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ORIGINAL ARTICLE

Structured and Unstructured Continuous Models for *Wolbachia* Infections

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Abstract We introduce and investigate a series of models for an infection of a diplodiploid host species by the bacterial endosymbiont *Wolbachia*. The continuous models are characterized by partial vertical transmission, cytoplasmic incompatibility and fitness costs associated with the infection. A particular aspect of interest is competitions between mutually incompatible strains. We further introduce an age-structured model that takes into account different fertility and mortality rates at different stages of the life cycle of the individuals. With only a few parameters, the ordinary differential equation models exhibit already interesting dynamics and can be used to predict criteria under which a strain of bacteria is able to invade a population. Interestingly, but not surprisingly, the age-structured model shows significant differences concerning the existence and stability of equilibrium solutions compared to the unstructured model.

Keywords *Wolbachia* · Cytoplasmic incompatibility · Age-structured population dynamics · Stability analysis

1. Introduction

Wolbachia is a maternally transmitted bacterium that lives in symbiosis with many arthropod species and some filarial nematodes (Werren, 1997; O'Neill et al., 1997). It inhabits testes and ovaries of its hosts and has the ability to interfere with their reproductive mechanisms, resulting in a variety of phenotypes. Well-known effects are cytoplasmic incompatibility, induction of parthenogenesis, and feminization of genetic males, depending on the host species and the *Wolbachia* type. Besides the intrinsic interest in these mechanisms, *Wolbachia* are investigated as tools to drive desirable genes into a target population (Rasgon and Scott, 2004), as reinforcers of speciation (Telschow et al. 2005a, 2005b; Keeling

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et al., 2003), and as potential means of biological control (McMeniman et al., 2009). It was recently shown by McMeniman et al. (2009) that infection with *Wolbachia* shortens the lifespan of the mosquito *Aedes aegypti*, a vector for the Dengue fever virus. Since only older mosquitoes are carriers, this is a promising strategy to reduce the transmission of pathogens, without the ethically untenable eradication of a vector species.

Beginning already a half a century ago (Caspari and Watson, 1959), various mathematical models for the spread of a *Wolbachia* infection have been proposed and studied in the literature (see e.g. Turelli, 1994; Rasgon and Scott, 2004; Telschow et al., 2005a; Keeling et al., 2003; Engelstädter et al., 2004; Schofield, 2002; Vautrin et al., 2007; Haygood and Turelli, 2009 and references therein). Largely, these models fall into two classes, depending on whether time proceeds in discrete steps or continuously. Examples for continuous models are the papers (Keeling et al., 2003 and Schofield, 2002) that employ ordinary, respectively partial differential equations (with a spatial structure in the latter case). In the paper (Keeling et al., 2003), the authors proposed and studied a simple continuous model for the infection of an arthropod population with cytoplasmic incompatibility (CI) causing *Wolbachia*. Cytoplasmic incompatibility in diplodiploid (i.e. with diploid males and females) species manifests itself in completely or partially unviable crosses of infected males with uninfected females. For a discussion of the more complex outcome of cytoplasmic incompatibility in haplodiploid species, see Vautrin et al. (2007).

In this paper, we introduce a series of models for different aspects of interest. We start in Section 2 with an ordinary differential equation model for a single *Wolbachia* strain that infects a population without separate sexes. In Section 3 we present a model for infections with multiple strains. The present theoretical literature offers a complex picture of infection with multiple strains. While some authors exclude the coexistence of multiple strains of *Wolbachia* in infected individuals (Keeling et al., 2003; Haygood and Turelli, 2009), others model doubly infected individuals as a class of their own (Engelstädter et al., 2004; Vautrin et al., 2007). Moreover, different assumptions are made about the mutual compatibility of individuals carrying different strains. We construct a general model that encompasses these different possibilities by suitable choices of parameter values and/or initial conditions. Finally, motivated by the study (McMeniman et al., 2009), in Section 4 we refine our model from Section 2, by considering age-structured populations. We refer the reader interested in basic concepts and results in structured population dynamics to Cushing (1998), Metz and Diekmann (1986), Webb (1985). Modeling structured populations usually involves partial differential equations which are more difficult to analyse. Analytical progress is still possible, and as we will see in Section 4, the age-structured model may exhibit richer dynamics. At this point it will be possible to study age-dependent killing of *Wolbachia* infected individuals. Our models contain parameters of only three types, namely transmission efficacies, levels of cytoplasmic incompatibility, and fitness costs for the infected individuals. The analysis of the models aims to give conditions for the stability of specific equilibrium solutions that correspond to successful invasions. The paper ends with a discussion in Section 5 and an outlook about future work.

2. Single-sex model for a singular *Wolbachia* strain

Assume that the ratio of infected males to infected females is the same as the ratio of uninfected males to uninfected females and hence the population can be formally considered hermaphroditic. Let I and U denote the number of infected, respectively uninfected,

individuals in the population. Vertical transmission is partial, let $\tau \in [0,1]$ be the fraction of infected offspring from infected parents (another common notation is $\mu = 1-\tau$ for the fraction of uninfected ova produced by an infected female, see e.g. Turelli, 1994; O'Neill et al., 1997; Vautrin et al., 2007). Furthermore, we follow Keeling et al. (2003) and assume that the birth rate for both infected and uninfected individuals is equal (no reduction in fecundity in infected individuals). Let this rate be denoted by $b > 0$. Death of the individuals is modeled by a logistic loss term with rate $d > 0$ that accounts for competition among the total population. However, infected individuals can suffer an additional loss of fitness given by $D \geq 0$. Cytoplasmic incompatibility arises when an infected male fertilizes an egg from an uninfected female. Then, with a probability $q \in [0,1]$, the offspring is nonviable. As we do not consider separate sexes in this simple model, we just reduce the amount of offspring from uninfected individuals based on the probability of an encounter with an infected individual. Uninfected individuals still arise due to incomplete transmission of the bacteria from infected parents. Our equations read

$$\begin{aligned}
\frac{\mathrm{d}I}{\mathrm{d}t} &= \big(\tau b - (d+D)(I+U)\big)I, \\
\frac{\mathrm{d}U}{\mathrm{d}t} &= (1-\tau)bI + \left(b\left(1 - q\frac{I}{I+U}\right) - d(I+U)\right)U.
\end{aligned}$$

Upon rescaling the time by $t \to bt$ and setting $\eta = \frac{d+D}{d}$, we obtain the reduced system for the quantities $i = \mathrm{d}I/b$, $u = \mathrm{d}U/b$:

$$\frac{\mathrm{d}i}{\mathrm{d}t} = \big(\tau - \eta(i+u)\big)i, \tag{1}$$

$$\frac{\mathrm{d}u}{\mathrm{d}t} = (1-\tau)i + \left(1 - q\frac{i}{i+u} - (i+u)\right)u. \tag{2}$$

Observe that $\eta^{-1} =: \xi \in (0,1]$ and that $1-\xi$ can be interpreted as the fitness cost associated with *Wolbachia* infection. The point $(0,0)$ can be added to the domain of the state space, with the understanding that it is an equilibrium solution. It is obvious that the subspace of uninfected populations $\{0\} \times \mathbb{R}$ is forward invariant (that is, if initially there are no infected individuals, then there will be none at later times) and if transmission is complete, $\tau = 1$, then so is the subspace of completely infected populations $\mathbb{R} \times \{0\}$.

