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A general multi-strain model with environmental transmission: Invasion conditions for the disease-free and endemic states

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ABSTRACT

Although many infectious diseases of humans and wildlife are transmitted via an environmental reservoir, the theory of environmental transmission remains poorly elaborated. Here we introduce an *SIR*-type multi-strain disease transmission model with perfect cross immunity where environmental transmission is broadly defined by three axioms. We establish the conditions under which a multi-strain endemic state is invaded by another strain which is both directly and environmentally transmitted. We discuss explicit forms for environmental transmission terms and apply our newly derived invasion conditions to a two-strain system. Then, we consider the case of two strains with matching basic reproduction numbers (i.e., R_0), one directly transmitted only and the other both directly and environmentally transmitted, invading each other's endemic state. We find that the strain which is only directly transmitted can invade the endemic state of the strain with mixed transmission. However, the endemic state of the first strain is neutrally stable to invasion by the second strain. Thus, our results suggest that environmental transmission makes the endemic state less resistant to invasion.

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1. Introduction

Empirical studies show that environmental transmission is an important pathway for viral infections in humans (e.g., gastroenteritis D'Souza et al., 2006) and animals (e.g., rabbit haemorrhagic disease Henning et al., 2005), water-borne pathogens (e.g., cholera King et al., 2008; Pascual et al., 2000, avian cholera Blanchong et al., 2006), bacterial infections (e.g., tetanus Roper et al., 2007, salmonella Xiao et al., 2007, epizootics of plague Webb et al., 2006), prion diseases (e.g., chronic wasting disease Miller et al., 2006, bovine spongiform encephalopathy Anderson et al., 1996) and zoonoses (e.g., Nipah and Hendra viral diseases Field et al., 2001). Environmentally transmitted diseases may differ substantially from those that are only directly transmitted in epidemiological dynamics and control implications. While the

first compartmental model to include environmental transmission was proposed for cholera three decades ago (Capasso and Paveri-Fontana, 1979), the modeling literature on the environmental transmission of cholera has substantially expanded just over the last decade (Codeco, 2001; Pascual et al., 2002; Jensen et al., 2006; Hartley et al., 2006; Codeco et al., 2008; Joh et al., 2009). Recently, environmental transmission has been considered in avian influenza models (Roche et al., 2009; Rohani et al., 2009; Breban et al., 2009). Although various questions about the dynamics of environmentally transmitted diseases have been addressed (Capasso and Paveri-Fontana, 1979; Codeco, 2001; Hartley et al., 2006; Codeco et al., 2008; Joh et al., 2009; Rohani et al., 2009; Breban et al., 2009), the evolution of environmental transmission has not been considered.

Our work was motivated by the recent emergence of highly pathogenic H5N1 strains in wild waterfowl (International Scientific Task Force, 2006), which are known to host a pool of influenza viruses rich in genetic and antigenic diversity (Webster et al., 1992). In particular, we considered it important to understand the conditions which favor newly emerging strains of highly pathogenic H5N1 to successfully invade the existing assemblage of avian influenza viruses. While there are conceptual similarities with evolutionary studies of the life cycle of macroparasites (e.g., Choisy et al., 2003), virulence of multi-host parasites

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(e.g., Gandon, 2004), and the tradeoff between transmissibility and virulence (e.g., Alizon and van Baalen, 2005), our focus on the evolutionary interplay between direct and environmental transmission is novel.

Accordingly, here we develop an *SIR*-type model to explore the dynamics of a multi-strain pathogen which may have either a direct or both direct and environmental transmission mechanism, depending on strain identity, and with perfect cross-immunity between strains. Our model is general in the sense that environmental transmission dynamics are broadly specified by a few unrestrictive axioms. We analyze the conditions under which a multi-strain endemic state is invaded by a strain that is both directly and environmentally transmitted. For concreteness, we then discuss explicit forms of environmental transmission. Finally, we apply our results to a two-strain model for avian influenza virus and discuss how two strains with matching basic reproduction numbers (i.e., R_0s) but different transmission pathways invade each other's endemic state. The key finding of this study is that the endemic state of a directly transmitted pathogen is neutrally stable to the invasion of a pathogen with mixed direct and environmental transmission, while a pathogen transmitted only directly is able to invade the endemic state of a mixed transmission pathogen. This result suggests that environmental transmission is a more fragile evolutionary strategy than direct transmission and that the evolution of strains transmitted wholly through long-term environmental persistence is unlikely.

2. Model

We consider n strains that are both directly and environmentally transmitted and propose the following multi-strain model

$$dS/dt = \pi - \mu S - S \sum_{i=1}^{n} \beta_i I_i - \rho S f(\mathbf{V}),$$

$$dI_j/dt = \beta_j S I_j - (\mu + \gamma_j) I_j + \rho S f(\mathbf{V}) \varepsilon_j(\mathbf{V}),$$

$$dV_j/dt = \omega_j I_j - \eta_j V_j, \tag{1}$$

where $j = 1, 2, \ldots, n$. S represents the number of susceptible individuals, I_j represents the number of individuals infected with strain j, and V_j represents the number of virions of strain j contaminating the environment; we denote the mixed viral population by $\mathbf{V} = \{V_1, V_2, \ldots, V_n\}$. The parameters β_j, $1/\gamma_j$, and η_j are the strain-specific transmissibility, infectious period, and clearance rate. ω_j represents the shedding rate of individuals infected with strain j. π is the susceptible inflow, μ is the natural death rate of individuals and ρ represents the contact rate with the environment. All variables and parameters are positively defined. We assume that infection with any particular strain provides permanent immunity to reinfection/infection with any other strain (i.e., perfect strain-transcending cross-immunity).

The environmental transmission rate is modeled by the term $\rho S f(\mathbf{V})$. The function $f : \mathbb{R}^n \to [0,1]$ represents the probability that an individual is infected when exposed to a mixed population $\mathbf{V}$ of virions in the environment. The environmental transmission rate for the pathogen j is given by $\rho S f(\mathbf{V}) \varepsilon_j(\mathbf{V})$, where $\varepsilon_j(\mathbf{V})$ ($\varepsilon_j : \mathbb{R}^n \to [0,1]$) is the probability that pathogen j has caused the infection when infection occurred. Evidently, $\sum_{i=1}^{n} \varepsilon_i(\mathbf{V}) = 1$.

For the time being, we leave the functions $f(\mathbf{V})$ and $\varepsilon_j(\mathbf{V})$ ($j = 1, 2, \ldots, n$) unspecified and we only make use of properties that derive from their biological meaning; later we discuss specific examples. We thus postulate the following for $f(\mathbf{V})$ and $\varepsilon_j(\mathbf{V})$ ($j = 1, 2, \ldots, n$):

Property 1. *The probability of infection vanishes in absence of virus [i.e., $f(\mathbf{V}) = 0$ when $V_j = 0$ ($j = 1, 2, \ldots, n$)] and approaches one as the*

viral load of every strain becomes very large [i.e., $f(\mathbf{V}) \to 1$ when $V_j \to \infty$ ($j = 1, 2, \ldots, n$)]. Furthermore, we assume that the probability of infection increases with the viral load [$f(\mathbf{V})$ is an increasing function in all arguments]. Obviously, when $V_j = 0$ for every $j = 1, 2, \ldots, n$ except a given integer k, $f(\mathbf{V}) = f^{\langle 1 \rangle}(V_k)$, where $f^{\langle 1 \rangle}$ is the probability of environmental infection in a single strain model.

