Pathogen evolution in switching environments: A hybrid dynamical system approach

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ABSTRACT

We propose a hybrid dynamical system approach to model the evolution of a pathogen that experiences different selective pressures according to a stochastic process. In every environment, the evolution of the pathogen is described by a version of the Fisher–Haldane–Wright equation while the switching between environments follows a Markov jump process. We investigate how the qualitative behavior of a simple single-host deterministic system changes when the stochastic switching process is added. In particular, we study the stability in probability of monomorphic equilibria. We prove that in a "constantly" fluctuating environment, the genotype with the highest mean fitness is asymptotically stable in probability while all others are unstable in probability. However, if the probability of host switching depends on the genotype composition of the population, polymorphism can be stably maintained.

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1. Introduction

Living organisms face changing environmental conditions. Parasites are a case in point: after each transmission event they find themselves in a new host that may be quite different from the previous one. For example, the immune system of the new host may respond differently to the parasite, and the new host may have a different genotype or even belong to a different species. Thus, a parasite genotype that is characterized by a high fitness in one host may have a low fitness in a different host. The question therefore arises how parasites evolve under the fluctuating selective pressures imposed on them through transmission events to different hosts.

Most of the studies so far have focused on models for host-pathogen interactions in a deterministic context [11,12]. In some applications however it is natural to assume that environment (and hence fitness landscape) switching is not deterministic. For example, a pathogen could switch to a different host. Evolution of the pathogen then takes place in the new host (or environment), where the pathogen genotypes face different selective pressures, hence the dynamics of the pathogen genotypes are different. We remark that the evolving organism need not be a pathogen, nor is the environment necessarily a "host".

Evolution of organisms in deterministically and randomly varying environments has been studied by many authors, see [2] for an early review. Karlin and collaborators [5,6] introduced both deterministic and stochastic models for the evolution of haploid and diploid organisms under changing selection intensities for fixed and varying population sizes. In case of a deterministic two-allele model they showed that the genotype with higher selection intensity goes to fixation and the time to fixation varies according to the selection intensities. Furthermore, they investigated a stochastic model where generational selection intensities are identically distributed independent random variables. They focused on the question how the probabilities of fixation and the times to fixation change in the stochastic model. In Kirzhner et al. [7], considered a 4-dimensional system of difference equations for the haplotype frequencies of a two-locus model. Typical two-locus models show either fixation in one or both loci or stable polymorphic cycles, with period equaling the period of the environmental changes, i.e. the periodic fitness values. They however showed the existence of so called supercycles that have 1100 times the period of the periodically changing environment. The questions of structural stability, i.e. sensitivity in terms of the fitness parameters and the size of the basin of attraction of these cycles were investigated. Similarly, Nagylaki [10] investigated the existence of genetic polymorphisms for two-allele models with periodically varying fitness values. He showed that in a continuous differential equation model genetic polymorphism will persist with periods equaling the periods of the varying fitness values, however in a discrete model fixation is also possible.

Hybrid switching differential equations and more generally hybrid switching diffusions have found many applications in wireless communications, queuing networks, ecology [15] and financial mathematics, to name but a few; see [14] and the references therein. The word "hybrid" refers to the coexistence of continuous dynamics and discrete events, see also the related concept of piecewise deterministic processes [1]. In this paper we study a simplified version of the continuous time Fisher–Haldane–Wright equation (also known as *standard replicator equation*, [3]) subject to fitnesses driven by a Markov jump process. It is well known that in the deterministic Fisher–Haldane–Wright model the pathogen genotype that has the highest fitness value will go to fixation. The coupling of different Fisher–Haldane–Wright equations by a Markov process however requires a new definition of the concept of "highest fitness". Hence we study the possible changes to the stability behaviors of the monomorphic equilibrium states depending on the stationary distribution of the switching Markov process. First we establish analytical results for the stability/instability of equilibria in the hybrid model. We show that in the case of a state-independent switching process, the monomorphic equilibrium of the genotype with highest mean fitness is asymptotically stable in probability while the monomorphic equilibria of all other genotypes are unstable in probability. As the stationary distribution of the switching Markov process varies, so does the mean fitness of each genotype. This results in exchanges of stability without the merger of the equilibria during the transition process. We may call this a "stochastic transcritical bifurcation". Finally, we present some numerical simulations to illustrate our result and also an example of a state-dependent switching process.