Model (1)–(2) always admits the disease-free equilibrium

$$(i_0, u_0) = (0,1). \tag{3}$$

Setting the left-hand side of Eq. (1) to zero and solving for an equilibrium point u yields

$$u = \tau\xi - i. \tag{4}$$

Inserting this into the equilibrium condition for (2) gives a quadratic equation for i,

$$\frac{q}{\tau\xi}i^2 + \big(\tau(\xi-1) - q\big)i + \tau\xi(1-\xi\tau) = 0. \tag{5}$$

Provided that

$$\big(\tau(\xi-1)-q\big)^2-4q(1-\xi\tau)\geq 0. \tag{6}$$

Equation (5) has the solutions

$$\begin{aligned} i_1 &= i_1(q,\tau,\xi)=\frac{\tau\xi(q-\tau(\xi-1)-\sqrt{(\tau(\xi-1)-q)^2-4q(1-\xi\tau)})}{2q},\\ i_2 &= i_2(q,\tau,\xi)=\frac{\tau\xi(q-\tau(\xi-1)+\sqrt{(\tau(\xi-1)-q)^2-4q(1-\xi\tau)})}{2q}, \end{aligned} \tag{7}$$

and these are always non-negative. The corresponding equilibrium values for the uninfected individuals are given by (4). For $u_2\geq 0$ it is necessary that

$$q+\tau(\xi-1)\geq 0. \tag{8}$$

This condition is also sufficient, since then one can derive from $\tau\leq 1$ the inequality

$$q+\tau(\xi-1)\geq\sqrt{\big(\tau(\xi-1)-q\big)^2-4q(1-\xi\tau)}$$

and hence $u_2\geq 0$. Condition (6) separates two regions in the parameter space, depending on whether other equilibrium solutions than the disease-free equilibrium are possible (see Fig. 1). We calculate the Jacobian of the right-hand side F of (1)–(2),

$$DF(i,u)=\begin{pmatrix} \tau-\eta(2i+u) & -\eta i\\ 1-\tau+qu\big(\frac{i}{(i+u)^2}-\frac{1}{i+u}\big)-u & 1+qi\big(\frac{u}{(i+u)^2}-\frac{1}{i+u}\big)-(2u+i)\end{pmatrix}. \tag{9}$$

At the disease-free equilibrium (3), we have

$$DF(0,1)=\begin{pmatrix}\tau-\eta & 0\\ -\tau-q & -1\end{pmatrix}.$$

This matrix has the eigenvalues -1 and $\tau-\eta\leq 0$. The latter eigenvalue is 0 only if $\tau=1$ (complete transmission) and $D=0$ (no penalty for infection); in all other cases it is strictly negative, and the disease-free equilibrium is locally asymptotically stable.

Explicit expressions (with respect to the parameters q, τ and ξ) can be obtained for the eigenvalues of the Jacobian (9) at the equilibrium solutions using e.g. MATHEMATICA (the MATHEMATICA notebook is available from the authors upon request). Unfortunately, these expressions are very complicated and not easily analyzed. We will present instead some representative numerical examples to demonstrate the possible behaviors.

Example 2.1. Assume that the infection is completely inherited, $\tau=1$, cytoplasmic incompatibility is complete, $q=1$, and that the cost of the infection is low, $\xi=0.9$. Then the three equilibrium solutions $(i_0,u_0)=(0,1)$, $(i_1,u_1)=(0.09,0.81)$ and $(i_2,u_2)=(0.9,0)$

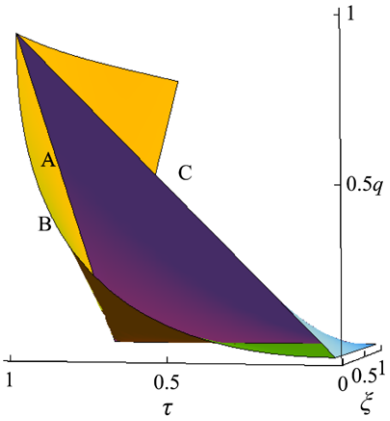

Fig. 1 The yellow surface separates the (ξ, τ, q)-parameter space of model (1)–(2) into a region where only the disease-free equilibrium (3) exists (A) and where coexistence of equilibrium solutions (u_1, i_1) and (u_2, i_2) given by (7) is possible (B). However, only in the region (C) above the blue surface given by (8) is $u_2 = \tau\xi - i_2 \geq 0$ (this belongs to the observed stable equilibrium (u_2, i_2)). (Color figure online.)

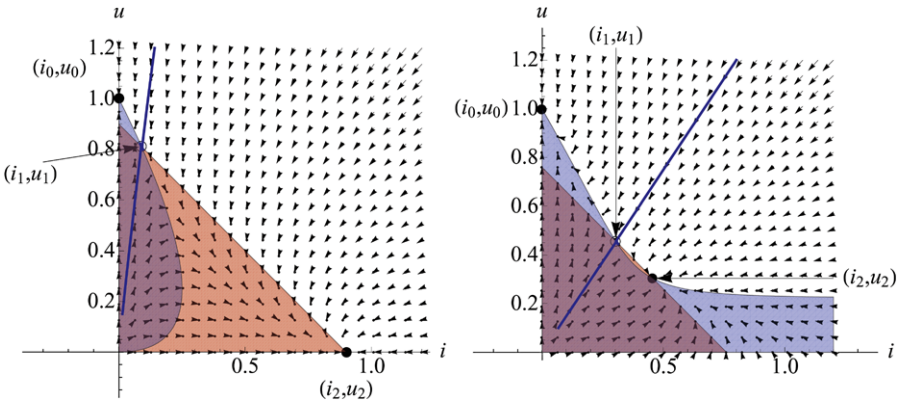

Fig. 2 (Left) The vector field (1)–(2) for the parameter triple $(\xi, \tau, q) = (0.9, 1, 1)$, together with the three equilibrium solutions. Solid disks indicate locally asymptotically stable equilibrium solutions, while the disk indicates an unstable equilibrium. Shown are also regions of growth of u (light blue) and growth of i (light red). The blue lines are the stable manifolds of the saddle point (i_1, u_1) and the separatrices of the equilibrium solutions (i_0, u_0) and (i_2, u_2). (Right) The vector field (1)–(2) for the parameter triple $(\xi, \tau, q) = (1, 0.76, 1)$, which admits bistability and true coexistence. The stable manifold of the saddle point (i_1, u_1) is shown in blue. (Color figure online.)

are present, of which (i_0, u_0) and (i_2, u_2) are locally asymptotically stable. The vector field is shown in Fig. 2 (left panel). The epidemic equilibrium (i_2, u_2) has a much bigger basin of attraction than the disease-free equilibrium (i_0, u_0); in other words, the threshold for an infection to establish itself is low.

Example 2.2. At high levels of cytoplasmic incompatibility, $q = 1$, and no penalty for the infection, $\xi = 1$, and a partial transmission, $\tau = 0.76$, besides the equilib-

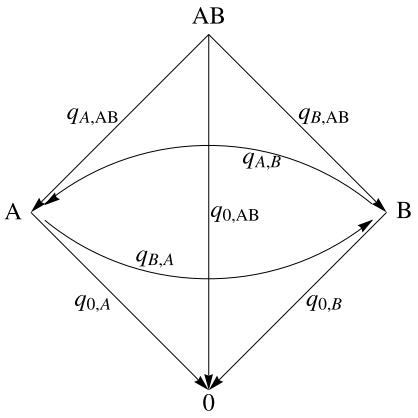

Fig. 3 The directed graph of possible incompatibility relations. An arrow from node X to node Y indicates that a $X\male \times Y\female$ cross is incompatible, with incompatibility level $q_{Y,X}$.

rium (i_0, u_0) there is the locally asymptotically stable coexistence equilibrium $(i_2, u_2) = (0.456, 0.304)$, see Fig. 2 (right panel). The basin of attraction of the disease-free equilibrium (i_0, u_0) is much bigger than in Example 2.1, indicating that the threshold for establishment of the infection is higher.