Property 2. *The probability that the infection occurred with strain j, $\varepsilon_j(\mathbf{V})$, is an increasing function in V_j that satisfies (i) $\varepsilon_j(\mathbf{V}) = 0$ when $V_j = 0$,[3](ii) $\varepsilon_j(\mathbf{V}) = 1$ when $V_j \neq 0$ and $V_i = 0$, for every $i = 1, 2, \ldots, n$, $i \neq j$, and (iii) $\varepsilon_j(\mathbf{V}) \to 1$ when $V_j \to \infty$.*

Property 3. *$f(\mathbf{V})$ and $\{\varepsilon_1(\mathbf{V}), \varepsilon_2(\mathbf{V}), \ldots, \varepsilon_n(\mathbf{V})\}$ are chosen such that our model is homogeneous in $\{I_i, V_i\}$, $i = 1, 2, \ldots, n$. In other words, if the parameters of two strains j and k are the same and we do not distinguish between the individuals in the I_j and I_k compartments and between the V_j and V_k viral populations, then we can introduce the variables $I = I_j + I_k$ and $V = V_j + V_k$. The ordinary differential equation of I is obtained by summing the equations for I_j and I_k; the equation for V is obtained by summing the equations for V_j and V_k. Thus, a change of variables is performed, leading to a dimensionally reduced, self-consistent model with the same structure as the one described by the Eqs. (1), except with a number of $n-1$ strains.[4]*

3. Main results

3.1. Model equilibria

We denote an equilibrium of the model by $\mathbf{E}^* = \{S^*, I_1^*, I_2^*, \ldots, I_n^*, V_1^*, V_2^*, \ldots, V_n^*\}$. The set of equations generating the equilibria is obtained by setting the LHS of Eqs. (1) to zero. It reduces to a system of n nonlinear equations in the unknowns $V_1^*, V_2^*, \ldots, V_n^*$

$$-(\mu + \gamma_j)\eta_j V_j^*/\omega_j + [\beta_j \eta_j V_j^*/\omega_j$$
$$+ \rho \varepsilon_j(\mathbf{V}^*)f(\mathbf{V}^*)]\left[\pi/\mu - \sum_{i=1}^{n}(1 + \gamma_i/\mu)\eta_i V_i^*/\omega_i\right] = 0, \tag{2}$$

where $\mathbf{V}^* \equiv \{V_1^*, V_2^*, \ldots, V_n^*\}$ and $j = 1, 2, \ldots, n$. The other entries of $\mathbf{E}^*$ are given by

$$I_j^* = \eta_j V_j^*/\omega_j, \tag{3}$$

$$S^* = \pi/\mu - \sum_{i=1}^{n}(1 + \gamma_i/\mu)\eta_i V_i^*/\omega_i. \tag{4}$$

By virtue of Property 2, $V_j^* = 0$, ($j = 1, 2, \ldots, n$) is a solution of Eqs. (2) which further implies $I_j^* = 0$, ($j = 1, 2, \ldots, n$) [see Eq. (3)] and $S^* = \pi/\mu$ [see Eq. (18)]. Thus the model admits a *disease-free equilibrium* which for further reference we denote by $\mathbf{E}_{DFE}^*$ and mark its components by the subscript DFE. The general problem of existence of endemic equilibria remains intractable, subject to further assumptions about f and ε_j.

3.2. On the stability of equilibria

Proposition. *Let $\mathbf{E}^* = \{S^*, I_1^*, I_2^*, \ldots, I_n^*, V_1^*, V_2^*, \ldots, V_n^*\}$ be an equilibrium of the model with n strains given by Eqs. (1) where $I_n^* = 0$ and $V_n^* = 0$. Then, the following statements hold:*

(i) *$\mathbf{F}^* = \{S^*, I_1^*, I_2^*, \ldots, I_{n-1}^*, V_1^*, V_2^*, \ldots, V_{n-1}^*\}$ is an equilibrium of the system modeling only the first $n-1$ strains;*

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[3] This implies $\partial \varepsilon_j(\mathbf{V})/\partial V_i = 0$ when $V_j = 0$ for every $i = 1, 2, \ldots, n$, $i \neq j$.
[4] Note that the model with $f(\mathbf{V}) = 0$ is homogeneous.

(ii) $\mathbf{E}^*$ *is linearly stable if and only if* $\mathbf{F}^*$ *is linearly stable and*

$$R_0^{[n]} \equiv \frac{S^*\beta_n}{\mu+\gamma_n} + \frac{S^*\rho\omega_n}{\eta_n(\mu+\gamma_n)} \frac{\partial[\varepsilon_n(\mathbf{V})f(\mathbf{V})]}{\partial V_n}\bigg|_{\mathbf{E}^*_{[n]}} < 1 \qquad (5)$$

Proof. See Appendix.

Corollary. *Let* $\mathbf{E}^* = \{S^*, I_1^*, I_2^*, \ldots, I_n^*, V_1^*, V_2^*, \ldots, V_n^*\}$ *be an equilibrium of the model with* n *strains where* $I_n^* = I_{n-1}^* = \cdots = I_{n-m}^* = 0$ *and* $V_n^* = V_{n-1}^* = \cdots = V_{n-m}^* = 0$, $0 \le m < n.$[5] *Then, the following statements hold:*

(i) $\mathbf{F}^*_{[m]} = \{S^*, I_1^*, I_2^*, \ldots, I_m^*, V_1^*, V_2^*, \ldots, V_m^*\}$ *is an equilibrium of the system modeling the first* m *strains;*

(ii) $\mathbf{E}^*$ *is linearly stable if and only if* $\mathbf{F}^*_{[m]}$ *is linearly stable and*

$$R_0^{[n]} \equiv \frac{S^*\beta_n}{\mu+\gamma_n} + \frac{S^*\rho\omega_n}{\eta_n(\mu+\gamma_n)} \frac{\partial[\varepsilon_n(\mathbf{V})f(\mathbf{V})]}{\partial V_n}\bigg|_{\mathbf{E}^*} < 1,$$

$$R_0^{[n-1]} \equiv \frac{S^*\beta_{n-1}}{\mu+\gamma_{n-1}} + \frac{S^*\rho\omega_{n-1}}{\eta_{n-1}(\mu+\gamma_{n-1})} \frac{\partial[\varepsilon_{n-1}(\mathbf{V})f(\mathbf{V})]}{\partial V_{n-1}}\bigg|_{\mathbf{F}^*_{[n-1]}} < 1,$$

$$\vdots$$

$$R_0^{[n-m]} \equiv \frac{S^*\beta_{n-m}}{\mu+\gamma_{n-m}} + \frac{S^*\rho\omega_{n-m}}{\eta_{n-m}(\mu+\gamma_{n-m})} \frac{\partial[\varepsilon_{n-m}(\mathbf{V})f(\mathbf{V})]}{\partial V_{n-m}}\bigg|_{\mathbf{F}^*_{[m+1]}} < 1.$$

