# INVARIANT MANIFOLDS IN A CLASS-STRUCTURED MODEL FROM ADAPTIVE DYNAMICS

# NIKOLA POPOVIĆ

ABSTRACT. We consider a family of structured population models from adaptive dynamics in which cells transition through a number of growth states, or classes, before division. We prove the existence and global asymptotic stability of invariant ("resident") manifolds in that family; furthermore, we re-derive conditions under which scarce mutants can invade established resident populations, and we show the existence of corresponding "invasion" manifolds which are obtained as critical manifolds under the additional assumption that resident has attained quasi-steady state, which induces a separation of scales. Our analysis is based on standard phase space techniques for ordinary differential equations, in combination with the geometric singular perturbation theory due to Fenichel.

## 1. INTRODUCTION

Adaptive dynamics is typically characterised as "a process by which natural selection, acting on variation within a population, promotes the survival of individuals that are more successful at reproducing and contributing to future generations" [7, Section 1.2]. The relevant terminology was coined in [4, 11] in an attempt to unify the fields of population genetics, replicator dynamics, and game theory [5], with the ultimate aim of describing the evolution of phenotypic traits in populations that interact with each other and their environments. Crucially, adaptive dynamics seeks to reconcile the disparate timescales that naturally emerge when mutants attempt to invade an established resident population. In the simplest scenario, it is assumed that all individuals in a given population are identical; a natural generalisation is hence obtained under the additional assumption that every individual can be assigned to one of a number of discrete classes that are, however, still characterised by the same value for the evolvable trait. Concurrently, individuals have to consider the trade-offs that ensue when various competing traits, or behaviours, cannot be optimised independently, but have to be balanced given resource limitations in the environment.

A class-structured modelling framework for resource allocation in microbial populations in chemostat-like well-mixed environments was developed in [7] on the basis of adaptive dynamics. For definiteness, allocation of resources ("nutrients") was limited to processes that can either promote biomass synthesis ("growth") or a nutrient-use pathway ("maintenance"). Here, it is worth noting that the family of models proposed in [7] is based on the classic notion of a chemostat [12] which allows for "the uninterrupted culture of microorganisms under controlled and reproducible conditions with continuous inputs and outputs", and which "has since been used as the laboratory analog for natural, open, systems" [7, Section 1.2]; that notion is extended by incorporation of concepts from the established theory of structured population models [10]. We refer the reader to [7] for a detailed discussion and further references.

In the simplest case, the framework proposed in [7] is realised in a family of nonlinear ordinary differential equation (ODE) models for a class-structured population of cells in the presence of a single nutrient. In that case, it was observed numerically that the induced flow converges to an appropriately defined family of invariant manifolds following an initial transient. Furthermore,

Key words and phrases. Adaptive dynamics; class-structured model; invariant manifolds; geometric singular perturbation theory.

the invasion of scarce mutant into an established ("resident") population was studied, again with reference to invariant manifold theory. Given the focus in [7] on the physiological interpretation of the family of models formulated therein, the existence and stability of the underlying invariant manifolds was assumed, rather than shown rigorously. Here, we fill that gap by constructing these manifolds – specifically, the so-called "resident", "invasion", and "mutant" manifolds – analytically for the simplest structured model proposed in [7]. Moreover, we show that these manifolds are globally attracting under suitable assumptions on model parameters which, not unexpectedly, echo the survival and invasion conditions derived in [7]. Our analysis is based on standard phase space techniques for ordinary differential equations in combination with the so-called "geometric singular perturbation theory" (GSPT) due to Fenichel [3, 6]; the latter applies naturally in the residentmutant scenario in which a separation of scales is present.

This article is organised as follows. In Section 2, we briefly introduce the family of class-structured "resident" models studied here; in Section 3, we modify that family by introducing a mutant into the environment. In Section 4, we present the two-class case and the three-class case as illustrative examples; finally, we conclude with a brief discussion in Section 5.

### 2. Resident model

We consider the class-structured model

(1a) 
$$\dot{x}_1 = uk_u(r_x)r_x(-x_1+2x_n)-x_1D,$$

(1b) 
$$\dot{x}_i = uk_u(r_x)r_x(-x_i + x_{i-1}) - x_iD$$
 for  $2 \le i \le n$ ,

(1c) 
$$\dot{u} = p - uD - uk_u(r_x) \sum_{i=1}^n x_i$$

that was introduced in [7, Section 2.3]. Here,  $x_i$  (i = 1, ..., n) is the *i*-th class in a resident population of cells, with  $n \ge 2$  an integer, while u is the concentration of some nutrient; the overdot denotes differentiation with respect to time t.

The model in (1) can be interpreted as follows [7]: a cell can exist in n growth states, or classes; nutrient uptake in class i, followed by biomass synthesis, forces the cell to transition to the next class i+1, where  $i = 1, \ldots, n-1$ . Once the cell has reached the highest "threshold" class (n), it divides into two daughter cells in the "basal" class 1. (Correspondingly, we will typically impose initial conditions of the form  $(x_1, x_2, \ldots, x_n, u)(0) = (x_{10}, 0, \ldots, 0, u_0)$  on (1), with  $x_{10}$  strictly positive.) Importantly, the "resource allocation parameter", or "evolvable trait",  $r_x \in (0, 1)$  determines the probability of allocating one unit of nutrient towards biomass synthesis; correspondingly,  $1 - r_x$  is the probability of the cell opting for the nutrient-use pathway, as detailed in [7, Section 2.2]. The function  $k_u(r_x)$  represents the rate of nutrient uptake, and is typically assumed to be monotonically decreasing in  $r_x$ ; following [7], we may assume it to be an inverted Hill-type function of the form

$$k_u(r_x) = k_{\min} + (k_{\max} - k_{\min}) \frac{(1 - r_x)^{\eta}}{(1 + K)^{\eta} + (1 - r_x)^{\eta}}$$

with  $k_{\min}$ ,  $k_{\max}$ , and K positive constants and the integer  $\eta$  the so-called Hill coefficient [7, Equation (2.36)]. Finally, p > 0 denotes the rate at which nutrient is added to the environment, whereas D > 0 is the "mortality rate" at which both cells and nutrient are removed.

**Remark 1.** As explained in [7, Section 2.2], each instance of nutrient uptake at stage i results in the formation of an intermediate species; however, since that species is assumed to be at quasi-steady state, it is neglected here, as was the case there.

2.1. **Preliminaries.** We begin by reasoning that, for physiologically relevant initial conditions, the total population  $X(t) := \sum_{i=1}^{n} x_i(t)$  of cells cannot go extinct in Equation (1) unless all classes are initiated at zero; furthermore, the amount of resource u in the network has to remain bounded – from both below and above – throughout:

**Lemma 1.** Let  $r_x \in (0,1)$ , let  $k_u(r_x)$  be defined as above, and assume an initial condition  $(x_1, \ldots, x_n, u)(0) = (x_{10}, \ldots, x_{n0}, u_0) \in \mathbb{R}^n_+ \times \mathbb{R}_+$  for Equation (1). Then, the total population X(t) is strictly positive for all t > 0 unless  $x_{i0} = 0$  for all  $i = 1, \ldots, n$ .