Example 2.3. If the cytoplasmic incompatibility is very weak, $q = 0.1$, and the fitness cost of the infection is higher, $\xi = 0.5$ (and again $\tau = 1$), then the equilibrium $(i_0, u_0) = (0, 1)$ is globally asymptotically stable in the set $\{i \geq 0, u \geq 0\}$ and the equilibrium $(i_1, u_1) = (0.5, 0)$ is a saddle point. The third equilibrium point has $u_2 < 0$ and has no biological meaning.

The above examples suggest that the equilibrium (i_1, u_1) is always a saddle point and that (i_2, u_2) is locally asymptotically stable, if $u_2 \geq 0$. If (i_2, u_2) exists and is locally asymptotically stable, then its basin of attraction is larger for larger values of the transmission rate τ (this is the intersection of regions (B) and (C) in Fig. 1).

3. Infection with multiple strains

Assume that two *Wolbachia* strains A and B are present in the population and let i_A, i_B and i_{AB} denote the number of individuals singly or doubly infected, in addition to u, the number of uninfected individuals. We use the same scaling as in the previous section, where time was scaled with respect to the birth rate b. There are seven incompatibility levels $q_{X,Y}$ where $X, Y \in \{0, A, B, AB\}$ are the infection statuses in the incompatible cross. These are shown in the directed graph of incompatibilities in Fig. 3.

We assume that the transmission of one strain in doubly infected individuals is independent of the transmission of the other strain (Vautrin et al., 2007). Moreover, the mortalities due to infection with either strain are additive. With these assumptions, and

setting $p = i_{AB} + i_A + i_B + u$ for the total population, our model is

$$\begin{aligned}
\frac{\mathrm{d}i_{AB}}{\mathrm{d}t} &= \tau_A\tau_B i_{AB} - \eta_{AB} p i_{AB},\\
\frac{\mathrm{d}i_A}{\mathrm{d}t} &= \tau_A(1-\tau_B)i_{AB} + \tau_A\left(1 - q_{A,B}\frac{i_B}{p} - q_{A,AB}\frac{i_{AB}}{p}\right)i_A - \eta_A p i_A,\\
\frac{\mathrm{d}i_B}{\mathrm{d}t} &= (1-\tau_A)\tau_B i_{AB} + \tau_B\left(1 - q_{B,A}\frac{i_A}{p} - q_{B,AB}\frac{i_{AB}}{p}\right)i_B - \eta_B p i_B,\\
\frac{\mathrm{d}u}{\mathrm{d}t} &= (1-\tau_A)(1-\tau_B)i_{AB} + (1-\tau_A)\left(1 - q_{A,B}\frac{i_B}{p} - q_{A,AB}\frac{i_{AB}}{p}\right)i_A\\
&\quad + (1-\tau_B)\left(1 - q_{B,A}\frac{i_A}{p} - q_{B,AB}\frac{i_{AB}}{p}\right)i_B\\
&\quad + \left(1 - q_{0,A}\frac{i_A}{p} - q_{0,B}\frac{i_B}{p} - q_{0,AB}\frac{i_{AB}}{p}\right)u - pu,
\end{aligned} \tag{10}$$

where

$$\eta_A = \frac{d + D_A}{d}, \quad \eta_B = \frac{d + D_B}{d} \quad \text{and} \quad \eta_{AB} = \frac{d + D_A + D_B}{d} = \eta_A + \eta_B - 1$$

are measures of the fitness costs of the individual infection types. This model can now be reduced in its complexity in a variety of ways. For example, if the initial condition lies in the space $\{0\} \times \mathbb{R}^3$, that is, there are no doubly infected individuals present initially, then the solution will also lie in that space at all times. Moreover, setting appropriate incompatibility levels $q_{X,Y}$ to zero allows to study cases of mutual compatibility.

As a first illustration, we want to consider the absence of doubly infected individuals, $i_{AB} \equiv 0$, mutual compatibility of infected individuals, $q_{A,B} = q_{B,A} = 0$, equal transmission efficacy $\tau_A = \tau_B =: \tau$ and equal infection costs $\eta_A = \eta_B =: \eta$ (again, we write $\xi = \eta^{-1}$). The symmetry is only broken by the levels of incompatibility $q_{0,A} \neq q_{0,B}$. Hence, Eq. (10) simplifies to

$$\begin{aligned}
\frac{\mathrm{d}i_A}{\mathrm{d}t} &= (\tau - \eta p)i_A,\\
\frac{\mathrm{d}i_B}{\mathrm{d}t} &= (\tau - \eta p)i_B,\\
\frac{\mathrm{d}u}{\mathrm{d}t} &= (1-\tau)(i_A + i_B) + \left(1 - q_{0,A}\frac{i_A}{p} - q_{0,B}\frac{i_B}{p}\right)u - pu.
\end{aligned} \tag{11}$$

Observe that model (11) has the property that planes orthogonal to the (i_A, i_B)-plane

$$R_\alpha = \left\{(i_A, i_B, u) \in \mathbb{R}^3_{\geq 0} : i_A - \alpha i_B = 0\right\}$$

are invariant under the flow generated by (11). This is seen from the fact that for every $\alpha \in [0, \infty]$,

$$\frac{\mathrm{d}}{\mathrm{d}t}(i_A - \alpha i_B) = (\tau - \eta p)(i_A - \alpha i_B) = 0$$

on R_α. This implies that the ratio $\frac{i_A}{i_A+i_B}$ remains constant along a trajectory. In other words, if transmission efficacies and death rates are equal for two strains (as are birth rates throughout in our model) then neither strain can replace the other among the infected individuals based on stronger cytoplasmic incompatibility. This is in line with recent theoretical predictions of Turelli (1994) and Haygood and Turelli (2009), who suggest that strains are selected for relative fecundity rather than high levels of cytoplasmic incompatibility. It needs to be pointed out, however, that even a small difference in transmission efficacies or death rates of the two strains helps the strain with the greater transmission rate or the lower mortality to establish itself in the population.

The disease-free equilibrium of (11) is easily found to be

$$(i_{A,0}, i_{B,0}, u_0) = (0, 0, 1). \tag{12}$$

It is clear that the subspaces $\{0\} \times \mathbb{R} \times \mathbb{R}$ and $\mathbb{R} \times \{0\} \times \mathbb{R}$ are forward invariant under the flow generated by (11) and that the equilibrium solutions (7) exist in the respective subspaces, with q in (7) replaced by either $q_{0,A}$ or $q_{0,B}$. That is, we have equilibrium solutions

$$\begin{aligned} &\big(i_{A,1}(q_{0,A}, \tau, \xi), 0, \tau\xi - i_{A,1}\big), \qquad &&\big(i_{A,2}(q_{0,A}, \tau, \xi), 0, \tau\xi - i_{A,2}\big), \\ &\big(0, i_{B,1}(q_{0,B}, \tau, \xi), \tau\xi - i_{B,1}\big), \qquad &&\big(i_{B,2}(0, q_{0,B}, \tau, \xi), \tau\xi - i_{B,2}\big). \end{aligned}$$

Besides that, it can be checked that there is a continuum of equilibrium solutions

$$\begin{pmatrix} i_A(u) \\ i_B(u) \end{pmatrix} = \begin{pmatrix} \frac{-\tau^3 - \eta q_{0,B}\tau u + \eta^2 q_{0,B} u^2 + \tau^2(1+(\eta-1)u)}{\eta^2(q_{0,A}-q_{0,B})u} \\ \frac{\tau^3 + \eta q_{0,A}\tau u - \eta^2 q_{0,A} u^2 - \tau^2(1+(\eta-1)u)}{\eta^2(q_{0,A}-q_{0,B})u} \end{pmatrix} \tag{13}$$

for every $u \in (0, \tau\xi)$, provided that these expressions are non-negative. The solutions of (13) satisfy

$$i_A(u) + i_B(u) = \frac{\tau}{\eta} - u = \tau\xi - u,$$

which corresponds to Eq. (4).