Proof. A proof is obtained by applying the main result $(n-m)$ times. $\square$

Remark. For the disease-free state [i.e., $I_{j\ \text{DFE}}^* = 0$ and $V_{j\ \text{DFE}}^* = 0$ $(j=1,2,\ldots,n)$], the stability condition reduces to $R_0 \equiv \max(R_0^{[1]}, R_0^{[2]}, \ldots, R_0^{[n]}) < 1$. Furthermore, we have $S_{\text{DFE}}^* = \pi/\mu$ and $R_0^{[i]} < 1$ becomes identical to the stability condition of the disease free state for the system that only models strain i

$$R_0^{[i]} = \frac{(\pi/\mu)\beta_i}{\mu+\gamma_i} + \frac{(\pi/\mu)\rho\omega_i}{\eta_i(\mu+\gamma_i)} \frac{\partial f^{\langle 1\rangle}(V_i)}{\partial V_i}\bigg|_{V_i=0} < 1. \qquad (6)$$

4. Functional forms for the environmental transmission terms

In this section we discuss how certain functional forms for f and ε_i result from several simple considerations. These analytical forms satisfy Properties 1 and 2, and, with some caveats, Property 3. However, other analytical forms satisfying Properties 1–3 might be possible. In this sense, our main result (i.e., the invasion condition) applies to more general situations than those described below.

4.1. Formulae for f in single strain models

In the case where we have only a single strain, the function $f : \mathbb{R} \to [0,1]$ represents the probability that an individual is infected when exposed to a population V of virions in the environment; evidently, $\varepsilon(V) = 1$. To obtain functional forms for $f(V)$, we develop an individual-level model where a susceptible explores a uniformly contaminated area at a constant rate, encountering infectious virions. We assume that the encounters have a cumulative effect and, as the number of accumulated virions increases, the probability of remaining susceptible decreases.

This model is a structural analogy to mating models where a female explores an area uniformly populated by males. One way of mathematically formalizing such mating models is the theory of birth processes; see Dennis (1989) for a review, general properties of f, and particular formulae for f. We adopt these results for our individual-level model of environmental transmission by giving them appropriate biological interpretation.

The fundamental assumption of these birth processes is that the probability of an encounter while exploring a small area Δa is proportional to the density of targets (i.e., pathogens in our case) and also depends on the number of previous encounters (as given by a function $\delta(\cdot)$, see below)

$$P[X(a+\Delta a) = x+1 \,|\, X(a) = x] = (V/A)\delta(x)\Delta a, \qquad (7)$$

where $X(a)$ is a random variable describing the number of encounters in an area a, and A is the total area of the habitat. The forward equations in the variables $P[X(a)=x]$ of the birth process can be formally solved. However, as explained by Dennis (1989), it might be reasonable to assume that the function $\delta(x)$ depends slowly on the number of contacts x and can be approximated by the first order truncation of its MacLaurin series

$$\delta(x) \approx b - cx, \qquad (8)$$

where b and c are positive constants. The positivity of c indicates that the likelihood of an encounter decreases with the cumulative number of encounters; i.e., the likelihood that newly ingested virions determine the state of the individual decreases with the number of virions already ingested. Using Eq. (8), it is immediately obtained that $P[X(a)=x]$ has a binomial form (say for simplicity that b/c is an integer)

$$P[X(a) = x] = \binom{-b/c}{x}(1 - e^{acV/A})^x(e^{acn})^{-(b/c)-x}, \qquad (9)$$

where $x = 0, 1, \ldots, -b/c$. (See Dennis, 1989 and references therein for all the details of the derivation.)

If we now consider a population of susceptible individuals that all have the same constants b and c then, the probability of ingesting one or more virions from the environment is the same negative exponential function for every individual in the population[6]

$$f_{\text{NE}}(V) \equiv P[X(A) \ge 1] = 1 - \exp^{-\alpha V}, \qquad (10)$$

where $\alpha \equiv b$. More generally, Dennis (1989) shows that if ab is distributed with finite variance, then f is concave, resembling f_{NE}. For example, if ab is exponentially distributed in the susceptible population, one obtains a rectangular hyperbola at the population level

$$f_{\text{RH}}(V) = \frac{V}{V+\kappa}, \qquad (11)$$

where κ is a constant. (See Dennis, 1989 for details.) On the basis of biological data, Dennis (1989) argues that both f_{NE} and f_{RH} are reasonable choices in mating modeling, with f_{NE} fitting their data slightly better, while f_{RH} providing much more analytical tractability. Both the exponential (Breban et al., 2009) and the hyperbolic (Roche et al., 2009; Rohani et al., 2009) forms have been used in modeling environmental transmission of a single viral strain. Currently, the available empirical data are too scarce to select one on the basis of evidence.

It is important to note that, even though they originate from stochastic birth processes, the f functions derived above can nevertheless be used in deterministic models based on ordinary differential equations; see Dennis (1989). It is not too difficult to build a stochastic multi-strain model of a pathogen that is both directly and environmentally transmitted by merging a

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[5] This includes all equilibria except those which have all viral strains present.

[6] For a different derivation of the negative exponential function in a similar context, see Breban et al. (2009).

multi-strain version of the traditional *SIR* stochastic model based on continuous-time Markov chains (see e.g., Bailey, 1975) with a birth process describing environmental transmission (see above) and a birth–death process describing the persistence of virions in the environment. Then, by applying the mean-field approximation (Bailey, 1975), the expectations of the state variables of this stochastic model would satisfy Eq. (1).

4.2. Formulae for ε_i and f in multi-strain models

If the infection processes are independent, then the probability that the infection occurred with strain i, $\varepsilon_i(\mathbf{V})$, is proportional to the number of infectious doses of strain i that the susceptible encountered. The infectious dose ID_{50} of a strain is defined as the quantity of virus of that strain which gives 50% probability of infection. Therefore, the $\varepsilon_i(\mathbf{V})$ function is

$$\varepsilon_i(\mathbf{V}) = \frac{V_i/ID_{50}^i}{\sum_{j=1}^n V_j/ID_{50}^j}, \tag{12}$$

where ID_{50}^j represents the infectious dose of strain j. We note that the parameters of the f-function of the single-strain model, $f^{\langle 1 \rangle}$ (e.g., f_{NE}, f_{RH}, etc.), are related to ID_{50} by $f^{\langle 1 \rangle}(ID_{50}) = 1/2$. For example, we obtain $\alpha = \log_e(2)/ID_{50}$ for f_{NE} and $\kappa = ID_{50}$ for f_{RH}.

Assuming that encounters of virions of various strains in the environment are independent, the probability of escaping infection equals the probability of escaping infection from each individual strain

$$1 - f(\mathbf{V}) = \prod_{i=1}^n [1 - f_i^{\langle 1 \rangle}(V_i)]. \tag{13}$$

It is important to note that Eqs. (12) and (13) do not imply homogeneity for our model (1). Requiring that Property 3 holds further constrains the functional forms of ε_i and f. It is straightforward to verify that homogeneity is satisfied given the above choices of ε_i and $f_i^{\langle 1 \rangle} = f_{NE}$, $(i=1,2,\ldots,n)$. However, if $f_i^{\langle 1 \rangle} = f_{RH}$, $(i=1,2,\ldots,n)$, homogeneity holds only in the limit of small virion populations.