Moreover, the solution u(t) to Equation (1c) satisfies

(2) 
$$0 < u(t) \le \max\left\{u_0, \frac{p}{D + k_u(r_x)\chi}\right\} < \infty$$

for any t > 0, where  $\chi := \inf_{t \ge 0} X(t) \ge 0$ .

*Proof.* Solving Equation (1c), which we write as  $\dot{u} = p - uD - uk_u(r_x)X$ , for u by variation of constants, we find

$$u(t) = u_0 e^{-\int_0^t (D + k_u(r_x)X(s))ds} + p \int_0^t e^{-\int_s^t (D + k_u(r_x)X(\sigma))d\sigma} ds;$$

since  $u_0 \ge 0$  and p is positive by assumption, it follows that u(t) > 0 for any t > 0.

Adding Equations (1a) and (1b) for i = 1, ..., n, we see that X satisfies the equation  $\dot{X} = uk_u(r_x)r_xx_n - XD$ , which has the solution

(3) 
$$X(t) = X_0 e^{-Dt} + \int_0^t u(s) k_u(r_x) r_x x_n(s) e^{-D(t-s)} ds,$$

with initial condition  $X_0 := \sum_{i=1}^n x_{i0}$ . Since u is positive throughout, by the above, it follows that  $X(t) \ge 0$  for all t > 0 if we can show that  $x_n$  is always non-negative, with equality holding if  $X_0 = 0$ . To that end, let us assume that  $x_n(t)$  may become negative, in which case there exists  $t_n \ge 0$  such that  $x_n(t_n) = 0$ ; in particular, let  $t_n$  be the minimal such time. Thus, Equation (1b) gives  $\dot{x}_n|_{t=t_n} = u(t_n)k_u(r_x)r_xx_{n-1}(t_n)$ , which can only be negative if  $x_{n-1}(t_n) < 0$ ; however, in that case, there must exist  $0 \le t_{n-1} \le t_n$  such that  $x_{n-1}(t_{n-1}) = 0$ . Then,  $\dot{x}_{n-1}|_{t=t_{n-1}} = u(t_{n-1})k_u(r_x)r_xx_{n-2}(t_{n-1})$ , which can only be negative if  $x_{n-2}(t_{n-2}) = 0$  for  $0 \le t_{n-2} \le t_{n-1}$ . Proceeding recursively, we finally find  $\dot{x}_1|_{t=t_1} = u(t_1)k_u(r_x)r_x2x_n(t_1)$ , by (1a), where  $0 \le t_1 \le t_2 \le \cdots \le t_n$ . Thus,  $\dot{x}_1(t_1)$  can only be negative if  $x_n(t_1) < 0$ ; however, since we assumed  $t_n$  to be minimal, it follows that  $t_i =: t^*$  must be independent of  $i = 1, \ldots, n$ . Since  $x_i(t^*) = 0 = \dot{x}_i|_{t=t^*}$  then for any  $i = 1, \ldots, n$ , it would follow that  $X(t) \equiv 0$  for all  $t \ge t^*$ , in contradiction to (3). Hence,  $t^* = 0$ , as claimed.

Finally, to show (2), we estimate

$$e^{-\int_0^t (D+k_u(r_x)X(s))ds} \le e^{-(D+k_u(r_x)\chi)t}$$
 and  $e^{-\int_s^t (D+k_u(r_x)X(s))d\sigma} \le e^{-(D+k_u(r_x)\chi)(t-s)}$ 

to find

$$|u(t)| \le u_0 e^{-(D+k_u(r_x)\chi)t} + p \int_0^t e^{-(D+k_u(r_x)\chi)(t-s)} ds$$
  
=  $u_0 e^{-(D+k_u(r_x)\chi)t} + \frac{p}{D+k_u(r_x)\chi} [1 - e^{-(D+k_u(r_x)\chi)t}] \le \max\left\{u_0, \frac{p}{D+k_u(r_x)\chi}\right\},$ 

as, trivially,  $0 \leq e^{-(D+k_u(r_x)\chi)t} \leq 1$  for all  $t \geq 0$ , and as the function  $u_0 e^{-(D+k_u(r_x)\chi)t} + p/(D+k_u(r_x)\chi)[1-e^{-(D+k_u(r_x)\chi)t}]$  must assume its supremum at either t=0 or for  $t \to \infty$ .

It particular, it follows from Lemma 1 that we must have  $x_i(t) \in \mathbb{R}_+$  for i = 1, ..., n and any t > 0.

**Remark 2.** For simplicity, we may without loss of generality take  $\chi = 0$  in Equation (2) above.



FIGURE 1. Dynamics of Equation (1) for n = 4, with p = 0.2, D = 0.02,  $r_x = 0.6$ , and  $k_u(r_x) = 2$  and initial condition  $(x_1, x_2, x_3, x_4, u)(0) = (0.1, 0, 0, 0, 0.5)$ .

2.2. Resident manifolds. Numerical simulation of Equation (1) in various parameter regimes [7] suggests that the corresponding flow converges to an invariant manifold, the "resident manifold", in time, with  $\frac{x_i}{x_1}$  tending to some constant for i = 2, ..., n; see Figure 1 for an example with n = 4, which clearly indicates that  $\frac{x_i(t)}{x_1(t)}$  (i = 2, 3, 4) approaches a limit after an initial transient. (As t increases,  $x_i(t)$  tends to its corresponding steady-state value  $x_i^*$ .) That intuition is confirmed by the following result:

**Proposition 1.** The manifold  $\mathcal{M}_x$  defined by

(4) 
$$x_i = 2^{\frac{1-i}{n}} x_1$$
 for  $i = 2, ..., n$ ,

with u varying in some compact subinterval of  $(0, \infty)$ , is invariant for the vector field in Equation (1); in other words, if  $x_i(t_0) = 2^{(1-i)/n}x_1(t_0)$  for i = 2, ..., n and some  $t_0 \ge 0$ , then  $x_i(t) = 2^{(1-i)/n}x_1(t)$  for all  $t \ge t_0$ .