2. The switching differential equation

We consider a model for m genotypes of a pathogen evolving in n possible environments. Let $w_i^k > 0$ denote the fitness value of genotype i in environment k. We assume for simplicity that for any fixed environment k, the fitness values w_i^k are all different. We write $\mathbf{w}_i$ for the vector of all fitness values of genotype i. Let P_i denote the frequency of pathogen i, so that the dynamics in each environment takes place in the $(m-1)$-dimensional simplex

$$\mathbb{T}^{m-1} = \left\{ P \in \mathbb{R}^m_{\geqslant 0} \Big| \sum_{i=1}^m P_i = 1 \right\}.$$

We write $P(t) = (P_1(t), P_2(t), \ldots, P_m(t))$ for the state of the system at time t. The frequency dynamics of pathogen genotype i in environment k is given by

$$\frac{dP_i(t)}{dt} = P_i(t)\left(w_i^k - \sum_{j=1}^m w_j^k P_j(t) \right) =: F_i(P(t), k). \quad (2.1)$$

This equation is the Fisher–Haldane–Wright equation for frequencies of genotypes of asexually proliferating organisms. The rate of growth or decay of a genotype is determined by the difference of its fitness and the average fitness of the population. Observe that the simplex $\mathbb{T}^{m-1}$ and any of its subsimplices are invariant under the dynamics given by Eq. (2.1). It can be shown by straightforward computation that the average fitness in environment k

$$\phi^k(P) = \sum_{i=1}^m w_i^k P_i \quad (2.2)$$

satisfies

$$\begin{aligned}
\frac{d}{dt}\phi^i(P(t)) &= \sum_{i=1}^m w_i^k P_i \left(w_i^k - \sum_{j=1}^m w_j^k P_j \right) = \sum_{i=1}^m P_i (w_i^k)^2 - \left(\sum_{i=1}^m P_i w_i^k \right)^2 \\
&= \sum_{i=1}^m P_i (w_i^k)^2 - 2\left(\sum_{i=1}^m P_i w_i^k \right)^2 + \sum_{i=1}^m \left(\sum_{j=1}^m P_j w_j^k \right)^2 P_i \\
&= \sum_{i=1}^m P_i \left(w_i^k - \sum_{j=1}^m w_j^k P_j \right)^2 \geqslant 0,
\end{aligned}$$

with equality if and only if P is an equilibrium. It follows from the global existence of solutions and LaSalle's theorem that every trajectory of (2.1) approaches one of the finitely many equilibria situated at the vertices of the simplex, see [8].

The environment switches according to a continuous time stochastic process $\alpha(t)$ that takes values in the set $\mathcal{M} = \{1, 2, \ldots, n\}$. The switching process α is a Markov process with (possibly state-dependent) generator matrix $Q(P)$ whose entries $q_{kl}(P)$ are defined by

$$\begin{aligned}
\mathbf{P}\{\alpha(t+\Delta t) &= l | \alpha(t) = k, (P(s), \alpha(s)), s \leqslant t\} \\
&= q_{kl}(P(t))\Delta t + o(\Delta t).
\end{aligned} \quad (2.3)$$

The elements q_{kl} of the generator matrix Q satisfy $q_{kl} \geqslant 0$ for all $k \neq l$ and $\sum_{l \in \mathcal{M}} q_{kl} = 0$ for every $k \in \mathcal{M}$ (such a matrix is said to have the *q-property*, see [13]). The complete hybrid switching ordinary differential equation can be cast in the form

$$\begin{aligned}
\frac{dP}{dt} &= F(P(t), \alpha(t)), \\
P(0) &= p \in \mathbb{T}^{m-1}, \quad \alpha(0) = \alpha \in \mathcal{M}, \quad \text{a.s.},
\end{aligned} \quad (2.4)$$

where $\alpha(t) = k$ determines the environment k at time t and $F = (F_1, \ldots, F_m)$ are defined by (2.1). The right hand side of the differential equation in (2.4) is globally Lipschitz continuous on the compact set $\mathbb{T}^{m-1} \times \mathcal{M}$. This implies global existence and uniqueness of solutions in the sense of stochastic processes, see [14, Theorem 2.1].