5. Analysis of a two strain model

5.1. The basic reproduction ratio

We now discuss the biological implications of a two-strain model where we choose $f_i^{\langle 1 \rangle} = f_{RH}$ $(i=1,2)$ for analytical tractability. Without worrying too much about losing homogeneity, we expect to recover the qualitative results of the model with $f_i^{\langle 1 \rangle} = f_{NE}$ $(i=1,2)$ if the strains are kept distinct. Note that by rescaling the unit for the amount of virus, the parameters $\kappa_{1,2}$ can be eliminated. In particular, the following change of variables

$$\hat{V}_i \equiv V_i/\kappa_i; \quad \hat{\omega}_i \equiv \omega_i/\kappa_i,$$

where $i=\{1,2\}$, reduces the dimensionality of the parameter space by two. The new quantities $\hat{V}_{1,2}$ and $\hat{\omega}_{1,2}$ are measured in infectious doses (i.e., units of corresponding κs) and infectious doses per unit time, respectively. This transformation is formally equivalent to setting $\kappa_{1,2} = 1$ in the original equations.

According to the Remark in Section 3.2, the basic reproduction ratio of the model is

$$R_0 = \max\{R_0^{[1]}, R_0^{[2]}\},$$

where

$$R_0^{[i]} = \frac{(\pi/\mu)\beta_i}{(\mu+\gamma_i)} + \frac{(\pi/\mu)\rho\hat{\omega}_i}{\eta_i(\mu+\gamma_i)}, \quad i=1,2.$$

We note that $R_0^{[i]}$ has two terms. One term, which is proportional to β_i, can be attributed to direct transmission

$$R_0^{[i]\text{dir}} \equiv \frac{\pi}{\mu}\frac{\beta_i}{\mu+\gamma_i}. \tag{14}$$

The other term contains parameters related to the infectious dose, and persistence and shedding of the virus in the environment and can be attributed to environmental transmission

$$R_0^{[i]\text{env}} \equiv \frac{\pi}{\mu}\frac{\rho\hat{\omega}_i}{\eta_i(\mu+\gamma_i)}. \tag{15}$$

A discussion of this $R_0^{[i]}$ formula can be found in Rohani et al. (2009).

5.2. Endemic states

Eqs. (2) lead to

$$\hat{V}_1^*\left\{\frac{\beta_1\eta_1 S^*}{\hat{\omega}_1} + \frac{\rho S^*}{\hat{V}_1^* + \hat{V}_2^*}\left[1 - \frac{1}{(1+\hat{V}_1^*)(1+\hat{V}_2^*)}\right] - \frac{\eta_1(\mu+\gamma_1)}{\hat{\omega}_1}\right\} = 0, \tag{16}$$

$$\hat{V}_2^*\left\{\frac{\beta_2\eta_2 S^*}{\hat{\omega}_2} + \frac{\rho S^*}{\hat{V}_1^* + \hat{V}_2^*}\left[1 - \frac{1}{(1+\hat{V}_1^*)(1+\hat{V}_2^*)}\right] - \frac{\eta_2(\mu+\gamma_2)}{\hat{\omega}_2}\right\} = 0, \tag{17}$$

where

$$S^* = \frac{\pi}{\mu} - \sum_{i=1}^2 \left(1 + \frac{\gamma_i}{\mu}\right)\frac{\eta_i\hat{V}_i^*}{\hat{\omega}_i}. \tag{18}$$

Therefore, three types of equilibria are possible for this model:

(a) $\hat{V}_1^* = \hat{V}_2^* = 0$, which is the disease-free state previously discussed,
(b) $\hat{V}_i = 0$ and $\hat{V}_j \neq 0$ where $i,j=1,2$ and $i \neq j$, which is an endemic state where either of the strain is present at the expense of the other,
(c) coexistence of the two strains.

In case (b), the equilibrium where only the first strain is present $\mathbf{E}^{[1]*} = \{S^*, I_1^*, 0, \hat{V}_1^*, 0\}$ has the entries given by

$$\hat{V}_1^* = \frac{1}{2}\left[\sqrt{\mathcal{C}^2 + \frac{4\mu R_0^{[1]\text{env}}}{\rho R_0^{[1]\text{dir}}}(R_0^{[1]}-1)} - \mathcal{C}\right], \tag{19}$$

$$\mathcal{C} \equiv \left(1 + \frac{\mu}{\rho}\right)\frac{R_0^{[1]\text{env}}}{R_0^{[1]\text{dir}}} - \frac{\mu}{\rho}R_0^{[1]\text{env}} + 1, \tag{20}$$

$$I_1^* = \eta_1\hat{V}_1^*/\hat{\omega}_1, \tag{21}$$

$$S^* = S_{\text{DFE}}^*\left(1 - \frac{\rho\hat{V}_1^*}{\mu R_0^{[1]\text{env}}}\right). \tag{22}$$

The entries of the equilibrium where only the second strain is present $\mathbf{E}^{[2]*} = \{S^*, 0, I_2^*, 0, \hat{V}_2^*\}$ are formally obtained by replacing the index 1 with 2 in the above equations.

In case (c), Eqs. (16) and (17) form a linear system in the variables S^* and $S^*[1 - 1/(1+\hat{V}_1^*)(1+\hat{V}_2^*)]/(\hat{V}_1^* + \hat{V}_2^*)$ which yields

$$S^* = \frac{\eta_1(\mu+\gamma_1)\hat{\omega}_2 - \eta_2(\mu+\gamma_2)\hat{\omega}_1}{\beta_1\eta_1\hat{\omega}_2 - \beta_2\eta_2\hat{\omega}_1}, \tag{23}$$

and

$$\frac{1}{\hat{V}_1^* + \hat{V}_2^*}\left[1 - \frac{1}{(1+\hat{V}_1^*)(1+\hat{V}_2^*)}\right] = \frac{\beta_1\eta_1\eta_2(\mu+\gamma_2) - \beta_2\eta_2\eta_1(\mu+\gamma_1)}{\eta_1(\mu+\gamma_1)\hat{\omega}_2 - \eta_2(\mu+\gamma_2)\hat{\omega}_1}. \tag{24}$$

Having thus determined S^*, Eqs. (18) and (23) provide a linear relationship between $\hat{V}_1^*$ and $\hat{V}_2^*$. Consequently, Eq. (24) can be rewritten as a cubic equation in either $\hat{V}_1^*$ or $\hat{V}_2^*$ that yields cumbersome analytic solutions for $\hat{V}_{1,2}^*$. However, in the case where one strain (say strain 1) is directly transmitted only (i.e., $R_0^{[1]} = R_0^{[1]\text{dir}}$) while the other (strain 2) has a mixed transmission mechanism, the algebra is more tractable and the coexistence equilibrium is given by $\mathbf{E}^* = \{S^*, I_1^*, I_2^*, 0, \hat{V}_2^*\}$ where

$$S^* = (\pi/\mu)/R_0^{[1]}, \tag{25}$$

$$I_2^* = \frac{\rho}{\beta_2}\frac{R_0^{[2]}}{R_0^{[1]} - R_0^{[2]\text{dir}}} - \frac{\eta_2}{\omega_2}, \tag{26}$$

$$I_1^* = \frac{\pi}{\mu+\gamma_1}\left(1 - \frac{1}{R_0^{[1]}}\right) - \frac{\mu+\gamma_2}{\mu+\gamma_1}I_2^*, \tag{27}$$

$$\hat{V}_2^* = \omega_2 I_2^*/\eta_2. \tag{28}$$

From $I_{1,2}^* > 0$, we immediately obtain that, in this case, coexistence is possible if

$$(R_0^{[1]} - R_0^{[2]\text{env}}) < R_0^{[2]\text{dir}} < R_0^{[1]}, \tag{29}$$

subject to further stability conditions.