*Proof.* We define new variables  $\phi_i = x_i - \alpha_i x_1$  for i = 2, ..., n, with  $\{\alpha_i\}$  to be determined appropriately, and we consider the time evolution of  $\{\phi_i\}$  under the flow of Equations (1a) and (1b): for i = 3, ..., n, we find

$$\dot{\phi}_{i} = \dot{x}_{i} - \alpha_{i}\dot{x}_{1} = uk_{u}(r_{x})(-x_{i} + x_{i-1}) - x_{i}D - \alpha_{i}\left[uk_{u}(r_{x})(-x_{1} + 2x_{n}) - x_{1}D\right]$$

$$= -uk_{u}(r_{x})r_{x}\left[\phi_{i} - x_{i-1} + 2\alpha_{i}x_{n}\right] - \phi_{i}D$$

$$= -uk_{u}(r_{x})r_{x}\left[\phi_{i} - \phi_{i-1} + 2\alpha_{i}\left(x_{n} - \frac{\alpha_{i-1}}{2\alpha_{i}}x_{1}\right)\right] - \phi_{i}D,$$
(5)

while for i = 2, an analogous argument shows

(6) 
$$\dot{\phi}_2 = -uk_u(r_x)r_x \Big[\phi_2 + 2\alpha_2 \Big(x_n - \frac{1}{2\alpha_2}x_1\Big)\Big] - \phi_2 D.$$

To determine the coefficients  $\{\alpha_i\}$  (i = 2, ..., n), we need to express the right-hand sides in Equations (5) and (6) in terms of the new variables  $\{\phi_i\}$ . Thus, for the final term in square brackets in

the last line of (5) to equal  $2\alpha_i\phi_n$ , we require  $\frac{\alpha_{i-1}}{2\alpha_i} = \alpha_n$  for  $i = 3, \ldots, n$ ; similarly, the final term in square brackets in (6) implies  $\frac{1}{2\alpha_2} = \alpha_n$ . It hence follows that

$$\frac{\alpha_2}{2\alpha_3} \cdot \frac{\alpha_3}{2\alpha_4} \cdot \dots \cdot \frac{\alpha_{n-1}}{2\alpha_n} = \alpha_n^{n-2} \quad \text{or} \quad \frac{\alpha_2}{2^{n-2}} = \alpha_n^{n-1}$$

which, in combination with  $\alpha_n = \frac{1}{2\alpha_2}$ , yields  $\alpha_2^n = \frac{1}{2}$  or  $\alpha_2 = 2^{-1/n}$  and  $\alpha_n = 2^{1/n-1}$ . Proceeding recursively, we find  $\alpha_i = 2^{(1-i)/n}$  for i = 3, ..., n-1, as claimed.

It then follows that the variables  $\{\phi_i\}$  satisfy the following system of equations,

(7a) 
$$\dot{\phi}_2 = -uk_u(r_x)r_x[\phi_2 + 2^{1-1/n}\phi_n] - \phi_2 D_2$$

(7b) 
$$\dot{\phi}_i = -uk_u(r_x)r_x[\phi_i - \phi_{i-1} + 2^{1+(1-i)/n}\phi_n] - \phi_i D \text{ for } i = 3, \dots, n,$$

which admits a steady state at  $(\phi_2, \ldots, \phi_n) = (0, \ldots, 0)$  irrespective of the value of u. Hence, the statement is obtained from the definition of  $\{\phi_i\}$ : if  $\phi_i(t_0) = 0$  for some  $t_0 \ge 0$  and  $i = 2, \ldots, n$ , then  $\phi_i(t) \equiv 0$  for all  $t \ge t_0$ , which implies  $x_i(t) \equiv 2^{(1-i)/n} x_1(t)$  and, thus, the invariance of  $\mathcal{M}_x$ .  $\Box$ 

Clearly, the definition of the variables  $\{\phi_i\}$  (i = 2, ..., n) in the proof of Proposition 1 is somewhat arbitrary; in other words, one could equivalently parametrise the manifold  $\mathcal{M}_x$  in terms of  $x_i$  for some i = 2, ..., n.

**Remark 3.** The proof of Lemma 1 shows that u must remain bounded – and, in fact, converge to some steady-state value  $u_x^*$  – in the large-time limit, *i.e.*, as  $t \to \infty$  in (1). Hence, it suffices to assume that u is restricted to some suitably defined compact interval about  $u_x^*$  in the definition of  $\mathcal{M}_x$  above.

**Remark 4.** The result of Proposition 1 is in agreement with the steady-state distribution for  $\{x_i\}$  derived in [7, Section 2.3]; see, in particular, Equations (2.49) and (2.58) therein. Furthermore, it allows for the reduction of Equation (1) to a minimal model for the "basal" class 1, which is also known as the "unstructured model" [7, Section 2.2], on the manifold  $\mathcal{M}_x$ .

A direct consequence of Proposition 1 is the following; see also [7, Equation (2.62)]:

**Lemma 2.** The per capita growth rates in Equation (1) are equal, and are given by

(8) 
$$\frac{x_i}{x_i}\Big|_{\mathcal{M}_x} = uk_u(r_x)r_x(2^{1/n}-1) - D \quad \text{for any } i = 1, \dots, n,$$

when evaluated on the manifold  $\mathcal{M}_x$ .

*Proof.* Since  $x_n = 2^{1/n-1}x_1$  on  $\mathcal{M}_x$ , Equation (8) follows from (1a) when i = 1; for  $i = 2, \ldots, n$ , we consider (1b) in combination with the fact that

$$\frac{x_{i-1}}{x_i} = \frac{2^{\frac{1-(i-1)}{n}}x_1}{2^{\frac{1-i}{n}}x_1} = 2^{\frac{1}{n}}$$

on  $\mathcal{M}_x$ .

Next, we show that the resident manifold  $\mathcal{M}_x$  obtained in Proposition 1 is globally attracting:

**Proposition 2.** Let  $r_x \in (0,1)$ , and let D > 0. Then, the manifold  $\mathcal{M}_x$  defined in Proposition 1 is globally attracting under the flow of Equation (1), i.e., given any initial condition  $(x_{10}, \ldots, x_{n0}, u_0) \in \mathbb{R}^n_+ \times \mathbb{R}_+$  at  $t_0 \geq 0$ , the unique orbit of (1) passing through  $(x_{10}, \ldots, x_{n0}, u_0)$  converges to  $\mathcal{M}_x$  as  $t \to \infty$ .

Sketch of proof. Without loss of generality, we assume that  $n \ge 4$  here; the simpler cases where n = 2 or n = 3 are discussed separately in Section 4 below.