For the Eq. (2.1) restricted to a fixed environment k, the vertices e_i of the simplex $\mathbb{T}^{m-1}$ (i.e. the unit vectors of $\mathbb{R}^m$) are all the equilibrium solutions. It is easy to show that all but one of these equilibria are unstable and that the stable equilibrium in environment k is the one for which the fitness value w_i^k is the largest. In the following section we investigate how this result generalizes to the case that stochastic switching is introduced. For this of course, we need to first generalize the concept of stability to switching ordinary differential equations.

3. Stability and instability in probability

In this section we establish results concerning the stability and instability of monomorphic steady states of the hybrid model. We first recall the following definition [14, Definition 8.1].

Definition 3.1. Let $(X^{x,\alpha}(t))_{t \geqslant 0}$ be the solution of a hybrid switching ordinary differential equation

$$\begin{aligned}
\dot{X}(t) &= F(X(t), \alpha(t)), \quad \mathbf{P}\{\alpha(t+\Delta t) = l | \alpha(t) = k, (X(s), \alpha(s)), s \leqslant t\} \\
&= q_{kl}(X(t))\Delta t + o(\Delta t), X(0) = x, \quad \alpha(0) = \alpha \text{ a.s.},
\end{aligned}$$

and let (without loss of generality) $x = 0$ be an equilibrium solution, i.e. a solution of the equation $F(0, \alpha) = 0$ for every $\alpha \in \mathcal{M}$. We say that 0 is *stable in probability* if

$$\lim_{x \to 0} \mathbf{P}\left\{ \sup_{t \geqslant 0} |X^{x,\alpha}(t)| > r \right\} = 0$$

for every $\alpha \in \mathcal{M}$ and every $r > 0$. We say that 0 is *asymptotically stable in probability* if it is stable in probability and

$$\lim_{x \to 0} \mathbf{P}\left\{\lim_{t \to \infty} X^{x,\alpha}(t) = 0\right\} = 1$$

for every $\alpha \in \mathcal{M}$. Finally, 0 is *unstable in probability* if it is not stable in probability.

For n-tuples of functions $g(\cdot, k) \in C^1(\mathbb{R}^m)$ one defines a linear operator $\mathcal{L}$, the *stochastic Lie derivative* (see [14, Eq. (8.3), p. 219])

$$\mathcal{L}g(x,k) = F(x,k) \cdot \nabla g(x,k) + \sum_{l=1}^{n} q_{kl}(x)g(x,k),$$

where ∇ denotes the gradient with respect to the x-variable for fixed $k \in \mathcal{M}$. This is a natural generalization of the derivative of a scalar function along a vector field well known in the theory of ordinary differential equations. The following is Proposition 8.6, [14, p. 223].

Theorem 3.2. *Let $D \subset \mathbb{R}^m$ be a neighborhood of 0 and assume that there exists a function $V : D \times \mathcal{M} \to [0, \infty)$ with the following properties*

- $V(\cdot, k)$ *is continuous and vanishes only at 0,*
- $V(\cdot, k)$ *is continuously differentiable in $D \setminus \{0\}$, and*
- *There exists a function $\kappa : (0, r) \to (0, \infty)$ such that for all $k \in \mathcal{M}$ and $|x| > \varrho$,*

$$\mathcal{L}V(x,k) \leqslant -\kappa(\varrho) < 0.$$

Then the equilibrium $x = 0$ is asymptotically stable in probability.

A function that satisfies the conditions of the theorem is called a *Lyapunov function* (for asymptotic stability).