We illustrate the above findings with numerical simulations because they are particularly relevant for later analysis; see Fig. 1. The parameter values and ranges used are inspired from the avian influenza literature (Rohani et al., 2009; Breban et al., 2009) and listed in Table 1. The two-strain model thus described here would correspond to a sedentary population that hosts influenza viruses. Fig. 1 shows that the parameter space $(R_0^{[2]\text{env}}, R_0^{[2]\text{dir}})$ of the second strain is divided into three regions: (i) $R_0^{[2]\text{dir}} > R_0^{[1]\text{dir}}$ where strain 2 drives strain 1 extinct; (ii) $R_0^{[2]\text{dir}} + R_0^{[2]\text{env}} < R_0^{[1]\text{dir}}$ where strain 1 drives strain 2 extinct; and (iii) the complementary region where the strains coexist. It thus becomes evident that environmental transmission may offer a survival mechanism to a strain which is not transmitted directly very well and would otherwise go extinct.
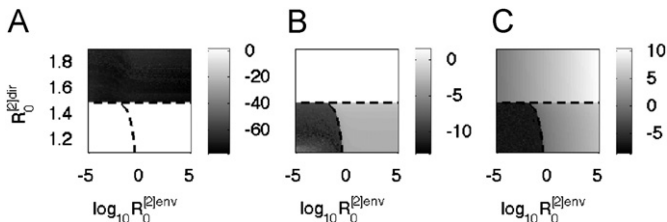
Fig. 1. Maps of logarithm in base 10 of I_1^* (panel **A**), I_2^* (panel **B**) and $\hat{V}_2^*$ (panel **C**) versus $R_0^{[2]\text{ env}}$ and $R_0^{[2]\text{ dir}}$ which were varied by changing $\hat{\omega}_2$ and β_2, respectively. (Note that the horizontal scales are logarithmic.) The parameter values are taken from Rohani et al. (2009), Breban et al. (2009); see Table 1. The horizontal dashed line represents $R_0^{[2]\text{ dir}} = R_0^{[1]\text{ dir}}$, while the dashed curve represents $R_0^{[2]\text{ dir}} + R_0^{[2]\text{ env}} = R_0^{[1]\text{ dir}}$; see Eq. (29). The figure shows that the dashed lines divide the parameter space into three regions: (i) top region where $R_0^{[2]\text{dir}} > R_0^{[1]\text{dir}}$ and strain 2 drives strain 1 extinct; (ii) bottom left where $R_0^{[2]\text{dir}} + R_0^{[2]\text{env}} < R_0^{[1]\text{dir}}$ and strain 1 drives strain 2 extinct; and (iii) the complementary region in the bottom right where the strains coexist. We performed the simulations with the MATLAB ® R2008b software; values below 10^{-6} are within the range of numerical noise. In particular, we note that all the values in the upper half of panel **A** and low left corners of panels **B** and **C** (i.e., the black regions) are in the range of numerical noise.

Table 1
A list of the two-strain model parameters, along with their biological description. The first strain is directly transmitted only, while the second strain has a mixed transmission mechanism. The values/ranges explored are tuned for the case of avian influenza in wild waterfowl; see Rohani et al. (2009), Breban et al. (2009) and for further details.

Parameter	Biological description	Value (range)
N	Host population size	10^4
μ	Natural death rate	$1/3$ year^{-1}
β_1	Direct transmission rate of strain 1	0.0078 year^{-1}
β_2	Direct transmission rate of strain 2	0.0058–0.01 year^{-1}
$1/\gamma_2$	Infectious period of strain 2	7 days
ρ	Consumption rate	10^{-6} liters/year
$1/\eta_2$	Persistence time of strain 2	30 days
$\hat{\omega}_2$	Shedding rate of strain 2	0.64–10^{10} EID$_{50}$/year

5.3. Invasion condition for the endemic state with only one strain

We now examine the condition for successful invasion of the endemic state that contains only the first strain $\mathbf{E}^{[1]*} = \{S^*, I_1^*, 0, \hat{V}_1^*, 0\}$ by the second strain—we assume that both strains have mixed transmission mechanisms. Our main result implies that $\mathbf{F}^* = \{S^*, I_1^*, \hat{V}_1^*\}$ is an equilibrium of the model describing strain 1 only. Assuming that $\mathbf{F}^*$ is stable (i.e., $R_0^{[1]} > 1$), the only condition for successful invasion is

$$R_0^{[2]*} \equiv \frac{S^*\beta_2}{(\mu+\gamma_2)} + \frac{S^*\rho\hat{\omega}_2}{\eta_2(\mu+\gamma_2)}\left(\frac{1}{1+\hat{V}_1^*}\right) > 1, \tag{30}$$

which can be rewritten as

$$R_0^{[2]*} \equiv \frac{S^*}{S_{\text{DFE}}^*}\left[R_0^{[2]\text{dir}} + R_0^{[2]\text{env}}\left(\frac{1}{1+\hat{V}_1^*}\right)\right] > 1, \tag{31}$$

Note that since $S^* \leq S_{\text{DFE}}^*$, we have $R_0^{[2]*} \leq R_0^{[2]}$, where equality occurs when $\mathbf{E}^*$ is the disease-free state. In other words, if the second strain cannot invade the disease-free state, it would also be unable to invade the endemic equilibrium. Furthermore, Eq. (31) explicitly shows that the difficulty in invading the endemic state of a pathogen with mixed transmission mechanism emerges not only from the fact that the number of susceptibles is reduced but also from the magnitude of the existent environmental reservoir.

5.4. Comparison between strains with matching R_0

The endemic level of a directly transmitted strain is linearly neutral to the invasion of a second directly transmitted strain with matching R_0. Furthermore, the strains can coexist at equilibrium when $R_0^{[1]} = R_0^{[2]} > 1$ (Castillo-Chavez et al., 1989). Here we discuss the case of strains with matching R_0 where the first strain is directly transmitted while the second strain is both directly and environmentally transmitted which corresponds to the dashed curved boundary in Fig. 1.