Let the variables  $\phi_i = x_i - \alpha_i x_1$  (i = 2, ..., n) be defined as in Proposition 1, where  $\alpha_i = 2^{(1-i)/n}$ , let  $\Phi := (\phi_2, ..., \phi_n)$ , and let  $\|\cdot\|$  denote the standard Euclidean norm, with

$$\|\Phi(t)\| := \sqrt{\phi_2^2(t) + \dots + \phi_n^2(t)}.$$

We begin by rewriting Equation (7) in matrix form, with

$$\dot{\Phi} = \begin{bmatrix} -uk_u(r_x)r_x - D & 0 & 0 & \cdots & -2^{1-1/n}uk_u(r_x)r_x \\ uk_u(r_x)r_x & -uk_u(r_x)r_x - D & 0 & \cdots & -2^{1-2/n}uk_u(r_x)r_x \\ 0 & uk_u(r_x)r_x & -ku(r_x)r_x - D & \cdots & -2^{1-3/n}uk_u(r_x)r_x \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & -uk_u(r_x)r_x(1+2^{1/n}) - D \end{bmatrix} \Phi,$$

and we note that  $\frac{d}{dt} \|\Phi\|^2 = 2(\phi_2 \dot{\phi}_2 + \dots + \phi_n \dot{\phi}_n) = 2\Phi^T \dot{\Phi}$ . Then, (9) implies

(10)

$$\begin{split} \frac{1}{2} \frac{d}{dt} \|\Phi\|^2 &= (\phi_2, \phi_3, \phi_4, \dots, \phi_n) \begin{pmatrix} -(uk_u(r_x)r_x + D)\phi_2 - 2^{1-1/n}uk_u(r_x)r_x\phi_n \\ uk_u(r_x)r_x\phi_2 - (uk_u(r_x)r_x + D)\phi_3 - 2^{1-2/n}uk_u(r_x)r_x\phi_n \\ uk_u(r_x)r_x\phi_3 - (uk_u(r_x)r_x + D)\phi_4 - 2^{1-3/n}uk_u(r_x)r_x\phi_n \\ \vdots \\ uk_u(r_x)r_x\phi_{n-1} - \left[ uk_u(r_x)r_x\left(1 + 2^{1/n}\right) + D \right] \phi_n \end{pmatrix} \\ &= -\left[ uk_u(r_x)r_x\left(1 + 2^{1/n}\right) + D \right] \|\Phi\|^2 + uk_u(r_x)r_x\sum_{i=2}^{n-1} \phi_i\phi_{i+1} \\ &+ 2^{1/n}uk_u(r_x)r_x\sum_{i=2}^{n-1} \phi_i^2 - 2uk_u(r_x)r_x\sum_{i=2}^{n-1} 2^{-(i-1)/n}\phi_i \cdot \phi_n \\ &\leq -\left[ uk_u(r_x)r_x\left(1 + 2^{1/n}\right) + D \right] \|\Phi\|^2 + uk_u(r_x)r_x\left[\frac{1}{2}\sum_{i=2}^{n-2}\left(\frac{\phi_i^2}{\delta_{i,i+1}} + \delta_{i,i+1}\phi_{i+1}^2\right) \\ &+ 2^{1/n}\sum_{i=2}^{n-1} \phi_i^2 + \sum_{i=2}^{n-2} 2^{-(i-1)/n}\left(\frac{\phi_i^2}{\delta_{in}} + \delta_{in}\phi_n^2\right) + \frac{2^{2/n} - 1}{2}\left(\frac{\phi_{n-1}^2}{\delta_{n-1,n}} + \delta_{n-1,n}\phi_n^2\right) \right]. \end{split}$$

Here,  $\{\delta_{ij}\}$ , with i = 2, ..., n-2 and j = 3, ..., n, are positive constants that remain to be chosen, and we have made use of the simple estimate

$$|uv| = \left|\frac{u}{\sqrt{\delta}}(\sqrt{\delta}v)\right| \le \frac{1}{2}\left(\frac{u^2}{\delta} + \delta v^2\right),$$

which follows from  $0 \le \left(\frac{u}{\sqrt{\delta}} \pm \sqrt{\delta}v\right)^2 = \frac{u^2}{\delta} \pm 2\frac{u}{\sqrt{\delta}}(\sqrt{\delta}v) + \delta v^2.$ 

In order to combine the terms in square brackets in (10) into one  $\|\Phi\|^2$ -dependent term, we need to fix the constants  $\{\delta_{ij}\}$  so that the coefficients of  $\{\phi_i^2\}$ , which are given by

$$\frac{1}{2\delta_{23}} + 2^{1/n} + 2^{-1/n} \frac{1}{\delta_{2n}} \quad \text{for } i = 2;$$

$$\frac{1}{2} \left( \delta_{i-1,i} + \frac{1}{\delta_{i,i+1}} \right) + 2^{1/n} + 2^{-(i-1)/n} \frac{1}{\delta_{in}} \quad \text{for } i = 3, \dots, n-2;$$

$$\frac{1}{2} \delta_{n-2,n-1} + 2^{1/n} + \frac{2^{2/n} - 1}{2} \frac{1}{\delta_{n-1,n}} \quad \text{for } i = n-1; \text{ and}$$

$$\sum_{i=2}^{n-2} 2^{-(i-1)/n} \delta_{in} + \frac{2^{2/n} - 1}{2} \delta_{n-1,n} \quad \text{for } i = n,$$

are equal for all i = 2, ..., n; we will denote the resulting value of these coefficients by  $\nu$ . In sum, we therefore have

(11) 
$$\frac{1}{2}\frac{d}{dt}\|\Phi(t)\|^2 \le -\left[u(t)k_u(r_x)r_x\left(1+2^{1/n}-\nu\right)+D\right]\|\Phi(t)\|^2.$$

Since  $0 < u(t) < \infty$  for all t > 0, by Lemma 1, and since it can be shown that  $1 + 2^{1/n} - \nu > 0$  for any  $n \ge 2$ , it follows from Equation (11) that  $\|\Phi(t)\|^2$  converges to zero exponentially as  $t \to \infty$ with exponential decay rate of at least -D for any initial value  $\|\Phi(t_0)\|^2$ , which implies that  $\mathcal{M}_x$ is globally attracting, as claimed.

While it is possible to derive explicit expressions for the constants  $\{\delta_{ij}\}$  in the proof of Proposition 2, those will become increasingly unwieldy with increasing n; hence, we do not quote them here.

**Remark 5.** An alternative proof of Proposition 2 can be given by considering the general stability theory of non-autonomous linear systems; see, for instance, [1].

2.3. Steady states. The above discussion immediately implies that the steady states of Equation (1) must be located on  $\mathcal{M}_x$ :

**Proposition 3.** Equation (1) admits the two steady states

(12a) 
$$O_x: (x_1^*, x_2^*, \dots, x_n^*, u_x^*) = (0, 0, \dots, 0, \frac{p}{D})$$
 and

(12b) 
$$P_x: (x_1^*, x_2^*, \dots, x_n^*, u_x^*) = \left(\xi^*, 2^{-1/n}\xi^*, \dots, 2^{1/n-1}\xi^*, \frac{D}{k_u(r_x)r_x(2^{1/n}-1)}\right),$$

where

$$\xi^* = 2\left(1 - 2^{-1/n}\right) \frac{pk_u(r_x)r_x(2^{1/n} - 1) - D^2}{Dk_u(r_x)};$$

for  $k_u(r_x)r_x(2^{1/n}-1) < D^2/p$  ( $k_u(r_x)r_x(2^{1/n}-1) > D^2/p$ ), the steady state at  $O_x$  is asymptotically stable (unstable), whereas the state at  $P_x$  is unstable (asymptotically stable). In particular,  $P_x$  is an attractor whenever it is physiologically relevant, i.e., when  $x_i^* > 0$  for all i = 1, ..., n.