Throughout the remainder of this section we consider the case of a state-independent generator matrix Q with a universal stationary distribution $\pi = (q_1, \ldots, q_n)$. This is the solution of the equations

$$\pi \cdot \mathbf{1} = 1, \quad \text{and} \quad \pi Q = \mathbf{0}.$$

If $q_{kl} > 0$ for all $k \neq l$ then the matrix Q is *irreducible* and $\pi > 0$ is unique [13, p. 21].

Theorem 3.3. *Let P_1 be the genotype with the highest mean fitness, that is*

$$\pi \cdot \mathbf{w}_1 > \pi \cdot \mathbf{w}_i \quad \text{for all} \quad i = 2, \ldots, m \tag{3.5}$$

Then the equilibrium e_1 is asymptotically stable in probability.

Remark 3.4. For almost every stationary distribution $\pi \in \mathbb{T}^{n-1}$, exactly one genotype satisfies a condition similar to (3.5).

Proof. The proof is split into two steps. We consider first two genotypes P_1 and P_2 in n environments. We assume that the generator matrix of the Markov process has the form

$$Q = \begin{pmatrix} q_1 - 1 & q_2 & q_3 & \cdots & q_n \\ q_1 & q_2 - 1 & q_3 & \cdots & q_n \\ \vdots & \vdots & \vdots & & \vdots \\ q_1 & q_2 & q_3 & \cdots & q_n - 1 \end{pmatrix}.$$

Throughout the paper, we set $a_i^k = w_i^k - w_1^k$ for the difference of fitness values with respect to genotype 1. Recall that by assumption $a_i^k \neq 0$. Using the constraint $P_1 + P_2 = 1$, we eliminate P_1 so that the system becomes a system of single equations

$$\dot{P}_2 = a_2^k P_2(1 - P_2).$$

The vector of eigenvalues of the Jacobian of the reduced right hand side at $P_2 = 0$ is thus $\mathbf{a}_2 = (a_2^1, \ldots, a_2^n)$. As in the proof of Theorem 8.8 of [14] we define

$$\beta_2 := -\pi \cdot \mathbf{a}_2 > 0,$$

with the last inequality holding true since genotype 1 has the higher mean fitness. We have to solve the system of equations

$$Qc_2 = \mathbf{a}_2 + \beta_2 \mathbf{1}$$

for the vector $\mathbf{c}_2 = (c_2^1, \ldots, c_2^n)$ where $\mathbf{1}$ is the column vector with n entries 1. Since the matrix Q has a null space spanned by $\mathbf{1}$, we can select $c_2^k = a_2^n - a_2^k$ for $k = 1, \ldots, n - 1$ and $c_2^n = 0$. With a constant $0 < \gamma < 1$ yet to be selected, we choose the Lyapunov function candidate

$$V(P_2, k) = (1 - \gamma c_2^k)P_2^\gamma, \quad P_2 \geqslant 0, \; k = 1, \ldots, n,$$

where γ is sufficiently small to make all the factors positive. Then for $k = 1, \ldots, n - 1$, and $P_2 \to 0$,

$$\mathcal{L}V(P_2, k) = P_2^\gamma \left(a_2^k \gamma (1 - \gamma(a_2^n - a_2^k))(1 - P_2) + \sum_{l=1}^{n-1} q_l (1 - \gamma(a_2^n - a_2^l)) \right.$$
$$\left. - (1 - \gamma(a_2^n - a_2^k)) + 1 - \sum_{l=1}^{n-1} q_l \right)$$
$$= \gamma P_2^\gamma \left(a_2^k(1 - \gamma(a_2^n - a_2^k)) - \sum_{l=1}^{n-1} q_l(a_2^n - a_2^l) + a_2^n - a_2^k + o(1) \right)$$
$$= \gamma P_2^\gamma \left(a_2^n - \gamma a_2^k(a_2^n - a_2^k) - \sum_{l=1}^{n-1} q_l(a_2^n - a_2^l) + o(1) \right).$$

The inequalities that guarantee that the all factors in parentheses are negative are

$$a_2^n - \sum_{l=1}^{n-1} q_l(a_2^n - a_2^l) < \gamma a_2^k(a_2^n - a_2^k), \quad k = 1, \ldots, n-1. \tag{3.6}$$