First, consider the case where the second strain invades the endemic state of the first strain. We take our previous results in the limit where the infectious dose of the first strain tends to infinity (i.e., drop the ODE for $\hat{V}_1$ and take $\hat{V}_1 = 0$ in the other equations of the two-strain model) and obtain that the equilibrium where only the first strain is present is given by $\mathbf{E}^{[1]*} = \{S^{[1]*}, I_1^{[1]*}, 0, 0, 0\}$ where

$$I_1^{[1]*} = \frac{\mu(R_0^{[1]} - 1)}{\beta_1},$$

$$S^{[1]*} = \frac{S_{\text{DFE}}^*}{R_0^{[1]}}.$$

Furthermore, we obtain that $\mathbf{E}^{[1]*}$ is linearly neutral to the invasion of the second strain[7]

$$R_0^{[2]*} = \frac{S^{[1]*}}{S_{\mathrm{DFE}}^*} R_0^{[2]} = \frac{R_0^{[2]}}{R_0^{[1]}} = 1. \tag{32}$$

Second, consider the case where the first strain invades the endemic state of the second strain. We denote the equilibrium where only the second strain is present by $\mathbf{E}^{[2]*} = \{S^{[2]*}, 0, I_2^{[2]*}, 0, \hat{V}_2^{[2]*}\}$ where the nonzero entries satisfy equations similar to Eqs. (19), (21), and (22); in this case we obtain

$$R_0^{[1]*} = \left(1 - \frac{\rho \hat{V}_2^{[2]*}}{\mu R_0^{[2]\mathrm{env}}}\right) R_0^{[1]}. \tag{33}$$

In the situation where $R_0^{[2]\mathrm{env}} \ll 1$, the series expansion of Eq. (33) up to second order in $R_0^{[2]\,\mathrm{env}}$ is

$$R_0^{[1]*} \approx \left\{1 + \frac{\mu(R_0^{[2]\mathrm{dir}} - 1)}{\rho}\left(\frac{R_0^{[2]\mathrm{env}}}{R_0^{[2]\mathrm{dir}}}\right)^2\right\} > 1.$$

Thus, we obtain that the directly transmitted strain can invade the endemic state of the strain with mixed transmission mechanism, while the endemic state of the directly transmitted strain is neutral to the invasion of the strain with mixed transmission mechanism.

Finally, we discuss the case where both strains have mixed transmission mechanisms and matching R_0. Say for concreteness that $R_0^{[1]\mathrm{dir}} = R_0^{[2]\mathrm{dir}} + \Delta$ and $R_0^{[1]\mathrm{env}} = R_0^{[2]\mathrm{env}} - \Delta$, where Δ is a positive number. The invasion condition given by Eq. (31) can be rewritten as

$$\frac{S^*}{S_{\mathrm{DFE}}^*}\left[R_0^{[1]\mathrm{dir}} + R_0^{[1]\mathrm{env}}\left(\frac{1}{1+\hat{V}_1^*}\right)\right] - \Delta \frac{S^*}{S_{\mathrm{DFE}}^*}\left(1 - \frac{1}{1+\hat{V}_1^*}\right) > 1. \tag{34}$$

The first term in the LHS of Eq. (34) provides the condition that strain 1 invades itself. Self-invasion relates to the homogeneity property which we gave up for our model in favor of analytical tractability. This prevents us from making a fair account of the situation. However, it is worth noting that the self-invasion condition should always be neutral (hence the corresponding term should be 1) in a homogeneous model since, in this case, a single strain endemic state is equivalent to a multi-strain endemic state of strains with identical parameters. Furthermore, since the second term in the LHS of Eq. (34) is always negative, it would result that the strain with smaller direct transmissibility cannot invade the endemic state of the strain with higher direct transmissibility while the reverse can happen (i.e., set $\Delta < 0$).

6. Discussion and conclusions

Whether an emerging strain becomes endemic by either eliminating or coexisting with existing strains is a central question in the population biology of infectious diseases. Here we addressed this question for the first time in the case where pathogens with perfect cross immunity are both directly and environmentally transmitted. We introduced an *SIR*-type multi-strain model in which environmental transmission is broadly defined and then established the conditions under which a multi-strain endemic state is invaded by a strain with mixed transmission mechanism. We expressed this condition in the form of a basic reproduction number where two terms can be distinguished: one corresponds to direct transmission and the other to environmental transmission. The generality of our definition of

environmental transmission enables these results to be applied broadly. In particular, the invasion condition derived in this work generalizes the results obtained on the basic reproduction number of single strain models (Rohani et al., 2009).

For concreteness, we then introduced some explicit forms for the environmental transmission terms and applied our invasion results to a two-strain paradigm model. After a brief analysis of the equilibria that can occur between two strains with mixed transmission mechanisms, we discussed coexistence and exclusive competition between a strain that is directly transmitted only and another one that has a mixed transmission mechanism. We found that environmental transmission may provide means for coexistence to a strain that otherwise would go extinct in competition with directly transmitted strains. This specification was suggested by our ongoing work on avian influenza viruses in North American waterfowl, but may also apply to other environmentally transmitted pathogens, such as cholera.

In the final section, we studied how two strains with equal R_0, one directly transmitted only and another one both directly and environmentally transmitted, invade each other's endemic state. We found that the first strain which is only directly transmitted can invade the endemic state of the strain with mixed transmission. However, the endemic state of the first strain is neutrally stable to the invasion of the second strain. Thus, our results suggest that environmental transmission makes the endemic state of a strain less robust to invasion than direct transmission. We are led to speculate that if a strain with mixed transmission occurs by accidental mutation in a pool of directly transmitted strain, and if the descendent and ancestral strain have matching R_0, then the mutant is given an evolutionary disadvantage by the mixed transmission mechanism. This result can be understood from the perspective that the environment acts like an inhospitable intermediary host where the pathogens do not undergo any other processes but death at a fairly high rate. It becomes thus intuitive that it is advantageous for the pathogen to avoid the environment. However, the epidemiological consequences (e.g., strain persistence) are not as obvious.

That co-circulation of a tremendous diversity of avian influenza viruses occurs in nature is well known. For instance, Hinshaw et al. (1980) collected 27 different antigenic subtypes in one local area of Canada in three years. More recently, Hanson et al. (2005) collected 7 subtypes from just 22 infected ducks Texas. These results are in stark contrast to the pattern of replacement that characterizes human influenza A (Smith et al., 2004). Indeed, even co-infections of the same animal are not uncommon (Sharp et al., 1997), giving rise to the concerns about recombination that lend urgency to understanding the evolution of this system and motivated our study in the first place. However, cross-immunity of antigenic subtypes is poorly understood and the ecological characterization of strains (i.e., relative infectivity and environmental persistence Brown et al., 2009) has just begun. Thus, the assumptions of cross-immunity and matched R_0 made here are only a starting point for understanding the evolutionary dynamics compatible with mixed transmission infections.

The empirical information necessary for a quantitative comparison of our predictions with any specific system remains elusive. In the case of avian influenza viruses, persistence times in the environment (Brown et al., 2009), shedding rates (Webster et al., 1992) and ID_{50} infectious dose estimates (Swayne and Slemon, 2008) for different strains have been obtained through direct measurements. However, key epidemiological data, such as reliable, consistently collected long-term prevalence estimates are hard to come by Krauss et al. (2004) and Sharp et al. (1993).