*Proof.* Steady states for Equation (1) are obtained by setting  $\dot{x}_i = 0 = \dot{u}$  (i = 1, ..., n) therein. It is then evident that  $O_x$  is a steady state, as claimed.

To show that the only further steady state is found at  $P_x$ , we note that any steady state must be located on  $\mathcal{M}_x$ , which implies  $x_i^* = 2^{(1-i)/n} x_1^*$  for the corresponding steady-state values of  $\{x_i\}$ , by (4). Substituting into (1c), we find

(13) 
$$0 = p - u_x^* D - u_x^* k_u(r_x) \sum_{i=1}^n 2^{\frac{1-i}{n}} x_1^* = p - u_x^* D - u_x^* k_u(r_x) \frac{1}{2} \frac{1}{1 - 2^{-1/n}} x_1^*,$$

see also [7, Equation (2.61)]. To solve for  $x_1^*$ , we need to determine  $u_x^*$ . To that end, we note that Equation (1a) gives  $0 = x_1^* \left[ u_x^* k_u(r_x) r_x(-1+2^{1/n}) - D \right]$  and, hence,

$$u_x^* = \frac{D}{k_u(r_x)r_x(2^{1/n} - 1)}$$

at the non-trivial steady state, as  $x_1^* > 0$  by assumption. Substituting for  $u_x^*$  in (13), we find

(14) 
$$x_1^* = 2\left(1 - 2^{-1/n}\right) \frac{pk_u(r_x)r_x(2^{1/n} - 1) - D^2}{Dk_u(r_x)} =: \xi^*,$$

which implies  $x_i^* = 2^{(1-i)/n} \xi^*$  (i = 1, ..., n), as claimed.

The stability properties of  $O_x$  and  $P_x$  can be decided by linearisation of (1) about those states; as was shown in [7, Section 2.3], the relevant Jacobian reads [7, Equation (2.54)]

$$J_x = \begin{bmatrix} -\frac{D}{2^{1/n}-1} - D & 0 & 2\frac{D}{2^{1/n}-1} & \cdots & D\frac{x_1^*}{u_x^*} \\ \frac{D}{2^{1/n}-1} & -\frac{D}{2^{1/n}-1} - D & 0 & \cdots & \frac{D}{2^{1/3}}\frac{x_1^*}{u_x^*} \\ 0 & \frac{D}{2^{1/n}-1} & -\frac{D}{2^{1/n}-1} - D & \cdots & \frac{D}{2^{2/3}}\frac{x_1^*}{u_x^*} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ -k_u(r_x)u_x^* & -k_u(r_x)u_x^* & -k_u(r_x)u_x^* & \cdots & -\frac{D}{u_x^*} \end{bmatrix}.$$

Since the maximum of the real parts of the eigenvalues of  $J_x$ , evaluated at  $P_x$ , is given by [7, Equation (2.55)]

$$D - \frac{pk_u(r_x)r_x(2^{1/n} - 1)}{D},$$

it follows that  $P_x$  must be asymptotically stable for  $k_u(r_x)r_x(2^{1/n}-1) > D^2/p$  and unstable for  $k_u(r_x)r_x(2^{1/n}-1) < D^2/p$ , as claimed. Hence, we conclude immediately that the stability of  $O_x$  is determined by reversing these inequalities. Finally, we see directly from (14) that  $x_1^*$  – and, hence, any  $x_i^*$  with  $i = 2, \ldots, n$  – will be positive if and only if  $P_x$  is an attractor, which completes the proof.

Propositions 1 through 3 combined show that any solution to (1) with  $(x_1, \ldots, x_n, u)(0) = (x_{10}, \ldots, x_{n0}, u_0) \in \mathbb{R}^n_+ \times \mathbb{R}_+$  must remain bounded for all time; see also Lemma 1: all such solutions are attracted to the invariant manifold  $\mathcal{M}_x$  in time, and subsequently tend either to the "extinction" state  $O_x$  or to the "survival" state  $P_x$ . Correspondingly, the stability condition in Proposition 3 is also known as the survival condition [7, Section 2.3]. In particular, Equation (1) undergoes a (transcritical) bifurcation when  $k_u(r_x)r_x(2^{1/n}-1) = D^2/p$ , with the steady states at  $O_x$  and  $P_x$  colliding and exchanging stability.

**Remark 6.** It seems natural to suspect that Equation (1) admits higher-dimensional invariant manifolds, in addition to the ones constructed in Proposition 1; however, for n = 3, an ansatz of the form  $\phi = x_3 - \beta_1 x_1 - \beta_2 x_2$  in combination with an analogous procedure as in the proof above only yields a non-physiological invariant hyperplane in that case, as  $\beta_1$  and  $\beta_2$  are both negative.

#### 3. Resident-mutant model

In this section, we consider the invasion of an established resident population by a mutant, the classes of which we denote by  $\{y_i\}$  (i = 1, ..., n):

(15a) 
$$\dot{x}_1 = uk_u(r_x)r_x(-x_1 + 2x_n) - x_1D,$$

(15b) 
$$\dot{x}_i = uk_u(r_x)r_x(-x_i + x_{i-1}) - x_iD$$
 for  $2 \le i \le n$ 

(15c) 
$$\dot{y}_1 = uk_u(r_y)r_y(-y_1+2y_n) - y_1D$$

(15d) 
$$\dot{y}_i = uk_u(r_y)r_y(-y_i + y_{i-1}) - y_iD$$
 for  $2 \le i \le n$ 

(15e) 
$$\dot{u} = p - uD - uk_u(r_x) \sum_{i=1}^n x_i - uk_u(r_y) \sum_{i=1}^n y_i;$$

here,  $r_y \in (0, 1)$  denotes the resource allocation parameter for mutant, where the function  $k_u(r_y)$  is defined as before. In accordance with [7, Section 2.2], we assume that  $r_y \neq r_x$ ; furthermore, without loss of generality, we make the generic assumption that  $k_u(r_y)r_y \neq k_u(r_x)r_x$ .

**Remark 7.** As resident and mutant in Equation (15) are coupled only through the dynamics of nutrient u, see (15e), the same argument as in the proofs of Propositions 1 and 2, with  $\{x_i\}$  and  $r_x$  replaced by  $\{y_i\}$  and  $r_y$ , respectively, will show the existence of an invariant ("mutant") manifold  $\mathcal{M}_y$  for the subsystem in  $\{(15c), (15d)\}$ .

