second strain declines exponentially with age: $\beta_2(a) = e^{-0.15a}$.

Numerical investigations reveal that the coexistence equilibrium that occurs when $\hat{\mathcal{R}}_1 > 1$ and $\hat{\mathcal{R}}_2 > 1$ is typically locally stable and results in the dynamical outcome of epidemiological coexistence of the two strains (see Fig. 3 for a numerical example). Each strain can increase when rare and the other is at equilibrium, so the coexistence is robust. (Our numerical studies always showed asymptotic approach to a stable coexistence equilibrium.) The coexistence equilibrium that occurs when $\hat{\mathcal{R}}_1 < 1$ and $\hat{\mathcal{R}}_2 < 1$ by contrast is unstable and the dynamical outcome of coexistence cannot be observed. Instead, in the corresponding parameter region, the model exhibits bistable dominance, that is, competitive exclusion occurs where one or the other pathogen type dominates depending on the initial conditions [33]. Clearly, under the scenario of bistable dominance, it is possible that the strain with the lower reproduction number can eliminate the strain with the higher reproduction number and dominate in the population, given appropriate initial conditions. The presence of a region where both invasion numbers are below one is usually associated with a

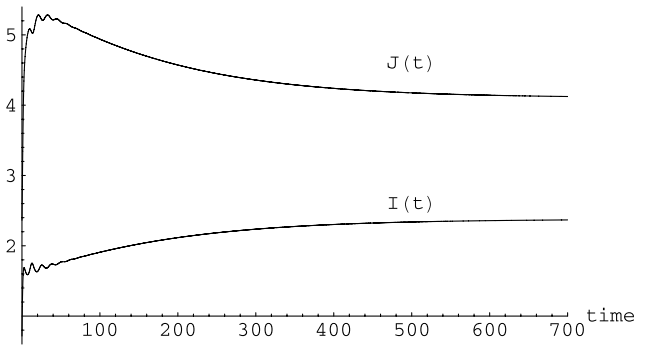

Fig. 3. The graph of the total number of infected with the first strain $I(t)$ and the total number of infected with the second strain $J(t)$ are plotted as functions of time. Both stabilize at non-zero values, that is, the two strains coexist in the population. Parameters are chosen as in Fig. 1.

region in a parameter space where the strain with suboptimal reproduction number dominates independently of the initial conditions. This phenomenon of a priority effect in competition, which contrasts with the competitive exclusion principle, occurs when point coexistence is possible, and particularly in the case when one or both of the boundaries of coexistence in the $(\mathcal{R}_1, \mathcal{R}_2)$ plane cross the bisector $\mathcal{R}_1 = \mathcal{R}_2$ (see [33] for a specific example). Dominance of a strain with suboptimal reproduction number independently of the initial conditions is possible in the model (2.3) and has been observed previously in conjunction with various alternative mechanisms that also lead to coexistence such as superinfection [37], coinfection [33], and mixed vertical and horizontal transmission [31].

5. Subthreshold dominance and coexistence

The dependence of the transmission rate in the model (2.3) on the host's chronological age leads to a model which although a very simple extension of its age-independent ODE counterpart (2.1) generates a much richer array of dynamical outcomes. For instance, model (2.1) only has one dominance equilibrium corresponding to each strain persisting (with the other being excluded) when the corresponding reproduction number is above one, which we refer to as *superthreshold*. In contrast, in the age-structured scenario, there might also be dominance equilibria occurring when the reproduction numbers are below one, which we refer to as *subthreshold*. As mentioned before, the λ_1^* value of the dominance equilibrium $\mathcal{E}_1 = (\lambda_1^*, 0)$ is obtained as a solution of the equation $F_1(\lambda)/\lambda = \gamma_1$, while the λ_2^* value of the dominance equilibrium $\mathcal{E}_2 = (0, \lambda_2^*)$ is obtained as a solution of the equation $F_2(\lambda)/\lambda = \gamma_2$. Since the question of existence of dominance equilibria is symmetric for the two strains, we discuss it for strain one only.