The expression on the left hand side is negative, since from inequality (3.5), $0 > \pi \cdot \mathbf{a}_2$, and $q_n = 1 - \sum_{l=1}^{n-1} q_l$ we obtain $0 > a_2^n - \sum_{l=1}^{n-1} q_l(a_2^n - a_2^l)$. Inequalities (3.6) can be solved for γ, depending on the sign of the factors on the right hand side. If $a_2^k(a_2^n - a_2^k) > 0$, then we obtain the condition

$$\frac{a_2^n - \sum_{l=1}^{n-1} q_l(a_2^n - a_2^l)}{a_2^k(a_2^n - a_2^k)} < 0 < \gamma,$$

which is satisfied trivially. Inequality (3.6) also holds trivially if $a_2^n = a_2^k$. If $a_2^k(a_2^n - a_2^k) < 0$ and the inequality sign is reversed, we can select γ sufficiently small, namely such that

$$0 < \gamma < \min_{k=1,\ldots,n-1} \left\{ \frac{a_2^n - \sum_{l=1}^{n-1} q_l(a_2^n - a_2^l)}{a_2^k(a_2^n - a_2^k)} : a_2^k(a_2^n - a_2^k) < 0 \right\}.$$

For the n-th environment we have

$$\mathcal{L}V(P_2, n) = P_2^\gamma \left(a_2^n \gamma (1 - P_2) + \sum_{l=1}^{n-1} q_l(1 - \gamma(a_2^n - a_2^l)) - \sum_{l=1}^{n-1} q_l \right)$$
$$= \gamma P_2^\gamma \left(a_2^n - \sum_{l=1}^{n-1} q_l(a_2^n - a_2^l) + o(1) \right).$$

Here the factor in parentheses is negative already. Thus the conditions of Theorem 3.2 are satisfied and the equilibrium $P_2 = 0$ is asymptotically stable in probability.

In the general case we consider $m \geqslant 3$. Using the constraint $\sum_{i=1}^{m} P_i = 1$, we eliminate P_1 and obtain the reduced systems

$$\dot{P}_i = a_i^k P_i(1 - P_i) - P_i \sum_{j=2, \; j \neq i}^{m} a_i^k P_j, \tag{3.7}$$

for $i = 2, \ldots, m$ and $k \in \mathcal{M}$. We construct a family of functions for every pair $(1, i)$. Setting $c_i^k = a_i^n - a_i^k$ for $k = 1, \ldots, n-1$ and $c_i^n = 0$ for $i = 2, \ldots, m$, we define

$$V_i(P_i, k) = (1 - \gamma c_i^k)P_i^\gamma, \quad P_i > 0, \quad i = 2, \ldots, m, \quad k = 1, \ldots, n$$

with

$$0 < \gamma < \min_{\substack{i = 2, \ldots m \\ k = 1, \ldots, n-1}} \left\{ \frac{a_i^n - \sum_{l=1}^{n-1} q_l(a_i^n - a_i^l)}{a_i^k(a_i^n - a_i^k)} : a_i^k(a_i^n - a_i^k) < 0 \right\}.$$

We now define the Lyapunov function

$$V(P_2, \ldots, P_m, k) = \sum_{i=2}^{m} (1 - \gamma c_i^k)P_i^\gamma, \quad P_i > 0, \quad k = 1, \ldots, n.$$

It follows from the linearity of the operator $\mathcal{L}$ and the choice of γ that for $k = 1, \ldots, n-1$,

$$\mathcal{L}V(P_2, \ldots, P_m, k) = \gamma \sum_{i=2}^{m} P_i^\gamma \left(a_i^n - \gamma a_i^k(a_i^n - a_i^k) - \sum_{l=1}^{n-1} q_l(a_i^n - a_i^l) + o(1) \right).$$

where every factor in parentheses is negative. Similarly, in the n-th environment

$$\mathcal{L}V(P_2, \ldots, P_m, n) = \gamma \sum_{i=2}^{m} P_i^\gamma \left(a_i^n - \sum_{l=1}^{n-1} q_l(a_i^n - a_i^l) + o(1) \right),$$

and again every factor in parentheses is negative. $\quad \square$

Instability in probability of an equilibrium can be proved similarly. The following is Proposition 8.7, [14, p. 223]. Notice however that the Lyapunov function does not vanish but has a pole at the unstable equilibrium.