3.1. Scale separation. We now interpret Equation (15) as a multiple-scale ("fast-slow") system of differential equations, which is motivated by the observation that we may expect resident to have reached steady state before being invaded; see [6, Sections 2.2 and 2.3] and the references therein. Specifically, we assume that  $\{x_i\}$  (i = 1, ..., n) vary on a "fast" timescale, whereas  $\{y_i\}$  evolve on a "slow" scale, with a (small) parameter  $\varepsilon$  denoting the ratio of the two scales. Correspondingly, we also assume that nutrient u reaches steady state on the same scale as  $\{x_i\}$ , which is supported by numerical simulation; recall Figure 1. Moreover, and without loss of generality, we rescale  $\{y_i\}$  with the same parameter  $\varepsilon$ , writing  $y_i = \varepsilon \tilde{y}_i$ , to reflect the initial scarcity of mutant in the environment; in analogy to the initial conditions imposed on the resident model, Equation (1), we will then have  $(\tilde{y}_1, \tilde{y}_2, \ldots, \tilde{y}_n)(0) = (\tilde{y}_{10}, 0, \ldots, 0)$ , where  $\tilde{y}_{10}$  is  $\mathcal{O}(1)$  and positive.

In sum, we obtain the following augmented resident-mutant model in which the scale separation is made explicit:

(16a) 
$$\varepsilon \dot{x}_1 = uk_u(r_x)r_x(-x_1+2x_n) - x_1D,$$

(16b) 
$$\varepsilon \dot{x}_i = u k_u(r_x) r_x(-x_i + x_{i-1}) - x_i D \quad \text{for } 2 \le i \le n,$$

(16c) 
$$\tilde{y}_1 = uk_u(r_y)r_y(-\tilde{y}_1 + 2\tilde{y}_n) - \tilde{y}_1D$$

(16d) 
$$\dot{\tilde{y}}_i = uk_u(r_y)r_y(-\tilde{y}_i + \tilde{y}_{i-1}) - \tilde{y}_i D \quad \text{for } 2 \le i \le n,$$

(16e) 
$$\varepsilon \dot{u} = p - uD - uk_u(r_x) \sum_{i=1}^n x_i - \varepsilon uk_u(r_y) \sum_{i=1}^n \tilde{y}_i.$$

Equation (16) is in the standard form of geometric singular perturbation theory (GSPT) [3, 6], written on the "slow" timescale t, with  $\{x_i\}$  and u the fast variables and  $\{\tilde{y}_i\}$  the slow ones.

Rescaling the time variable via  $s = t/\varepsilon$ , we obtain the corresponding "fast" system

(17a) 
$$x'_1 = uk_u(r_x)r_x(-x_1 + 2x_n) - x_1D$$

(17b) 
$$x'_{i} = uk_{u}(r_{x})r_{x}(-x_{i} + x_{i-1}) - x_{i}D \quad \text{for } 2 \le i \le n_{x}$$

(17c) 
$$\tilde{y}_1' = \varepsilon \left[ uk_u(r_y)r_y(-\tilde{y}_1 + 2\tilde{y}_n) - \tilde{y}_1 D \right]$$

(17d) 
$$\tilde{y}'_i = \varepsilon \left[ uk_u(r_y)r_y(-\tilde{y}_i + \tilde{y}_{i-1}) - \tilde{y}_i D \right] \quad \text{for } 2 \le i \le n,$$

(17e) 
$$u' = p - uD - uk_u(r_x) \sum_{i=1}^n x_i - \varepsilon uk_u(r_x) \sum_{i=1}^n \tilde{y}_i,$$

where the prime now denotes differentiation with respect to s.

The limit of  $\varepsilon \to 0$  in Equations (16) and (17) yields two very different singular systems: the "layer problem" obtained from (17) again gives Equation (1) for the resident states  $\{x_i\}$  (i = 1, ..., n)and nutrient u, which correspondingly evolve as discussed in Section 2. By contrast, it follows from  $\tilde{y}'_i = 0$  that mutant languishes at its (low) initial population. The "reduced problem" that is found for  $\varepsilon = 0$  in (16), on the other hand, implies that  $\{\tilde{y}_i\}$  evolve according to Equations (16c) and (16d), under the additional algebraic constraints

(18)  
$$0 = uk_u(r_x)r_x(-x_1 + 2x_n) - x_1D, \\ 0 = uk_u(r_x)r_x(-x_i + x_{i-1}) - x_iD \quad \text{for } 2 \le i \le n, \\ 0 = p - uD - uk_u(r_x)\sum_{i=1}^n x_i;$$

in other words,  $\{x_i\}$  and u have attained their steady-state values  $\{x_i^*\}$  and  $u_x^*$ , respectively, as defined in Proposition 3. Correspondingly, the reduced flow in  $\{\tilde{y}_i\}$  evolves on a "critical manifold"  $S_x$  that is defined by  $(x_1, \ldots, x_n, u) = (x_1^*, \ldots, x_n^*, u_x^*)$  constant, with  $\{\tilde{y}_i\}$  varying in some compact subspace of  $\mathbb{R}^n_+$ ; in fact, given Proposition 3,  $S_x$  will consist of two branches  $\mathcal{O}_x$  and  $\mathcal{P}_x$  that correspond to the steady states at  $O_x$  and  $P_x$  of Equation (1), respectively. Given that  $u = u_x^*$ is constant to leading order in  $\varepsilon$ , we obtain the following linear, constant-coefficient system of equations for the evolution of  $\{\tilde{y}_i\}$  under the reduced flow on  $S_x$ :

(19)  
$$\begin{aligned} \dot{\tilde{y}}_1 &= u_x^* k_u(r_y) r_y(-\tilde{y}_1 + 2\tilde{y}_n) - \tilde{y}_1 D, \\ \dot{\tilde{y}}_i &= u_x^* k_u(r_y) r_y(-\tilde{y}_i + \tilde{y}_{i-1}) - \tilde{y}_i D \quad \text{for } 2 \le i \le n. \end{aligned}$$

By Fenichel's Theorem [3, 6], the restriction of the critical manifold  $S_x$  to compact subspaces of  $\mathbb{R}^n_+$  will persist as a slow manifold for  $\varepsilon$  positive, but sufficiently small, provided it is normally hyperbolic; here, normal hyperbolicity follows immediately from Proposition 3, given that the steady states of Equation (1) are determined precisely from Equation (18). Hence, the two branches  $\mathcal{O}_x$  and  $\mathcal{P}_x$  of  $\mathcal{S}_x$  inherit their stability properties from the steady states at  $O_x$  and  $\mathcal{P}_x$ , respectively:

**Corollary 1.** The critical manifold  $S_x = \mathcal{O}_x \cup \mathcal{P}_x$  for Equation (16) is normally hyperbolic provided  $k_u(r_x)r_x(2^{1/n}-1) \neq D^2/p$ ; specifically, for  $k_u(r_x)r_x(2^{1/n}-1) < D^2/p$  ( $k_u(r_x)r_x(2^{1/n}-1) > D^2/p$ ), the branch  $\mathcal{O}_x$  is normally attracting (repelling), whereas the branch  $\mathcal{P}_x$  is normally repelling (attracting).