In the *subthreshold* case $\mathcal{R}_1 < 1$, the function $F_1(\lambda_1)$ is positive for all $\lambda_1 > 0$. Furthermore, $\lim_{\lambda_1 \to 0} F_1(\lambda_1)/\lambda_1 = +\infty$ and also $\lim_{\lambda_1 \to \infty} F_1(\lambda_1)/\lambda_1 = 1$. Introducing m to be the infimum of the function $F_1(\lambda_1)/\lambda_1$ for all $\lambda_1 > 0$, we observe that $m \leqslant 1$, and m is the true minimal value whenever $m < 1$. It easily follows that the equation $F_1(\lambda)/\lambda = \gamma_1$ admits an even number of positive roots (corresponding to *subthreshold* semitrivial equilibria) if and only if $m < \gamma_1$. This scenario is illustrated in Fig. 4.

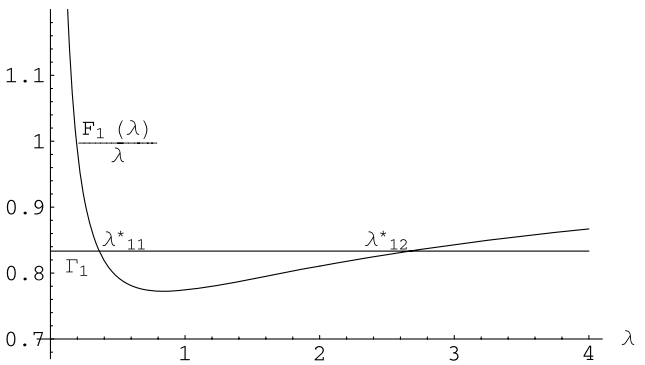

Fig. 4. The graph of the function $F_1(\lambda)/\lambda$ in the subthreshold case, that is, when $\mathcal{R}_1 < 1$. It intersects the horizontal line Γ_1 at two points which give two subthreshold dominance equilibria of the first strain $\mathcal{E}_{11} = (\lambda_{11}^*, 0)$ and $\mathcal{E}_{12} = (\lambda_{12}^*, 0)$. The parameters are chosen as follows: $\mu = 1$, $\alpha_1 = 5$, $\beta_1(a) = 12.87e^{-a}$.

In the previous section we showed that coexistence occurs in a *superthreshold* case, that is, when the reproduction numbers of both pathogen variants are above one. However, model (2.3) allows also for *subthreshold* coexistence. Because coexistence depends on the reproduction numbers and the invasion reproduction numbers of all strains present, there are two basic types of subthreshold coexistence equilibria: *weakly subthreshold* coexistence equilibria – these occur when at least one but not all reproduction numbers are below one, and *strongly subthreshold* coexistence equilibria – those occur when all reproduction numbers are below one.

Both weakly subthreshold and strongly subthreshold coexistence equilibria occur in model (2.3). To see the presence of weakly subthreshold coexistence equilibria, assume again without loss of generality that $\gamma_1 > \gamma_2$. Two cases are possible:

(1) $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$. In this case the graph of $F_1(\lambda)/\lambda$ has the general form shown in Fig. 1 and we assume the resulting dominance equilibrium of strain one is unique. On the other hand, the graph of $F_2(\lambda)/\lambda$ has the form shown in Fig. 4 and may or may not cross the line Γ_2. Assume it does not cross that line, that is, there are no associated subthreshold dominance equilibria of strain two. Then there is a weakly subthreshold coexistence equilibrium if and only if $\hat{\mathcal{R}}_2 > 1$ (see Fig. 5). We expect that this coexistence equilibrium is locally stable at least for some parameter values because the second strain can invade the stable equilibrium of the first. Under this scenario the first strain which can exist alone superthreshold induces the second strain, which cannot persist alone, to coexist with it even when the reproduction number of the second strain is below one. We note that the virulence of the 'induced' strain two corresponds to γ_2 and is lower than the virulence of the strain that can persist by itself, related to γ_1.