Example 3.1. We consider the case $\tau = 1$ of complete transmission. One checks by direct calculation that system (11) then has another manifold of equilibrium solutions,

$$i_A + i_B = \xi, \qquad u = 0.$$

The intersection of this line with each plane R_α orthogonal to the (i_A, i_B)-plane is an equilibrium for the flow restricted to that plane. In addition, each R_α contains a saddle point. A numerical example is shown in Fig. 4, left panel. If, in contrast, different costs are associated with the infection, the strain with the lower cost will dominate the population, see Fig. 4, right panel. Similarly, if infection costs are equal, but one strain transmits more efficiently, then it is going to dominate the population.

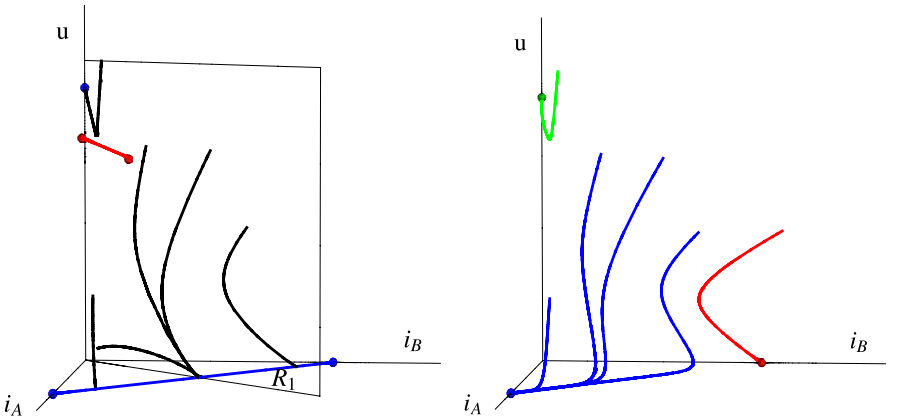

Fig. 4 (Left) Dynamics of model (11) in the case that $q_{0,A} = 0.95$, $q_{0,B} = 0.5$, $\tau = 1$ and $\eta = 1.1$. The solid blue line is a family of attractors for the flow restricted to planes R_α; the red line is a branch of saddle points in each of these subspaces. Several individual trajectories are shown, and the space $R_1 = \{i_A = i_B\}$ is marked. (Right) If we choose instead $\eta_A = 1.1$ and $\eta_B = 1.2$ (while keeping all other parameters the same) then the less costly strain A dominates the population. (Color figure online.)

We return to model (10) and consider mutual incompatibility of singly infected individuals. The equations are

$$\begin{aligned}
\frac{\mathrm{d}i_A}{\mathrm{d}t} &= \left(\tau\left(1 - q_{A,B}\frac{i_B}{p}\right) - \eta p\right) i_A, \\
\frac{\mathrm{d}i_B}{\mathrm{d}t} &= \left(\tau\left(1 - q_{B,A}\frac{i_A}{p}\right) - \eta p\right) i_B, \\
\frac{\mathrm{d}u}{\mathrm{d}t} &= (1-\tau)\left(\left(1 - q_{A,B}\frac{i_B}{p}\right) i_A + \left(1 - q_{B,A}\frac{i_A}{p}\right) i_B\right) \\
&\quad + \left(1 - q_0\frac{i_A + i_B}{p}\right) u - pu.
\end{aligned} \tag{14}$$

It is clear that if either strain is not present initially then it will remain absent at all times. On the marginal spaces $\{i_A = 0\}$ and $\{i_B = 0\}$, Eqs. (14) reduce to the single strain model (1)–(2) and have the corresponding equilibrium solutions where only one strain is present, with the common disease-free equilibrium (12). It follows from (14) that

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}(q_{B,A}i_A - q_{A,B}i_B) &= q_{B,A}\left(\tau\left(1 - q_{A,B}\frac{i_B}{p}\right) - \eta p\right) i_A \\
&\quad - q_{A,B}\left(\tau\left(1 - q_{B,A}\frac{i_A}{p}\right) - \eta p\right) i_B \\
&= \tau\left(q_{B,A}\left(1 - q_{A,B}\frac{i_B}{p}\right) i_A - q_{A,B}\left(1 - q_{B,A}\frac{i_A}{p}\right) i_B\right) \\
&\quad - \eta p(q_{B,A}i_A - q_{A,B}i_B) \\
&= (\tau - \eta p)(q_{B,A}i_A - q_{A,B}i_B).
\end{aligned}$$

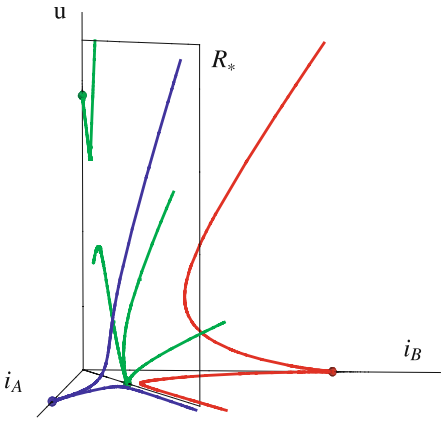

Fig. 5 Mutually incompatible strains as described in (14) do not show coexistence. The marginal equilibrium solutions are marked by dots, the disease-free equilibrium (Eq. (12), green) attracts some solutions from the plane R_* and other trajectories beginning in the wedges on either side that are not shown here. (Color figure online.)

This implies that the plane orthogonal to the (i_A, i_B)-plane,

$$R_* = \left\{(i_A, i_B, u) \in \mathbb{R}^3_{\geq 0} \,:\, q_{B,A} i_A = q_{A,B} i_B\right\},$$

is forward invariant, and hence so are the wedges on either side. Solving Eqs. (14) for the total population yields that if $i_A \neq 0$, $i_B \neq 0$, then

$$0 = p^2 - \frac{\tau}{\eta} p + \frac{\tau}{\eta} q_{A,B} i_B,$$
$$0 = p^2 - \frac{\tau}{\eta} p + \frac{\tau}{\eta} q_{B,A} i_A.$$

For this system to be consistent, it is necessary that if $i_A \neq 0$, $i_B \neq 0$ then

$$q_{B,A} i_A = q_{A,B} i_B,$$

hence any coexistence equilibrium of the two infected strains has to lie in the plane R_*. Indeed, there may be a saddle point equilibrium solution in R_* that is locally asymptotically stable for flows that start in R_*.

Example 3.2. Let $q_{A,B} = 0.99$, $q_{B,A}$ and $q_{0,A} = q_{0,B} = 1$. Choose the transmission efficacy $\tau = 1$ and the cost of the infection $\eta = 1.1$. We see in Fig. 5 that every solution starting outside the space R_* converges to an equilibrium in one of the marginal spaces. The plane R_* contains a locally stable equilibrium for trajectories starting in R_* which has $u_2 = 0$ and it contains a saddle point for trajectories starting within R_* (not shown, compare to Example 2.1 and Fig. 2).

Again, we need to recall that this dynamical behavior is not generic, in the sense that the complement of the set $\{\tau_A = \tau_B,\ \eta_A = \eta_B\}$ is dense in the parameter space.