3.2. Invasion manifolds. In analogy to the proof of Proposition 1 – with u replaced by  $u_x^*$  – one can show that Equation (19) admits a globally attracting invariant manifold  $\mathcal{M}_{\tilde{y}}^*$  – the so-called "invasion manifold" for the mutant population – to which the reduced flow on  $S_x$  will converge in a first approximation. Since we consider the dynamics of invasion of a mutant into an established resident population, we will restrict to the branch  $\mathcal{P}_x$  of  $S_x$ , as that branch corresponds to the survival state  $P_x$  of resident; correspondingly, we assume  $k_u(r_x)r_x(2^{1/n}-1) > D^2/p$  here:

**Corollary 2.** The manifold  $\mathcal{M}^*_{\tilde{y}} \subset \mathcal{P}_x$  defined by

(20) 
$$\tilde{y}_i = 2^{\frac{1-i}{n}} \tilde{y}_1 \quad for \ i = 2, \dots, n,$$

with  $u = u_x^* (= D/[k_u(r_x)r_x(2^{1/n}-1)])$ , is invariant for the vector field in Equation (19). Moreover,  $\mathcal{M}_{\tilde{u}}^*$  is globally attracting under the flow of (19) for any  $r_x, r_y \in (0,1)$  and D > 0.

*Proof.* The first statement can be shown exactly as in the proof of Proposition 1, with u(t) replaced by  $u_x^*$  throughout.

The second statement follows verbatim as in the proof of Proposition 2.

In analogy to Lemma 2, we have the following result on the per capita growth rates of  $\{\tilde{y}_i\}$  on  $\mathcal{M}^*_{\tilde{y}}$ :

**Lemma 3.** The per capita growth rates in Equation (19) are equal, and are given by

$$\frac{\tilde{y}_i}{\tilde{y}_i}\Big|_{\mathcal{M}^*_{\tilde{y}}} = u_x^* k_u(r_y) r_y(2^{1/n} - 1) - D \quad for \ any \ i = 1, \dots, n$$

when evaluated on the manifold  $\mathcal{M}_{\tilde{y}}^* \subset \mathcal{P}_x$ ; here,  $u_x^* = D/[k_u(r_x)r_x(2^{1/n}-1)]$ .

**Remark** 8. An analogous result holds for the growth rates of unscaled mutant, as

$$\frac{\dot{y}_i}{y_i} = \frac{\varepsilon \dot{\tilde{y}}_i}{\varepsilon \tilde{y}_i} = \frac{\dot{\tilde{y}}_i}{\tilde{y}_i} \quad \text{for } i = 2, \dots, n,$$

at least as long as our assumption of  $y_i = \mathcal{O}(\varepsilon)$  is valid.

We emphasise again that persistence of the manifold  $\mathcal{M}_{\tilde{y}}^*$  for  $\varepsilon$  positive can only be guaranteed on suitably defined, compact subsets of  $\mathbb{R}^n_+$ , in accordance with [3, 6].

3.3. Steady states. Since the unique steady state of the reduced problem on  $\mathcal{P}_x$ , Equation (19), is located at the origin  $O_{\tilde{y}}$ :  $(\tilde{y}_1, \ldots, \tilde{y}_n) = (0, \ldots, 0)$ , as  $k_u(r_y)r_y \neq k_u(r_x)r_x$  by assumption, the question of whether mutant will invade or, rather, go extinct, reduces to the question of whether  $O_{\tilde{y}}$ is an attractor or a repellor for (19). (While the unscaled resident-mutant model, Equation (15), will admit other steady states, those are not visible after scaling in the singular limit of  $\varepsilon = 0$ .)

**Proposition 4.** The origin  $O_{\tilde{y}}$  is an asymptotically stable steady state for Equation (19) on  $\mathcal{P}_x$  provided  $k_u(r_y)r_y < k_u(r_x)r_x$ , whereas it is unstable when  $k_u(r_y)r_y > k_u(r_x)r_x$ .

*Proof.* Linearisation of Equation (19) about  $O_{\tilde{y}}$  yields the Jacobian [7, Equation (2.65)]

$$(21) \quad J_{\tilde{y}} = \begin{bmatrix} -u_x^* k_u(r_y) r_y - D & 0 & 0 & \cdots & 2u_x^* k_u(r_y) r_y \\ u_x^* k_u(r_y) r_y & -u_x^* k_u(r_y) r_y - D & 0 & \cdots & 0 \\ 0 & u_x^* k_u(r_y) r_y & -u_x^* k_u(r_y) r_y - D & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & -u_x^* k_u(r_y) r_y - D \end{bmatrix},$$

where  $u_x^* = D/[k_u(r_x)r_x(2^{1/n}-1)]$ , as before. Since the maximum of the real parts of the eigenvalues of  $J_{\tilde{y}}$  reads [7, Equation (2.66)]

,

(22) 
$$D\left(\frac{k_u(r_y)r_y}{k_u(r_x)r_x} - 1\right)$$

the statement follows.

Importantly, it follows from Proposition 4 that mutant may invade the resident population when the invasion condition  $k_u(r_y)r_y > k_u(r_x)r_x$  is satisfied. Dynamically, that condition can be interpreted as follows: when  $k_u(r_y)r_y < k_u(r_x)r_x$ , the origin  $O_{\tilde{y}}$  in the reduced problem, Equation (19), on the branch  $\mathcal{P}_x$  of the critical manifold  $\mathcal{S}_x$  is asymptotically stable, which implies that mutant  $\{\tilde{y}_i\}$  will go extinct as time tends to infinity; for  $k_u(r_y)r_y > k_u(r_x)r_x$ , on the other hand,  $O_{\tilde{y}}$  is unstable, *i.e.*,  $\{\tilde{y}_i\}$  will grow "without bound" along  $\mathcal{M}_{\tilde{y}}^*$  until our scaling of  $\{y_i\}$  with  $\varepsilon$  breaks down and the persistence of  $\mathcal{M}_{\tilde{y}}^*$  can no longer be guaranteed. (In fact, after a transitional period where  $\{y_i\}$  and  $\{x_i\}$  are of comparable orders of magnitude, a "role reversal" becomes feasible whereby the resident population is overwhelmed by mutant [2].) In particular, the invasion manifold  $\mathcal{M}_{\tilde{y}}^*$ hence corresponds to the weakest stable eigendirection -i.e., to the "weak stable manifold" - of  $O_{\tilde{y}}$  when  $k_u(r_y)r_y < k_u(r_x)r_x$ . Conversely, if  $k_u(r_y)r_y > k_u(r_x)r_x$ ,  $\mathcal{M}_{\tilde{y}}^*$  corresponds to the unstable eigendirection - or, equivalently, to the unstable manifold - of  $Q_{\tilde{y}}$ ; by Corollary 2, that manifold has to be one-dimensional. Finally, the origin undergoes a bifurcation at  $k_u(r_y)r_y = k_u(r_x)r_x$ .