(2) $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 > 1$. In this case the graph of $F_1(\lambda)/\lambda$ has the general form of that in Fig. 4 and we assume that it intersects the line Γ_1 (otherwise there will be no coexistence). The two intersections result in two dominance equilibria of strain one $\mathcal{E}_{11} = (\lambda^*_{11}, 0)$ and $\mathcal{E}_{12} = (\lambda_{12}0)$.

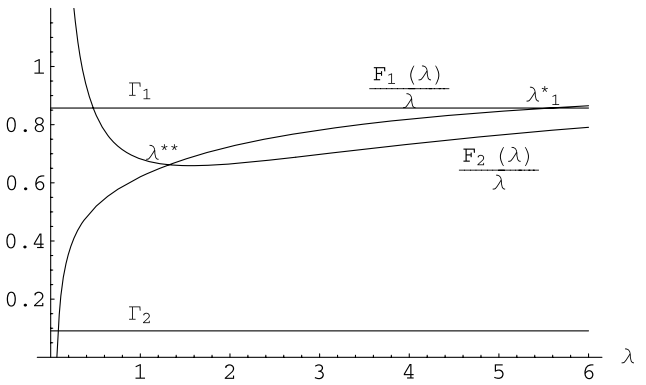

Fig. 5. The graphs of the functions $F_1(\lambda)/\lambda$ and $F_2(\lambda)/\lambda$ in the weakly subthreshold case, when $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$. The two functions intersect between the lines $\Gamma_1{:}y = \gamma_1$ and $\Gamma_2{:}y = \gamma_2$ to form a unique weakly subthreshold coexistence equilibrium $\mathcal{E}^{**} = (\lambda^{**}_1, \lambda^{**}_2)$, denoted by λ^{**} in the Figure. There is also a unique superthreshold equilibrium $\mathcal{E} = (\lambda^*_1, 0)$ obtained when the graph of $F_1(\lambda)/\lambda$ crosses the line Γ_1. The parameters are chosen as follows: $\mu = 1$, $\alpha_1 = 6$, $\alpha_2 = 0.1$, $\beta_1(a) = 16.55e^{-a}$, $\beta_2(a) = 25.5\sin(a)$ for $0 \leqslant a \leqslant \pi/6$ and zero otherwise.

On the other hand, the graph of $F_2(\lambda)/\lambda$ has the form in Fig. 1 and crosses both the line Γ_2 and the line Γ_1. Then there is a weakly subthreshold coexistence equilibrium if and only if $\hat{\mathcal{R}}_1 < 1$, $\hat{\mathcal{R}}_2(\mathcal{E}_{11}) > 1$ and $\hat{\mathcal{R}}_2(\mathcal{E}_{12}) < 1$. We note that the inequality $\hat{\mathcal{R}}_2(\mathcal{E}_{11}) > 1$ is equivalent to $F_2(\lambda^*_{11})/\lambda^*_{11} < \gamma_1$ while the inequality $\hat{\mathcal{R}}_2(\mathcal{E}_{12}) < 1$ is equivalent to $F_2(\lambda^*_{12})/\lambda^*_{12} > \gamma_1$. We conjecture that the coexistence equilibrium that results is, however, unstable because neither strain can invade the stable equilibrium of the other.

We now focus on the strongly subthreshold equilibria. Many times neither microparasite can persist subthreshold by itself, however they can persist strongly subthreshold by coexisting [33]. We call this type of strong coexistence *cooperative subthreshold coexistence*. Strong cooperative subthreshold coexistence does not occur in the model (2.3). This is not hard to see. In the case when $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$ both curves $F_1(\lambda)/\lambda$ and $F_2(\lambda)/\lambda$ will have the form in Fig. 4. Assuming again without loss of generality that $\gamma_1 > \gamma_2$, the two curves can intersect in the interval (γ_2, γ_1) if both cross the line Γ_1 to go below it. That means that the equation $F_1(\lambda)/\lambda = \gamma_1$ will have two solutions and there will be two subthreshold dominance equilibria of the first strain.