Theorem 3.5. *Let $D \subset \mathbb{R}^m$ be a neighborhood of 0 and assume that there exists a function $V : D \times \mathcal{M} \to [0, \infty)$ with the following properties*

- $V(\cdot, k)$ *is continuously differentiable in $D \setminus \{0\}$, and*
- *there exists a function $\kappa : (0, r) \to (0, \infty)$ such that for all $k \in \mathcal{M}$ and $|x| > \varrho$,*

  $$\mathcal{L}V(x, k) \leqslant -\kappa(\varrho) < 0,$$

- *for all $k \in \mathcal{M}$,*

  $$\lim_{|x| \to 0} V(x, k) = \infty.$$

Then the equilibrium $x = 0$ is unstable in probability.

Theorem 3.6. *Under the assumption (3.5) of Theorem 3.3, the equilibrium e_i, $i = 2, \ldots, m$ is unstable in probability.*

Proof. The proof is very similar to that of Theorem 3.3, so we only give a sketch here. This time it is P_i that is being eliminated from the system containing P_1 and P_i, leaving behind equations

$$\dot{P}_1 = -a_i^k P_1(1 - P_1), \quad k = 1, \ldots, n.$$

With $c_i^k = a_i^k - a_i^n$ for $k = 1, \ldots, n-1$, $c_i^n = 0$ and a constant $-1 < \gamma < 0$, we define

$$V(P_1, k) = (1 - \gamma c_i^k)P_1^\gamma, \quad P_1 > 0, \quad k = 1, \ldots, n,$$

where γ is sufficiently close to zero, such that $1 - \gamma c_i^k > 0$. Then we select

$$0 > \gamma > \max_{k=1, \ldots, n-1} \left\{ \frac{a_i^n - \sum_{l=1}^{n-1} q_l(a_i^n - a_i^l)}{a_i^k(a_i^k - a_i^n)} : a_i^k(a_i^k - a_i^n) > 0 \right\},$$

where the fractions on the right hand side are all negative. Detailed calculations that we omit show that for a constant $C > 0$,

$$\mathcal{L}V(P_1, k) \leqslant \gamma C P_1^\gamma < 0,$$

for all $k \in \mathcal{M}$. $\quad \square$

Remark 3.7. The notion of "highest mean fitness" requires that the generator matrix Q is independent of the state and so has a universal stationary distribution π. If Q depends continuously on P, it is still possible to formulate the corresponding "local" stability results for the equilibria e_i by taking π to be a stationary distribution of $Q(e_i)$.

4. Numerical simulations and examples

The following is an interesting example of how stability can arise through stochastic coupling. Let the fitness values of three genotypes in two environments be given by

$$w_1^1 = 1, \quad w_2^1 = \frac{7}{10}, \quad w_3^1 = \frac{11}{10},$$
$$w_1^2 = 1, \quad w_2^2 = \frac{11}{10}, \quad w_3^2 = \frac{7}{10}.$$

Although genotype 1 does not have the highest fitness in any environment, it has the highest mean fitness for stationary distributions $(q, 1-q)$ with $\frac{1}{4} < q < \frac{3}{4}$, see Fig. 1. If the generator matrix Q of the Markov process does not depend explicitly on the state $P(t)$, we can determine the switching times *a priori* according to $t_{i+1} = t_i + \tau$, where τ is an exponentially distributed random variable with mean 1 (for example).