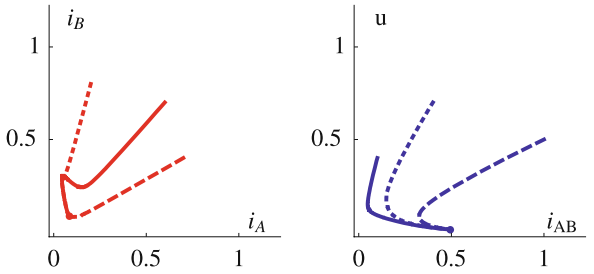

Fig. 6 With the parameters chosen as described in Example 3.3, we observe stable coexistence of all three infection types. Solid, dashed and dotted lines, respectively, show parts of the solution starting at the same initial values.

Finally, we want to explore the full model (10) when doubly infected individuals are present. To somewhat reduce the number of parameters, we assume

$$q_{A,B} = q_{A,AB} = q_{0,B}, \qquad q_{B,A} = q_{B,AB} = q_{0,A},$$

that is, the presence of one strain in the fertilizing male that is missing in the female, has the same effect regardless of the other infections that the female may carry (Hoffmann and Turelli, 1997, p. 66). Moreover, the escape from cytoplasmic incompatibility for the offspring of an uninfected female and a doubly infected male is the product of the two individual escape probabilities (Vautrin et al., 2007),

$$1 - q_{0,AB} = (1 - q_{0,A})(1 - q_{0,B}).$$

Example 3.3. Under the above assumptions, let $q_{A,B} = 0.9 = q_{B,A}$, the transmission efficacy $\tau_A = \tau_B = 0.9$ and the cost of the infection $\eta_A = \eta_B = 1.1$. Then there exists a coexistence equilibrium of doubly infected and both types of singly infected individuals, where however the proportion of doubly infected individuals is much larger (Fig. 6).

4. Introduction of age-structure

In the previous sections we have seen that infection with *Wolbachia* gives rise to interesting dynamic behavior already in unstructured populations. Clearly, individuals of different ages are subject to different fertility and mortality rates. We therefore expand our model (1)–(2) to include age-dependent fertility and mortality rates for infected and uninfected individuals. This leads to nonlinear partial differential equations with nonlocal boundary conditions that represent the birth process (Webb, 1985; Farkas, 2006; Farkas and Hagen 2007, 2008; Gurtin and MacCamy, 1974). Although this results in more complex models, they are still amenable to analytical study. Here we focus on qualitative questions, when analytical progress is possible; in particular: How do the stability results for equilibrium solutions compare to the unstructured case?

Let $i(a,t)$ and $u(a,t)$ denote the densities of infected and uninfected individuals of age a at time t, respectively, where $a \in [0,m]$ (this is not to be confused with the notation

in Section 2, where they denoted scaled numbers of infected and uninfected individuals). Then the evolution of the population is governed by

$$i_t(a,t) + i_a(a,t) = -\eta_1(a)(I(t)+U(t))i(a,t), \tag{15}$$

$$u_t(a,t) + u_a(a,t) = -\eta_2(a)(I(t)+U(t))u(a,t), \tag{16}$$

$$i(0,t) = \tau \int_0^m \beta_1(a) i(a,t)\,\mathrm{d}a, \tag{17}$$

$$u(0,t) = (1-\tau)\int_0^m \beta_1(a) i(a,t)\,\mathrm{d}a + \left(1 - q\frac{I(t)}{I(t)+U(t)}\right)\int_0^m \beta_2(a)u(a,t)\,\mathrm{d}a, \tag{18}$$

where

$$I(t) = \int_0^m i(a,t)\,\mathrm{d}a, \qquad U(t) = \int_0^m u(a,t)\,\mathrm{d}a,$$

and η_1, η_2, β_1 and β_2 denote the age-specific mortality and fertility rates for infected and uninfected individuals, respectively. System (15)–(18) is equipped with initial conditions

$$i(a,0) = i_0(a), \qquad u(a,0) = u_0(a).$$

The parameters τ and q have the same meaning as in Section 2.

4.1. Existence of equilibrium solutions

We find the time-independent solutions of Eqs. (15) and (16) as

$$i_*(a) = i_*(0)\exp\left\{-(I_*+U_*)\int_0^a \eta_1(r)\,\mathrm{d}r\right\}, \tag{19}$$

$$u_*(a) = u_*(0)\exp\left\{-(I_*+U_*)\int_0^a \eta_2(r)\,\mathrm{d}r\right\}, \tag{20}$$

where $i_*(0)$ and $u_*(0)$ satisfy

$$i_*(0) = \tau i_*(0)\int_0^m \beta_1(a)\exp\left\{-(I_*+U_*)\int_0^a \eta_1(r)\,\mathrm{d}r\right\}\mathrm{d}a, \tag{21}$$

$$u_*(0) = (1-\tau)i_*(0)\int_0^m \beta_1(a)\exp\left\{-(I_*+U_*)\int_0^a \eta_1(r)\,\mathrm{d}r\right\}\mathrm{d}a + \left(1 - q\frac{I_*}{I_*+U_*}\right)u_*(0)\int_0^m \beta_2(a)\exp\left\{-(I_*+U_*)\int_0^a \eta_2(r)\,\mathrm{d}r\right\}\mathrm{d}a. \tag{22}$$

Here

$$I_* = \int_0^m i_*(a)\,\mathrm{d}a, \qquad U_* = \int_0^m u_*(a)\,\mathrm{d}a.$$

First we note that the trivial steady state $(0, 0)$ always exists. Next we note that if $i_*(\cdot) \equiv 0$ then Eq. (22) reduces to

$$1 = \int_0^m \beta_2(a) \exp\left\{-U_* \int_0^a \eta_2(r)\,\mathrm{d}r\right\} \mathrm{d}a. \tag{23}$$

It then immediately follows from the monotonicity and continuity of the right-hand side of (23) (as a function of U_*) and the Intermediate Value Theorem, that a unique disease-free equilibrium, given by

$$u_*(a) = \frac{U_* \exp\{-U_* \int_0^a \eta_2(r)\,\mathrm{d}r\}}{\int_0^m \exp\{-U_* \int_0^a \eta_2(r)\,\mathrm{d}r\}\,\mathrm{d}a},$$

exists if and only

$$\int_0^m \beta_2(a)\,\mathrm{d}a > 1 \tag{24}$$

holds. If we look for strictly positive equilibrium solutions $(i_*(a), u_*(a))$, we find that I_* and U_* have to satisfy

$$1 = \tau \int_0^m \beta_1(a) \exp\left\{-(I_* + U_*) \int_0^a \eta_1(r)\,\mathrm{d}r\right\} \mathrm{d}a, \tag{25}$$

$$\frac{U_*\left(1 - \left(1 - q\,\frac{I_*}{I_*+U_*}\right) \int_0^m \beta_2(a) \exp\{-(I_* + U_*) \int_0^a \eta_2(r)\,\mathrm{d}r\}\,\mathrm{d}a\right)}{\int_0^m \exp\{-(I_* + U_*) \int_0^a \eta_2(r)\,\mathrm{d}r\}\,\mathrm{d}a}$$

$$= \frac{I_*(\tau^{-1} - 1)}{\int_0^m \exp\{-(I_* + U_*) \int_0^a \eta_1(r)\,\mathrm{d}r\}\,\mathrm{d}a}. \tag{26}$$