Another interesting scenario, worth mentioning, is the case when one of the pathogen variants can exist subthreshold by itself but the other one cannot. In this case it is possible that the first strain can mediate the existence of the second strain subthreshold in the form of strongly subthreshold coexistence. We call this effect *induced strongly subthreshold coexistence*. This effect is possible in the model (2.3). We illustrate it in Fig. 6, which shows the graphs of the functions $F_1(\lambda)/\lambda$ and $F_2(\lambda)/\lambda$ in the strongly subthreshold case, that is, when $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$. The graph of the function $F_1(\lambda)/\lambda$ intersects the horizontal line Γ_1 at two points which give two subthreshold dominance equilibria of the first strain $\mathcal{E}_{11} = (\lambda^*_{11}, 0)$ and $\mathcal{E}_{12} = (\lambda^*_{12}, 0)$. Typically, $\mathcal{E}_{11}$ is unstable while $\mathcal{E}_{12}$ is locally stable [34]. The graph of the function $F_2(\lambda)/\lambda$ does not intersect the line Γ_2 so the second strain cannot dominate by itself when $\mathcal{R}_2 < 1$. The graphs of $F_1(\lambda)/\lambda$ and $F_2(\lambda)/\lambda$ intersect in the interval (γ_2, γ_1) giving rise to a unique coexistence equilibrium $\mathcal{E}^{**} = (\lambda^{**}_1, \lambda^{**}_2)$. We note that $F_2(\lambda^*_{11})/\lambda^*_{11} > \gamma_1$, or equivalently, $\hat{\mathcal{R}}_2(\mathcal{E}_{11}) < 1$ and that $F_2(\lambda^*_{12})/\lambda^*_{12} < \gamma_1$, or equivalently,

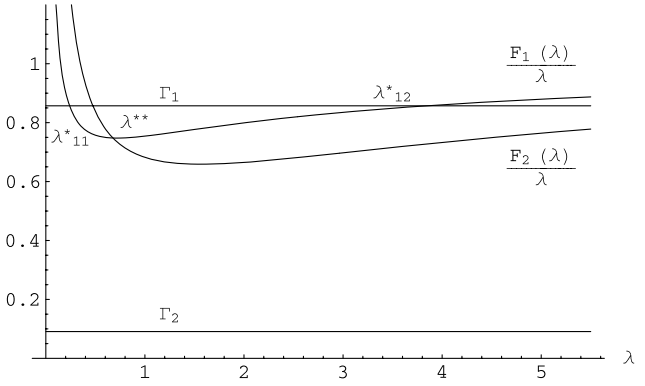

Fig. 6. The graphs of the functions $F_1(\lambda)/\lambda$ and $F_2(\lambda)/\lambda$ in the strongly subthreshold case, that is, when $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$. The two functions intersect between the lines Γ_1 and Γ_2 to form a unique strongly subthreshold coexistence equilibrium $\mathcal{E}^{**} = (\lambda^{**}_1, \lambda^{**}_2)$, denoted by λ^{**} in the Figure. The parameters are chosen as follows: $\mu = 1$, $\alpha_1 = 6$, $\alpha_2 = 0.1$, $\beta_1(a) = 14.95e^{-a}$, $\beta_2(a) = 25.5\sin(a)$ for $0 \leqslant a \leqslant \pi/6$ and zero otherwise.