To finish this section, we present two example with a state-dependent generator matrix $Q(P)$. Let $n = m = 2$,

$$w_1^1 = w_2^2 = 1, \quad w_2^1 = w_1^2 = \frac{8}{10},$$

and define two switching matrix functions

$$Q_1(P_1, P_2) = \begin{pmatrix} -P_2 & P_2 \\ P_1 & -P_1 \end{pmatrix},$$
$$Q_2(P_1, P_2) = \begin{pmatrix} -P_1 & P_1 \\ P_2 & -P_2 \end{pmatrix}.$$

This choice of the generator matrix means that the jump process favors jumps into the environment that is beneficial (in case Q_1), respectively disadvantageous (in case Q_2) for the genotype that currently dominates. In contrast to the previous simulations with state-independent generator matrix, it is now necessary to update the transition matrix of the Markov chain, namely $\exp(Q(P)\Delta t)$ during each time step of length Δt. Following [14, Chapter 5.3], we use the approximation $I + Q(P)\Delta t$. The stationary distribution of $Q_1(e_i)$ is, incidentally, e_i for $i = 1, 2$. It follows from Theorem 3.3 and Remark 3.7 that both equilibria are locally asymptotically stable in probability. Conversely, the stationary distribution of $Q_2(e_1)$ is e_2 and vice versa. Under this regime, both equilibria are locally unstable in probability. The results in Fig. 2 show that stochastic bistability may arise (for the choice $Q_1(P)$, left panel) or that solutions do not converge to a monomorphic steady state (for the choice $Q_2(P)$, right panel).

In terms of biological interpretation, one can conceive of competing pathogen genotypes that cause different behaviors in the affected host. For example, if the dominating pathogen genotype has only mild effects on their host's well-being, infected individuals may retain their usual mobility and thereby make a transition into a new environment more likely. On the other hand, if the dominating pathogen causes severe morbidity, the host may exhibit restricted mobility so that a transition into a new environment becomes less likely.
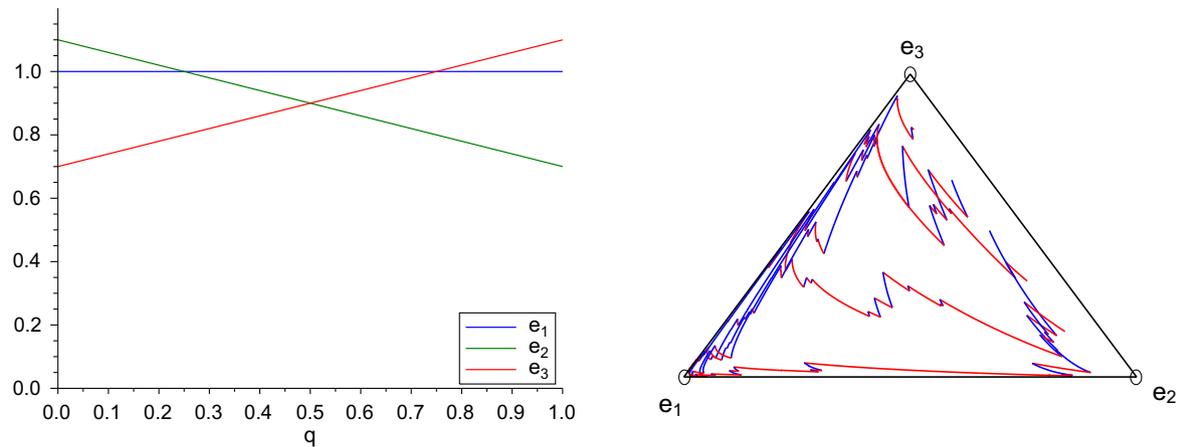
Fig. 1. (Left panel) The mean fitness of the three equilibria as a function of the parameter q of the stationary distribution. (Right panel) trajectories converging to e_1 when $q = \frac{1}{2}$. Parts of the trajectory in red indicate that environment 1 is active (when e_3 is attracting) while parts of the trajectory in blue indicate that environment 2 is active (when e_2 is attracting). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
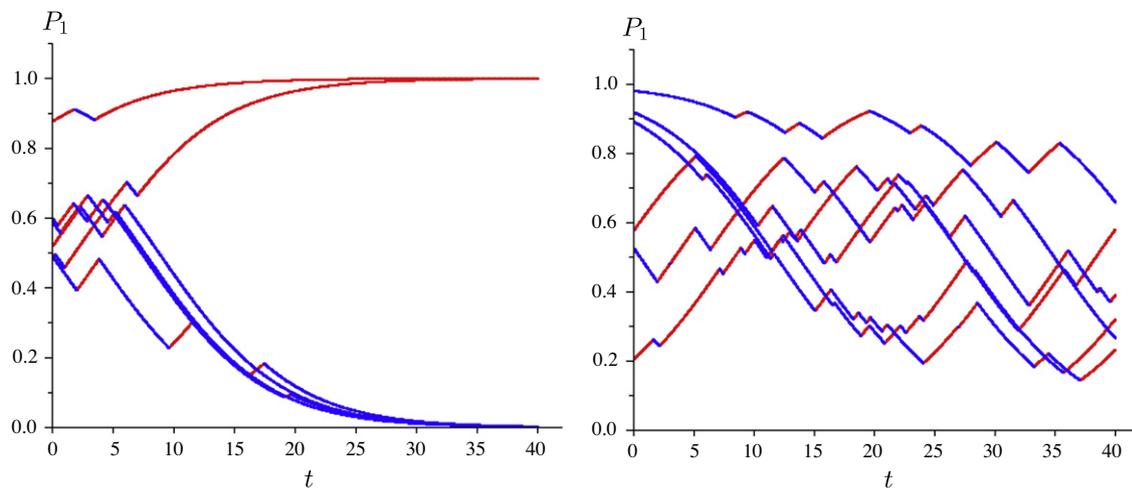
Fig. 2. A state-dependent generator matrix $Q_1(P)$ leads to bistability (left panel) whereas matrix $Q_2(P)$ results in failure to converge to an equilibrium (right panel). Parts of the trajectory in red indicate that environment 1 is active (when e_1 is attracting) while parts of the trajectory in blue indicate that environment 2 is active (when e_2 is attracting). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