Conversely, if I_* and U_* satisfy Eqs. (25)–(26), then Eqs. (19)–(20) determine uniquely a positive equilibrium solution. We also see from Eq. (25) that

$$\int_0^m \beta_1(a)\,\mathrm{d}a > \frac{1}{\tau} \tag{27}$$

is a necessary condition for the existence of a positive equilibrium. In fact, if Eq. (27) holds true, then we can solve Eq. (25) to obtain a unique positive value

$$c_1 = I_* + U_*. \tag{28}$$

A straightforward calculation then leads from Eq. (26) to the following quadratic equation for I_*:

$$I_*^2 c_3 + I_*(1 - c_2 - c_1 c_3 + c_4) + c_1 c_2 - c_1 = 0, \tag{29}$$

where we have defined

$$c_2 = \int_0^m \beta_2(a) \exp\left\{-c_1 \int_0^a \eta_2(r)\,\mathrm{d}r\right\} \mathrm{d}a, \quad c_3 = \frac{q c_2}{c_1}, \quad \text{and}$$
$$c_4 = \frac{(\tau^{-1}-1)\int_0^m \exp\{-c_1 \int_0^a \eta_2(r)\,\mathrm{d}r\}\,\mathrm{d}a}{\int_0^m \exp\{-c_1 \int_0^a \eta_1(r)\,\mathrm{d}r\}\,\mathrm{d}a}.$$

Similarly to the unstructured case, see Eq. (5), we arrive at a quadratic equation (unless $q = 0$) for the infected population size I_*. Of course, the calculations now are much more involved since we have age-dependent fertility and mortality rates. However, for fixed model ingredients the equilibrium solutions can be determined explicitly, via Eqs. (19)–(20). In contrast to the unstructured case, we have necessary conditions on the birth rates for the existence of non-trivial equilibria.

We summarize our findings in the following theorem.

Theorem 4.1. *The equilibrium solutions to equation system* (15)–(18) *are given by functions* (19)–(20) *with initial values* (21)–(22), *provided that the total populations of infected and uninfected individuals I_* and U_* given by Eqs.* (29) *and* (28) *are non-negative.*

We note the formal similarity of Eqs. (28) and (29) to the conditions (4) and (5) for the unstructured model in Section 2.

4.2. (In)stability

In the previous section we established necessary and sufficient conditions for the existence of a non-trivial steady state of the system (15)–(18). In this section we study stability properties of the steady states. To this end, first we formally linearize system (15)–(18) around a steady-state solution $(i_*(a), u_*(a))$. We introduce the perturbations $p(a,t) = i(a,t) - i_*(a)$ and $s(a,t) = u(a,t) - u_*(a)$ and we use Taylor series expansions of the fertility and mortality functions. Then we drop the nonlinear terms to arrive at the linearized system

$$p_t(a,t) + p_a(a,t) = -\eta_1(a)\big(p(a,t)(I_*+U_*) + i_*(a)\big(P(t)+S(t)\big)\big), \tag{30}$$
$$s_t(a,t) + s_a(a,t) = -\eta_2(a)\big(s(a,t)(I_*+U_*) + u_*(a)\big(P(t)+S(t)\big)\big), \tag{31}$$
$$p(0,t) = \tau \int_0^m \beta_1(a)\,p(a,t)\,\mathrm{d}a, \tag{32}$$
$$s(0,t) = (1-\tau)\int_0^m \beta_1(a)\,p(a,t)\,\mathrm{d}a + \left(1 - q\frac{I_*}{I_*+U_*}\right)\int_0^m \beta_2(a)s(a,t)\,\mathrm{d}a$$
$$- q\left(\frac{U_*}{(I_*+U_*)^2}P(t) - \frac{I_*}{(I_*+U_*)^2}S(t)\right)\int_0^m \beta_2(a)u_*(a)\,\mathrm{d}a, \tag{33}$$

where

$$P(t) = \int_0^m p(a,t)\,\mathrm{d}a, \qquad S(t) = \int_0^m s(a,t)\,\mathrm{d}a.$$

For more detailed calculations we refer the reader to Farkas (2006), Farkas and Hagen (2007, 2008), where similar types of age- and size-structured models were treated. It can be shown that the linearized system is governed by a strongly continuous semigroup of linear operators, which is eventually compact (see e.g. Farkas and Hagen 2007, 2008). However, this governing semigroup cannot be shown to be positive, since mortality of both infected and uninfected individuals is an increasing function of the total population size. Eventual compactness of the governing linear semigroup implies that to study stability of steady states it is sufficient to study the point spectrum of the linearized operator (see e.g. Engel and Nagel, 2000). The standard way how this can be carried out is to solve the eigenvalue equation and deduce a characteristic equation (if possible) whose roots are the eigenvalues of the linearized operator. We note that the lack of positivity implies that we cannot expect to establish even local stability results unless the characteristic equation can be cast in a simple form. We substitute

$$\begin{pmatrix} p(a,t) \\ s(a,t) \end{pmatrix} = \exp\{\lambda t\} \begin{pmatrix} v(a) \\ w(a) \end{pmatrix}$$

into the linearized equations (30)–(33). This yields

$$v'(a) = -v(a)\big(\lambda + \eta_1(a)(I_* + U_*)\big) - \eta_1(a) i_*(a)(V + W), \tag{34}$$

$$w'(a) = -w(a)\big(\lambda + \eta_2(a)(I_* + U_*)\big) - \eta_2(a) u_*(a)(V + W), \tag{35}$$

$$v(0) = \tau \int_0^m \beta_1(a) v(a)\,\mathrm{d}a, \tag{36}$$

$$\begin{aligned} w(0) = {} & (1-\tau)\int_0^m \beta_1(a) v(a)\,\mathrm{d}a + \left(1 - q\frac{I_*}{I_* + U_*}\right)\int_0^m \beta_2(a) w(a)\,\mathrm{d}a \\ & + q\frac{I_* W - U_* V}{(I_* + U_*)^2}\int_0^m \beta_2(a) u_*(a)\,\mathrm{d}a, \end{aligned} \tag{37}$$

where

$$V = \int_0^m v(a)\,\mathrm{d}a, \qquad W = \int_0^m w(a)\,\mathrm{d}a.$$

Hence $\lambda \in \mathbb{C}$ is an eigenvalue if and only if the nonlocal system (34)–(37) admits a nontrivial solution. The solution of the differential equations (34) and (35) is

$$v(a) = f_\lambda^1(a)\left(v(0) - \int_0^a \frac{\eta_1(x) i_*(x)(V+W)}{f_\lambda^1(x)}\,\mathrm{d}x\right), \tag{38}$$

$$w(a) = f_\lambda^2(a)\left(w(0) - \int_0^a \frac{\eta_2(x) u_*(x)(V+W)}{f_\lambda^2(x)}\,\mathrm{d}x\right), \tag{39}$$

where we have introduced

$$f_\lambda^i(a) = \exp\left\{-\int_0^a \lambda + \eta_i(y)(I_* + U_*)\,\mathrm{d}y\right\}, \quad i = 1, 2.$$

Next we substitute the solutions (38) and (39) into the boundary conditions (36) and (37) and integrate the solutions (38) and (39) from zero to m to arrive at a four-dimensional homogeneous system for the unknowns $v(0),\ w(0),\ V$ and W. This homogeneous system admits a non-trivial solution if and only if the determinant of the coefficient matrix equals zero. We can formulate the following theorem.