$\hat{\mathcal{R}}_2(\mathcal{E}_{12}) > 1$. These conditions guarantee the presence of a coexistence equilibrium. We surmise that this coexistence equilibrium is locally stable since the second strain can invade the stable equilibrium of the first strain. We note that the 'induced' strain, strain two, *always* has lower virulence than the pathogen variant that can persist subthreshold by itself (see Fig. 6 and note that the induced strain has virulence corresponding to γ_2 and $\gamma_2 < \gamma_1$). Thus, with host-age structure as a mechanism that leads to coexistence a less virulent strain cannot cause a more virulent strain to persist subthreshold, unless the more virulent strain can also persist by itself.

Many more scenarios are theoretically possible. The ones we have included so far testify to the emergent dynamical complexity of the model (2.3), arising because host age structure is a dependent feature of the system.

6. Conclusions

Stable coexistence of pathogen variants permits maintenance of the diversity of microorganisms. Although under the most general conditions a competitive exclusion principle is valid [7], strains can coexist if some trade-off mechanism moderates competition. Polymorphism of two or more types has been found to stem from within-host interactions among the strains. One such mechanism is co-infection, where one host is simultaneously infected with two or more variants that coexist within the host [36]. Another such mechanism is super-infection. In super-infection a host infected with one pathogen strain becomes infected with another strain. The second strain wins the within-host competition and then takes over the host. Super-infection can lead to coexistence of the pathogens at the population level [37,35]. Within-host mutation of one pathogen into another variant has also been found on several occasions to lead to coexistence of the wild type and the mutant [6,29] in a selection-mutation balance. Another mechanism of coexistence involves heterogeneity among the hosts, such as in [5,17] where the incomplete drug-treatment of tuberculosis permits hosts infected with the wild strain to become infected with a drug-resistant strain. Cross-immunity can also have significant impact on the competitive outcome. For instance, it has been shown that while strains that impart strong cross-immunity tend to eliminate each other, strains that impart weak cross-immunity are more likely to coexist [38,28]. Cross-immunity has been observed to lead to coexistence in models of influenza [10,11,3] and dengue [18,16]. Another group of mechanisms that result in coexistence stems from external demographic factors. Lipsitch and Nowak [30] demonstrated that the competitive exclusion principle is not valid and coexistence of two pathogen variants may be possible if the baseline population experiences exponential growth. Andreasen and Pugliese observed coexistence in a two-strain epidemic model with density-dependent natural mortality of the host [4]. More recently this framework has been extended to density-dependent recruitment and mortality, leading to coexistence of two genotypes [1].

In this paper we have introduced and investigated a mathematical model which seeks to elucidate the role of host age in fostering microparasite polymorphism. We incorporate host age only in infectivity, but similar effects might be possible if other pathogen-related epidemiological characteristics, such as virulence, or susceptibility, are age dependent. We find that in contrast to the age-independent case where a competitive exclusion principle is valid, the effect of age is to permit both coexistence and competitive exclusion. We show that coexistence occurs superthreshold

when each pathogen variant can invade the equilibrium of the other. Mutual invasion of equilibria is possible in the structured case because disease-induced mortality creates dependence of the total population size and its age structure on the prevalence of infected individuals with each strain (see (2.2)), and therefore, on the force of infection. This, in turn, through the proportionate mixing incidence creates a non-monotone dependence of the invasion reproduction number of each strain on the equilibrium force of infection of the other. In other words, with age structure present, if the force of infection is assumed to be of the (pseudo) mass-action type and/or there is no disease-induced mortality ($\alpha_1 = \alpha_2 = 0$) stable equilibrial coexistence in model (2.3) will *not* occur. The introduction of age structure leads to mutual invasibility and coexistence and can generate a diversity of dynamical outcomes.