5. Conclusions

In this work we consider the dynamics of a simple host-pathogen system, where pathogen genotype frequencies evolve according to a simple deterministic model. The selective pressures switch according to a Markov process. We use the framework of switching differential equations to compare the evolution of the pathogen in a single deterministic versus a hybrid system. In the switching system interesting new stability patterns emerge, depending on the stationary distribution of the underlying Markov process. We assume a fixed number of environments (and corresponding fitnesses), in contrast to previous works. For example, Karlin and collaborators [5,6] assumed that the fitnesses during each generation are independent identically distributed random variables. Gillespie on the other hand in [4] proposed a stochastic differential equation where the fitness is a process with continuous sample paths.

In the case of a state-independent generator matrix of the Markov process Q, we have a partition of the simplex $\mathbb{T}^{n-1}$ of all possible stationary distributions π into regions where one genotype has a greater mean fitness than all others, except for a set of measure zero where two genotypes have equal mean fitness (where bifurcations

occur). This complete classification relies on the diagonal structure of the Jacobian of the reduced system (3.7) at the equilibrium 0. Due to this decoupling, it is possible to use a sum of Lyapunov functions that all depend on one variable only. In this way, we obtain a condition for asymptotic stability using convex combinations of corresponding elements of the spectra of the Jacobians in the different environments. We expect such a result to hold in the greater context of switching ordinary differential equations and diffusion processes with regime switching.

Our work can be refined and extended in various ways. Firstly, we use a very simple deterministic competition model (2.1), where the pathogen genotypes are ordered according to their fitness values and the only equilibria are the vertices of the simplex $\mathbb{T}^{m-1}$. A straightforward extension would be to consider the continuous time Fisher–Haldane–Wright equation for diploid organisms for which there exist equilibria in the interior of $\mathbb{T}^{m-1}$. Other competition models may lead to deterministic bistability or to periodic orbits (for example the rock-paper-scissors game [3]). Secondly, although the host switching process is stochastic, we model within-host evolution in a deterministic way. A more realistic approach would incorporate random genetic drift into the model. This may be particularly important during transmission events, which often

involve population bottlenecks due to small inoculum sizes. Finally, our model only considers a single chain of transmission events and neglects between-host selection as well as superinfections. It may be possible to also consider multiple (branching and coalescing) transmission chains and thus fully couple within-host and epidemiological dynamics [9].

Acknowledgments

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