Theorem 4.2. *λ is an eigenvalue of the linearized operator if and only if it satisfies the equation*

$$K(\lambda) = \det \begin{pmatrix} \tau a_5(\lambda) - 1 & 0 & -\tau a_6(\lambda) & -\tau a_6(\lambda) \\ (1-\tau)a_5(\lambda) & a_7(\lambda) - \frac{q\, I_* a_7(\lambda)}{I_* + U_*} - 1 & a_8(\lambda) & a_{10}(\lambda) \\ a_1(\lambda) & 0 & -a_2(\lambda) - 1 & -a_2(\lambda) \\ 0 & a_3(\lambda) & -a_4(\lambda) & -a_4(\lambda) - 1 \end{pmatrix} = 0, \tag{40}$$

where

$$a_1(\lambda) = \int_0^m f_\lambda^1(a)\,\mathrm{d}a, \qquad a_2(\lambda) = \int_0^m f_\lambda^1(a) \int_0^a \frac{\eta_1(x) i_*(x)}{f_\lambda^1(x)}\,\mathrm{d}x\,\mathrm{d}a,$$

$$a_3(\lambda) = \int_0^m f_\lambda^2(a)\,\mathrm{d}a, \qquad a_4(\lambda) = \int_0^m f_\lambda^2(a) \int_0^a \frac{\eta_2(x) u_*(x)}{f_\lambda^2(x)}\,\mathrm{d}x\,\mathrm{d}a,$$

$$a_5(\lambda) = \int_0^m \beta_1(a) f_\lambda^1(a)\,\mathrm{d}a, \qquad a_6(\lambda) = \int_0^m \beta_1(a) f_\lambda^1(a) \int_0^a \frac{\eta_1(x) i_*(x)}{f_\lambda^1(x)}\,\mathrm{d}x\,\mathrm{d}a,$$

$$a_7(\lambda) = \int_0^m \beta_2(a) f_\lambda^2(a)\,\mathrm{d}a, \qquad a_9(\lambda) = \int_0^m \beta_2(a) f_\lambda^2(a) \int_0^a \frac{\eta_2(x) u_*(x)}{f_\lambda^2(x)}\,\mathrm{d}x\,\mathrm{d}a,$$

$$a_8(\lambda) = (\tau - 1)a_6(\lambda) + \left(\frac{q\, I_*}{I_* + U_*} - 1\right) a_9(\lambda) - \frac{q\, U_*}{(I_* + U_*)^2} \int_0^m \beta_2(a) u_*(a)\,\mathrm{d}a,$$

$$a_{10}(\lambda) = (\tau - 1)a_6(\lambda) + \left(\frac{q\, I_*}{I_* + U_*} - 1\right) a_9(\lambda) + \frac{q\, I_*}{(I_* + U_*)^2} \int_0^m \beta_2(a) u_*(a)\,\mathrm{d}a.$$

It follows from the growth behavior of the functions f_λ^i that

$$\lim_{\lambda \to +\infty} K(\lambda) = \det \begin{pmatrix} -1 & 0 & 0 & 0 \\ 0 & -1 & C_1 & C_2 \\ 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & -1 \end{pmatrix} = 1, \tag{41}$$

the limit being taken in $\mathbb{R}$, and C_1, C_2 are constants. Hence we can formulate the following general instability criterion, which follows immediately from the Intermediate Value theorem.

Theorem 4.3. *The stationary solution $(i_*(a), u_*(a))$ of Eqs. (15)–(18) is unstable if $K(0) < 0$.*

As we can see, the characteristic equation (40) is rather complicated in general, hence we only consider some interesting special cases when analytical progress is possible.

4.2.1. The trivial steady state
We consider the stability of the steady state $i_* \equiv 0$, $u_* \equiv 0$. Note that in this case the characteristic equation (40) reduces to

$$K(\lambda) = \det \begin{pmatrix} \tau a_5(\lambda) - 1 & 0 & 0 & 0 \\ (1-\tau)a_5(\lambda) & a_7(\lambda) - 1 & 0 & 0 \\ a_1(\lambda) & 0 & -1 & 0 \\ 0 & a_3(\lambda) & 0 & -1 \end{pmatrix} = 0, \tag{42}$$

which leads to the equation

$$\big(\tau a_5(\lambda) - 1\big)\big(a_7(\lambda) - 1\big) = 0. \tag{43}$$

Therefore, $\lambda \in \mathbb{C}$ is an eigenvalue if and only if λ satisfies either of the two equations

$$1 = \tau \int_0^m \beta_1(a) e^{-\lambda a}\,\mathrm{d}a, \qquad 1 = \int_0^m \beta_2(a) e^{-\lambda a}\,\mathrm{d}a. \tag{44}$$

We can formulate the following theorem.

Theorem 4.4. *The trivial steady state is locally asymptotically stable if*

$$\tau \int_0^m \beta_1(a)\,\mathrm{d}a < 1 \quad \textit{and} \quad \int_0^m \beta_2(a)\,\mathrm{d}a < 1. \tag{45}$$

On the other hand, if either

$$\tau \int_0^m \beta_1(a)\,\mathrm{d}a > 1 \quad \textit{or} \quad \int_0^m \beta_2(a)\,\mathrm{d}a > 1 \tag{46}$$

holds, then the trivial steady state is unstable.

4.2.2. The disease-free steady state
Consider the disease-free steady state, i.e. $i_* \equiv 0$, which exists by condition (24) if and only if $\int_0^m \beta_2(a)\,\mathrm{d}a > 1$. In this case the characteristic equation (40) can be written as

$$\begin{aligned} K(\lambda) &= \big(\tau a_5(\lambda) - 1\big) \det \begin{pmatrix} a_7(\lambda) - 1 & -a_9(\lambda) - \frac{q\int_0^m \beta_2(a)u_*(a)\,\mathrm{d}a}{U_*} & -a_9(\lambda) \\ 0 & -1 & 0 \\ a_3(\lambda) & -a_4(\lambda) & -a_4(\lambda) - 1 \end{pmatrix} \\ &= \big(\tau a_5(\lambda) - 1\big)\big[\big(-a_4(\lambda) - 1\big)\big(a_7(\lambda) - 1\big) + a_3(\lambda)a_9(\lambda)\big] \\ &= 0. \end{aligned} \tag{47}$$

This again splits into two equations. The first one is easy to analyse, since it can be written as

$$1 = \tau \int_0^m \beta_1(a) \exp\left\{-U_* \int_0^a \eta_1(x)\,\mathrm{d}x\right\} e^{-\lambda a}\,\mathrm{d}a. \tag{48}$$

Theorem 4.5. *If*

$$\tau \int_0^m \beta_1(a) \exp\left\{-U_* \int_0^a \eta_1(x)\,\mathrm{d}x\right\} \mathrm{d}a > 1, \tag{49}$$

where U^* satisfies (23), then the disease-free steady state is unstable.

Remark 4.6. Provided that Eq. (47) has a dominant real solution λ, it is shown that condition (49) in Theorem 4.5 is indeed necessary and sufficient for the instability of the disease-free steady state. However, as we have noted before, the governing linear semigroup cannot shown to be positive, hence we cannot establish the existence of a dominant real root of the characteristic function (40).

4.2.3. Complete transmission of the disease
In case of complete transmission of the disease, i.e. when $\tau = 1$, Eqs. (15)–(18) can be written in the following form:

$$i_t(a,t) + i_a(a,t) = -\mu_1\big(a, I(t), U(t)\big) i(a,t), \tag{50}$$

$$u_t(a,t) + u_a(a,t) = -\mu_2\big(a, I(t), U(t)\big) u(a,t), \tag{51}$$

$$i(0,t) = \int_0^m \beta_1(a) i(a,t)\,\mathrm{d}a, \tag{52}$$

$$u(0,t) = \int_0^m \beta_2^q\big(a, I(t), U(t)\big) u(a,t)\,\mathrm{d}a, \tag{53}$$

where

$$\mu_i\big(a, I(t), U(t)\big) = \eta_i(a)\big(I(t) + U(t)\big), \quad i = 1, 2, \tag{54}$$

$$\beta_2^q\big(a, I(t), U(t)\big) = \beta_2(a)\left(1 - q\frac{I(t)}{I(t) + U(t)}\right). \tag{55}$$

Hence model (50)–(53) is a special case of the n-species age-structured system considered in Farkas (2006), where the coupling occurs due to competition for resources and due to the inhibition of the proliferation of the uninfected population.