We summarize what we have found below:

(1) We find that multiple subthreshold equilibria of each strain alone exist, possibly as a result of backward bifurcation. These equilibria will be present even if a second strain is not included in the model. Multiple subthreshold equilibria resulting from backward bifurcation have been found in a chronological age-structured model before [12], but in our case they do not occur without the age-structure. Thus, host age-structure is a primary causal mechanism for the subthreshold equilibria. Since it is well known that disease transmission models with multiple susceptible compartments and proportionate mixing incidence may possess multiple equilibria, it is reasonable to expect such in the age-structured model (2.3). We want to note, however, that usually the different susceptible compartments are associated with different susceptibilities, while in our case all susceptible individuals have the same, age-independent susceptibility.
(2) We find that if neither strain can persist subthreshold alone, then they cannot coexist in a strongly subthreshold mode, that is, when both reproduction numbers are below one. We conclude that cooperative coexistence in the model (2.3) is not possible.
(3) On the other hand, the strains can coexist in a weakly subthreshold coexistence, that is, when only one of the reproduction numbers is below one. When the strain with higher virulence has a reproduction number above one it can 'induce' the strain with lower virulence and reproduction number below one to coexist with it in what we expect is a stable equilibrium. When the strain with higher virulence has a reproduction number below one, the resulting coexistence equilibrium is unstable – stable coexistence does not occur.
(4) Strongly subthreshold coexistence is possible under the following scenario: one of the strains can exist subthreshold by itself, but the other one cannot. We find that the strain that can persist subthreshold by itself can 'induce' the other strain to exist in a stable coexistence equilibrium if the second strain can invade the stable equilibrium of the first strain, but it cannot invade the unstable equilibrium of the first strain.
(5) When a strain that can persist alone allows another strain that cannot persist alone, to persist in a coexistence mode the 'induced' strain always has lower virulence than the 'inducing' strain.
(6) When one of the strains eliminates the other, in most cases the strain with the larger reproduction number will persist in the population. However, there are exceptions, where the strain with the larger reproduction number will be eliminated and the strain with the suboptimal reproduction number will dominate. Two modes lead to this scenario. The first mode is bistable dominance ('priority effects'), when the dominant strain is determined by the initial conditions. The second mode is when the dominance equilibrium of the strain with the sub-

optimal reproduction number is the locally stable one, that is, when it cannot be invaded by the strain with the larger reproduction number. This phenomenon is observed when coexistence occurs, although not all trade-off mechanisms that cause coexistence also lead to dominance of a strain with suboptimal reproduction number, even in very complex models [38].

(7) Finally, we have shown that age structure can permit stable coexistence of pathogen strains for proportionate mixing incidence (frequency dependent transmission) but not for mass-action incidence (density dependent transmission).

Multiple equilibria with alternating stability behavior have not been detected to date in epidemiology, despite the extensive theoretical literature that predicts their existence (see [34] and the references there in). Empirical evidence for their occurrence in nature has been found in the context of metapopulation dynamics [23]. Conceivably, several populations, each of which exhibiting multiple equilibria can be interacting. Whether these are metapopulations, populations in ecological or epidemiological context, in order to explain the interplay between coexistence and extinction resulting from their interaction we need to know what invasibility criteria govern the outcome. From a theoretical perspective, an interesting question that we have touched on but remains largely not understood is: if multiple dominance equilibria are present (subthreshold or superthreshold), what invasibility conditions guarantee coexistence, and when is this coexistence stable and when – unstable? This remains a challenge for future explorations.

In conclusion, we mention that in this paper we allow only the infectivity of infectious individuals with strain one and strain two to vary with age. All other parameters in the age-structured model (2.3) are assumed constant. Clearly, our results will extend to the case when in addition to infectivity, we also allow other parameters in the model to vary with age, such as susceptibility of susceptible individuals, disease-induced death rates and/or natural death rate. A more interesting question to be addressed is: What if we assume all parameters constant (including infectivity) except, say the susceptibilities to the two strains of susceptible individuals, which are assumed age-dependent. Would coexistence and multiple equilibria still occur? The analysis in this paper cannot be easily adapted to answer that question. Different approach may be necessary, possibly one based entirely on simulations. We believe that the answer to this question is yes, but further investigations are required to confirm or rule out coexistence and multiple equilibria due to other modes of age dependent variation.

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