In closing, we remark that the ubiquity of evolutionary tradeoffs entails that other evolutionary consequences of

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[7] In fact, using Eqs. (36) and (37) in the Appendix, it can be shown that all eigenvalues of $\mathbf{E}^{[1]*}$ except one have strictly negative real parts.

environmental transmission are likely to result. The results presented here suggest that there is an evolutionary disadvantage to environmental transmission. What downstream consequences might such evolution have? The most immediate consequence is likely to be selection on structural properties of the infectious particle, for instance selection on properties that influence environmental durability and host infectiousness. Evolutionary consequences are not likely to end there, however. Cascading evolutionary consequences might also include virulence, which is predicted by the sit-and-wait hypothesis to correlate positively with environmental durability (Ewald, 1994). It follows, then, that evolution of phenotypic properties of great significance for host health are only slightly removed from the mechanisms by which transmission occurs. The extent of such evolutionary consequences remains to be determined.

Acknowledgments

Appendix A. Proof of the main result

Proof of statement (i). The proof follows immediately from the fact that the equilibrium $\mathbf{E}^*$ has $I_n^*=0$ and $V_n^*=0$. $\square$

Proof of statement (ii). We first introduce necessary notation. We denote by $\mathbf{J}$ the jacobian matrix of the n-strain model and by

$$\mathbf{D}_{(n-1)\times 1}^{\mathbf{v}} \equiv \begin{pmatrix} \partial[\varepsilon_1(\mathbf{V})f(\mathbf{V})]/\partial V_n \\ \partial[\varepsilon_2(\mathbf{V})f(\mathbf{V})]/\partial V_n \\ \vdots \\ \partial[\varepsilon_{n-1}(\mathbf{V})f(\mathbf{V})]/\partial V_n \end{pmatrix},$$

$$\mathbf{D}_{1\times(n-1)}^{\mathbf{h}} \equiv (\partial[\varepsilon_n(\mathbf{V})f(\mathbf{V})]/\partial V_1 \quad \partial[\varepsilon_n(\mathbf{V})f(\mathbf{V})]/\partial V_2 \quad \ldots \quad \partial[\varepsilon_n(\mathbf{V})f(\mathbf{V})]/\partial V_{n-1}),$$

$$\hat{\mathbf{B}}_{\square n} \equiv \begin{pmatrix} S\beta_1-(\mu+\gamma_1) & 0 & \ldots & 0 \\ 0 & S\beta_2-(\mu+\gamma_2) & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \ldots & S\beta_n-(\mu+\gamma_n) \end{pmatrix},$$

$$\mathbf{B}_{n\times 1}' \equiv \begin{pmatrix} \beta_1 I_1 + \rho\varepsilon_1(\mathbf{V})f(\mathbf{V}) \\ \beta_2 I_2 + \rho\varepsilon_2(\mathbf{V})f(\mathbf{V}) \\ \vdots \\ \beta_n I_n + \rho\varepsilon_n(\mathbf{V})f(\mathbf{V}) \end{pmatrix},$$

$$\mathbf{D}_{1\times n}' \equiv (\partial f(\mathbf{V})/\partial V_1 \quad \partial f(\mathbf{V})/\partial V_2 \quad \ldots \quad \partial f(\mathbf{V})/\partial V_n),$$

$$\mathbf{B}_{1\times n} \equiv (\beta_1 \quad \beta_2 \quad \ldots \quad \beta_n),$$

and the scalar $J_{11} \equiv -\sum_{i=1}^n \beta_i I_i - \rho f(\mathbf{V}) - \mu$. With these notations, $\hat{J}$ can be written in the following block-matrix form

$$\hat{J} = \begin{vmatrix} J_{11} & -S\mathbf{B}_{1\times n} & -\rho S\mathbf{D}_{1\times n}' \\ \mathbf{B}_{n\times 1}' & \hat{\mathbf{B}}_{\square n} & \rho S\mathbf{D}_{\square n} \\ \mathbf{0}_{n\times 1} & \mathbf{\Omega}_{\square n} & -\mathbf{H}_{\square n} \end{vmatrix}. \tag{35}$$

Our aim is to evaluate the characteristic polynomial $\det[\mathbf{J}-\lambda\mathbf{1}_{\square(2n+1)}]$ at $\mathbf{E}^*$. We first separate the columns and rows that refer to the variables I_n^* and V_n^* and their equations in the block-matrix form of $\hat{J}$ given by Eq. (35)

$$\hat{J} = \begin{vmatrix} J_{11} & -S\mathbf{B}_{1\times(n-1)} & -S\beta_n & -\rho S\mathbf{D}_{1\times(n-1)}' & -\rho S\frac{\partial f(\mathbf{V})}{\partial V_n} \\ \mathbf{B}_{(n-1)\times 1}' & \hat{\mathbf{B}}_{\square(n-1)} & \mathbf{0}_{(n-1)\times 1} & \rho S\mathbf{D}_{\square(n-1)} & \rho S\mathbf{D}_{(n-1)\times 1}^{\mathbf{v}} \\ \beta_n I_n - \rho\varepsilon_n(\mathbf{V})f(\mathbf{V}) & \mathbf{0}_{1\times(n-1)} & S\beta_n-(\mu+\gamma_n) & \rho S\mathbf{D}_{1\times(n-1)}^{\mathbf{h}} & \rho S\frac{\partial[\varepsilon_n(\mathbf{V})f(\mathbf{V})]}{\partial V_n} \\ \mathbf{0}_{(n-1)\times 1} & \mathbf{\Omega}_{\square(n-1)} & \mathbf{0}_{(n-1)\times 1} & -\mathbf{H}_{\square(n-1)} & \mathbf{0}_{(n-1)\times 1} \\ 0 & \mathbf{0}_{1\times(n-1)} & \omega_n & \mathbf{0}_{1\times(n-1)} & -\eta_n \end{vmatrix}.$$

$\hat{J}$ its corresponding determinant. $\mathbf{0}_{l\times m}$ is the matrix with l lines and m columns having all entries equal to zero ($\mathbf{0}_{m\times m} \equiv \mathbf{0}_{\square m}$) and $\mathbf{1}_{\square m}$ the unit matrix with m lines and m columns. We also introduce the following matrices

$$\mathbf{H}_{\square n} \equiv \begin{pmatrix} \eta_1 & 0 & \ldots & 0 \\ 0 & \eta_2 & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \ldots & \eta_n \end{pmatrix},$$

$$\mathbf{\Omega}_{\square n} \equiv \begin{pmatrix} \omega_1 & 0 & \ldots & 0 \\ 0 & \omega_2 & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \ldots & \omega_n \end{pmatrix},$$

$$\mathbf{D}_{\square n} \equiv \begin{pmatrix} \partial[\varepsilon_1(\mathbf{V})f(\mathbf{V})]/\partial V_1 & \partial[\varepsilon_1(\mathbf{V})f(\mathbf{V})]/\partial V_2 & \ldots & \partial[\varepsilon_1(\mathbf{V})f(\mathbf{V})]/\partial V_n \\ \partial[\varepsilon_2(\mathbf{V})f(\mathbf{V})]/\partial V_1 & \partial[\varepsilon_2(\mathbf{V})f(\mathbf{V})]/\partial V_2 & \ldots & \partial[\varepsilon_2(\mathbf{V})f(\mathbf{V})]/\partial V_n \\ \vdots & \vdots & \ddots & \vdots \\ \partial[\varepsilon_n(\mathbf{V})f(\mathbf{V})]/\partial V_1 & \partial[\varepsilon_n(\mathbf{V})f(\mathbf{V})]/\partial V_2 & \ldots & \partial[\varepsilon_n(\mathbf{V})f(\mathbf{V})]/\partial V_n \end{pmatrix},$$