In Farkas (2006) we deduced a very general instability condition, which we recall for the case $n = 2$ for the readers' convenience (see Theorem 2.3 in Farkas, 2006).

Theorem 4.7. *A strictly positive stationary solution $(i_*, u_*) \in (\mathbb{R}_{>0})^2$ of (50)–(53) is unstable if the partial derivatives of the net reproduction rates of the infected, respectively uninfected, populations satisfy*

$$R_I^1(I_*, U_*) R_U^2(I_*, U_*) - R_U^1(I_*, U_*) R_I^2(I_*, U_*) < 0. \tag{56}$$

Taking into account (54)–(55), we have

$$R^1(I,U) = \int_0^m \beta_1(a) \exp\left\{-(I+U)\int_0^a \eta_1(x)\,\mathrm{d}x\right\}\mathrm{d}a, \tag{57}$$

$$R^2(I,U) = \int_0^m \beta_2(a)\left(1 - q\frac{I}{I+U}\right)\exp\left\{-(I+U)\int_0^a \eta_2(x)\,\mathrm{d}x\right\}\mathrm{d}a. \tag{58}$$

From Eq. (57) we obtain

$$\begin{aligned} R^1_I(I_*,U_*) &= R^1_U(I_*,U_*) \\ &= -\int_0^m \beta_1(a)\left(\int_0^a \eta_1(x)\,\mathrm{d}x\right)\exp\left\{-(I_*+U_*)\int_0^a \eta_1(x)\,\mathrm{d}x\right\}\mathrm{d}a < 0, \end{aligned}$$

unless $\beta_1 \equiv 0$ or $\eta_1 \equiv 0$. Also, from Eq. (58) we obtain

$$\begin{aligned} &R^2_I(I_*,U_*) \\ &= -\int_0^m \beta_2(a)\left(1 - q\frac{I_*}{I_*+U_*}\right)\left(\int_0^m \eta_2(x)\,\mathrm{d}x\right)\exp\left\{-(I_*+U_*)\int_0^a \eta_2(x)\,\mathrm{d}x\right\}\mathrm{d}a \\ &\quad -\int_0^m \beta_2(a)\exp\left\{-(I_*+U_*)\int_0^a \eta_2(x)\,\mathrm{d}x\right\} q\frac{U_*}{(I_*+U_*)^2}\,\mathrm{d}a, \\ &R^2_U(I_*,U_*) \\ &= -\int_0^m \beta_2(a)\left(1 - q\frac{I_*}{I_*+U_*}\right)\left(\int_0^m \eta_2(x)\,\mathrm{d}x\right)\exp\left\{-(I_*+U_*)\int_0^a \eta_2(x)\,\mathrm{d}x\right\}\mathrm{d}a \\ &\quad +\int_0^m \beta_2(a)\exp\left\{-(I_*+U_*)\int_0^a \eta_2(x)\,\mathrm{d}x\right\} q\frac{I_*}{(I_*+U_*)^2}\,\mathrm{d}a. \end{aligned}$$

Hence $R^2_U(I_*,U_*) > R^2_I(I_*,U_*)$ for every strictly positive steady state, unless $\beta_2 \equiv 0$ or $q = 0$ (in which case, 0 is the strictly dominant eigenvalue of the linearized operator). We summarize our findings in the following theorem.

Theorem 4.8. *Assume that* $\tau = 1$, $q \neq 0$, *and* β_1, β_2, η_1 *are not identically zero. Then any strictly positive steady state of Eqs.* (15)–(18) *is unstable.*

In other words, there is no coexistence of infected and uninfected populations. This corresponds to the instability of the equilibrium solution (i_1, u_1) in the left panel of Fig. 2 for the unstructured case.

5. Discussion

In the present work we introduced and studied differential equation models for the dynamics of populations infected with *Wolbachia*. First we built ordinary differential equation models, in which we have implemented fitness costs of an infection as increased mortalities while keeping the birth rates equal for all infection statuses. It is equally appropriate

to reduce birth rates for infected individuals and (for the sake of simplicity) then to assign the same mortality to all individuals. This leads to the following model for the case of a single *Wolbachia* in an asexual population:

$$\frac{\mathrm{d}i}{\mathrm{d}t} = \big(\mu\tau - (i+u)\big)i,$$
$$\frac{\mathrm{d}u}{\mathrm{d}t} = \mu(1-\tau)i + \left(1 - q\frac{i}{i+u} - (i+u)\right)u,$$

where $\mu \in [0,1]$ is the reduced fecundity of infected individuals. This results in similar formulas for equilibrium solutions as (7) and vector fields as in Fig. 2. An experimentally testable prediction of our model (1)–(2) is that there are no persistent *Wolbachia* strains with a transmission efficacy less than $\frac{3}{4}$ (see the region for existence of the observed stable equilibrium (u_2, i_2) in Fig. 1).

Our model for multiple infections is novel insofar it allows the theoretical biologist to adapt it to a case of special interest (with or without doubly infected individuals, with or without mutual incompatibility). This should help to gain a more unified perspective than what was possible from models created for each purpose individually. In the case of mutual compatibility we saw that strains with higher transmission efficacy or lower mortality due to infection establish themselves over competitors. This is in good agreement with other predictions from discrete population genetics models (Turelli, 1994; Haygood and Turelli, 2009). Although the model for infections with multiple mutually incompatible strains in Section 3 is too complicated for all of its equilibrium solutions to be written down explicitly, it can be analyzed to a certain degree by identifying invariant subspaces. By numerical simulations we provided evidence for the absence of coexistence of singly infected individuals, apart from exceptional choices of parameters and initial values. This situation changes, if doubly infected individuals are present that can lose one of their strains when giving birth.

We have expanded the simple ordinary differential equation model from Section 2 by introducing age-structure. Of the extensive literature about structured populations, let us mention the monographs (Cushing, 1998; Webb, 1985; Metz and Diekmann, 1986), the classical paper (Gurtin and MacCamy, 1974) and the recent collection (Magal and Ruan, 2008). Clearly, age-structured models allow a much finer level of detail to be incorporated, but also pose greater analytical challenges. Nevertheless, we have shown that existence of equilibrium solutions and their stability properties can be investigated in a straightforward fashion. We saw that unlike in the unstructured case, existence of a disease-free equilibrium is now subject to a condition on the integral of the birth rate. We also obtained analytical results in some special cases which allow at least a partial characterization of the dynamic behavior of the system once the model parameters are fixed.

Wolbachia together with *Cardinium* are the two bacterial infections of arthropods that cause cytoplasmic incompatibility. In this work we have focused on the case of diplodiploid species where cytoplasmic incompatibility results, with a certain probability, in embryonic death. In future work we intend to include separate sexes into our models, see the book by Iannelli et al. (2005) for a comprehensive introduction to gender-structured populations. Then it will be possible to study gender-specific effects of the *Wolbachia* infection. These become even more important in haplodiploid organisms such as bees, ants and wasps, where cytoplasmic incompatibility is vastly more complex (Vautrin et al., 2007; Stouthamer, 1997) (male-development, thelytokous parthenogenesis, etc.).

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