Using Properties 2 and 3, we obtain that if $I_n^*=0$ and $V_n^*=0$ then $\beta_n I_n^* - \rho\varepsilon_n(\mathbf{V}^*)f(\mathbf{V}^*) = 0$ and $\mathbf{D}_{1\times(n-1)}^{\mathbf{h}}$ evaluated at $\mathbf{E}^*$ equals $\mathbf{0}_{1\times(n-1)}$. Therefore, only two particular entries in the third block-matrix line of $\hat{J}|_{E^*}$ may not be zero, one of them [i.e., $S\beta_n-(\mu+\gamma_n)$] being a diagonal entry. Since $\lambda\mathbf{1}_{\square(2n+1)}$ is a diagonal matrix, the same holds for $\det[\mathbf{J}-\lambda\mathbf{1}_{\square(2n+1)}]_{E^*}$. We expand $\det[\mathbf{J}-\lambda\mathbf{1}_{\square(2n+1)}]_{E^*}$ over its third block-matrix line (i.e., (n+1)th line) and obtain

$$\det[\mathbf{J}-\lambda\mathbf{1}_{\square(2n+1)}]_{E^*} = [S^*\beta_n-(\mu+\gamma_n)-\lambda]$$

$$\times \begin{vmatrix} J_{11}|_{E^*}-\lambda & -S\mathbf{B}_{1\times(n-1)} & -\rho S\mathbf{D}_{1\times(n-1)}' & -\rho S\partial f(\mathbf{V})/\partial V_n \\ \mathbf{B}_{(n-1)\times 1}' & \hat{\mathbf{B}}_{\square(n-1)}-\lambda\mathbf{1}_{\square(n-1)} & \rho S\mathbf{D}_{\square(n-1)} & \rho S\mathbf{D}_{(n-1)\times 1}^{\mathbf{v}} \\ \mathbf{0}_{(n-1)\times 1} & \mathbf{\Omega}_{\square(n-1)} & -\mathbf{H}_{\square(n-1)}-\lambda\mathbf{1}_{\square(n-1)} & \mathbf{0}_{(n-1)\times 1} \\ 0 & \mathbf{0}_{1\times(n-1)} & \mathbf{0}_{1\times(n-1)} & -\eta_n-\lambda \end{vmatrix}_{E^*}$$

$$+(-1)^{n+1}\rho S^*\frac{\partial[\varepsilon_n(\mathbf{V})f(\mathbf{V})]}{\partial V_n}\bigg|_{E^*}$$

$$\times \begin{vmatrix} J_{11}|_{E^*}-\lambda & -S\mathbf{B}_{1\times(n-1)} & -S\beta_n & -\rho S\mathbf{D}_{1\times(n-1)}' \\ \mathbf{B}_{(n-1)\times 1}' & \hat{\mathbf{B}}_{\square(n-1)}-\lambda\mathbf{1}_{\square(n-1)} & \mathbf{0}_{(n-1)\times 1} & \rho S\mathbf{D}_{\square(n-1)} \\ \mathbf{0}_{(n-1)\times 1} & \mathbf{\Omega}_{\square(n-1)} & \mathbf{0}_{(n-1)\times 1} & -\mathbf{H}_{\square(n-1)}-\lambda\mathbf{1}_{\square(n-1)} \\ 0 & \mathbf{0}_{1\times(n-1)} & \omega_n & \mathbf{0}_{1\times(n-1)} \end{vmatrix}_{E^*},$$

where $J_{11}|_{E^*} = -\sum_{i=1}^{n-1} \beta_i I_i - \rho f(\mathbf{V}) - \mu$. Further expanding the determinants in the RHS of the above equation over their last

lines, we finally obtain

$$\det[\mathbf{J}-\lambda\mathbf{1}_{\square(2n+1)}]_{\mathbf{E}^*} = -\left\{(\eta_n+\lambda)[S^*\beta_n-(\mu+\gamma_n)-\lambda]+\omega_n\rho S^*\frac{\partial[\varepsilon_n(\mathbf{V})f(\mathbf{V})]}{\partial V_n}\bigg|_{\mathbf{E}^*}\right\}$$

$$\times\begin{vmatrix} -\sum_{i=1}^{n-1}\beta_i i_i-\rho f(\mathbf{V})-\mu-\lambda & -S\mathbf{B}_{1\times(n-1)} & -\rho S\mathbf{D}'_{1\times(n-1)} \\ \mathbf{B}'_{(n-1)\times1} & \hat{\mathbf{B}}_{\square(n-1)}-\lambda\mathbf{1}_{\square(n-1)} & \rho S\mathbf{D}_{\square(n-1)} \\ \mathbf{0}_{(n-1)\times1} & \mathbf{\Omega}_{\square(n-1)} & -\mathbf{H}_{\square(n-1)}-\lambda\mathbf{1}_{\square(n-1)} \end{vmatrix}_{\mathbf{E}^*}.$$

Remark now that the remaining determinant is the characteristic equation of $\mathbf{F}^*$. The pre-factor provides the extra stability condition as follows. $\mathbf{E}^*$ is stable if and only if the following equation in λ

$$(\eta_n+\lambda)[S^*\beta_n-(\mu+\gamma_n)-\lambda]+\omega_n\rho S^*\frac{\partial[\varepsilon_n(\mathbf{V})f(\mathbf{V})]}{\partial V_n}\bigg|_{\mathbf{E}^*} = 0,$$

has solutions λ_1 and λ_2 with negative real parts. This happens if and only if the following two conditions are simultaneously satisfied:

(a) $\lambda_1+\lambda_2 = -\eta_n+[S^*\beta_n-(\mu+\gamma_n)] < 0,$

which further yields

$$\frac{S^*\beta_n}{\mu+\gamma_n}-\frac{\eta_n}{\mu+\gamma_n} < 1; \tag{36}$$

(b) $\lambda_1\lambda_2 = \eta_n[S^*\beta-(\mu+\gamma_n)]+\omega_n\rho S^*\frac{\partial[\varepsilon_n(\mathbf{V})f(\mathbf{V})]}{\partial V_n}\big|_{\mathbf{E}^*} > 0,$

which can be rewritten as

$$R_0^{[n]} \equiv \frac{S^*\beta_n}{\mu+\gamma_n}+\frac{S^*\rho\omega_n}{\eta_n(\mu+\gamma_n)}\frac{\partial[\varepsilon_n(\mathbf{V})f(\mathbf{V})]}{\partial V_n}\bigg|_{\mathbf{E}^*} < 1. \tag{37}$$

Note however that since the biological parameters are positively defined and $\varepsilon_n(\mathbf{V})f(\mathbf{V})$ is an increasing function of V_n (Properties 1 and 2), Eq. (37) implies Eq. (36). Thus, the condition given by Eq. (37) is both necessary and sufficient for $\lambda_{1,2}$ to have negative real parts. $\square$

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