**Remark 9.** Evidently, the per capita growth rates  $\dot{\tilde{y}}_i/\tilde{y}_i$  in Lemma 3 equal the maximum real part of the eigenvalues of  $J_{\tilde{y}}$  in (22) when evaluated on  $\mathcal{P}_x$ , which is hence consistent with the resulting invasion condition.

Furthermore, that condition is equivalent to the requirement that  $u_x^* > u_y^*$ , where  $u_y^* = D/[k_u(r_y) r_y(2^{1/n}-1)]$  is the steady-state value of u in a mutant-only analogue of Equation (1). Hence, mutant invades successfully if it is superior at depleting nutrient in the environment, in accordance with the "competitive exclusion principle", as observed already in [7, Section 2.2].

## 4. Illustrative Examples

In this section, we illustrate our findings for the two-class case and the three-class case that result for n = 2 and n = 3, respectively, in Equations (1) and (16).

4.1. The case n = 2. We first discuss the simplest possible case of n = 2 where two classes are present in both the resident model and the resident-mutant model.

4.1.1. Resident model. The resident model that is obtained from (1) when n = 2 reads

(23a) 
$$\dot{x}_1 = uk_u(r_x)r_x(-x_1+2x_2)-x_1D,$$

(23b) 
$$\dot{x}_2 = uk_u(r_x)r_x(-x_2+x_1) - x_2D,$$

(23c) 
$$\dot{u} = p - uD - uk_u(r_x)(x_1 + x_2);$$

while the general results in Propositions 1 and 2 apply here, we give an explicit proof of the following combined result to illustrate the simplification ensuing for n = 2:

**Corollary 3.** Let  $r_x \in (0,1)$ . Then, the invariant manifold  $\mathcal{M}_x$  for Equation (23) is defined by (24)  $x_2 = 2^{-1/2} x_1.$ 

Moreover,  $\mathcal{M}_x$  is globally attracting under the flow of (23) for any D > 0.

*Proof.* We define the new variable  $\phi_2 = x_2 - \alpha_2 x_1$  and calculate

(25) 
$$\dot{\phi}_2 = \dot{x}_2 - \alpha_2 \dot{x}_1 = -uk_u(r_x)r_x \Big[\phi_2 + 2\alpha_2 \Big(x_2 - \frac{1}{2\alpha_2}x_1\Big)\Big] - \phi_2 D,$$

which implies  $\alpha_2 = (2\alpha_2)^{-1}$  or  $\alpha_2 = 2^{-1/2}$ , as claimed. Hence, (25) reduces to  $\dot{\phi}_2 = -uk_u(r_x)r_x[1 + \sqrt{2}]\phi_2 - \phi_2 D$ , which can be integrated for a given initial value  $\phi_2(t_0)$  to yield

(26) 
$$\phi_2(t) = \phi_2(t_0) \exp\left\{-\int_{t_0}^t \left[u(\tau)k_u(r_x)r_x(1+\sqrt{2})+D\right]d\tau\right\}.$$

In particular, it follows from  $\phi_2(t_0) = 0$  that  $\phi_2(t) \equiv 0$  for all  $t \geq t_0$  and, hence, that  $x_2(t) \equiv 2^{-1/2}x_1(t)$  by the definition of  $\phi_2$ , which shows the invariance of  $\mathcal{M}_x$ .

Finally, since  $0 < u(\tau) < \infty$  for all  $\tau > 0$ , by Lemma 1, we have  $0 < D < u(\tau)k_u(r_x)r_x(1+\sqrt{2})+D$ uniformly in  $\tau$  in (26); it follows that

$$0 \le |\phi_2(t)| \le |\phi_2(t_0)| e^{-D(t-t_0)} \to 0 \text{ as } t \to \infty$$

for any D > 0. Hence,  $|\phi(t)| \to 0$  exponentially for  $t \to \infty$  irrespective of the choice of  $\phi_2(t_0)$ , which implies that  $\mathcal{M}_x$  is globally attracting, as claimed.

**Remark 10.** An alternative proof for the existence and stability of the invariant manifold  $\mathcal{M}_x$  when n = 2 is based on a transformation of Equation (23) to the well-known Riccati equation [13, Section 1.2]: to that end, we define the new variable  $\psi_2 = \frac{x_2}{x_1}$ ; then,

(27) 
$$\dot{\psi}_2 = \frac{\dot{x}_2 x_1 - x_2 \dot{x}_1}{x_1^2} = u k_u (r_x) r_x [1 - 2\psi_2^2],$$

where we have made use of (23a) and (23b) and rewritten the resulting equation in terms of  $\psi_2$ . Now, we note that the factor  $uk_u(r_x)r_x$  in (27) is always positive; hence, we may introduce a *t*-dependent rescaling of time, with  $\frac{d}{dt} = u(t)k_u(r_x)r_x\frac{d}{d\tau}$ , where  $\tau$  denotes the new rescaled time. (That rescaling effectively introduces a factor of  $uk_u(r_x)r_x$  on the left-hand side of (27), allowing us to divide it out; moreover, it does not alter the phase portrait of (27), as it only affects the time parametrisation of solutions.) Solving the resulting equation with some initial value  $\psi_2(\tau_0) = \psi_{20}$ , we find

(28) 
$$\psi_2(\tau) = \frac{1}{\sqrt{2}} \frac{(\sqrt{2}\psi_{20} + 1)\mathrm{e}^{2\sqrt{2}(\tau - \tau_0)} + \sqrt{2}\psi_{20} - 1}{(\sqrt{2}\psi_{20} + 1)\mathrm{e}^{2\sqrt{2}(\tau - \tau_0)} - \sqrt{2}\psi_{20} + 1};$$

since (28) implies that  $\psi_2(\tau) \to 2^{-1/2}$ , its steady-state value, as  $\tau \to \infty$ , the above argument constitutes an alternative proof of Corollary 3 when n = 2. (That conclusion could equally be drawn by rewriting (27) as an equivalent linear second-order equation [13, Section 0.1.4].)

In Figure 2, we illustrate the dynamics of (23) numerically in the two scenarios where either the extinction state  $O_x$ :  $(0, 0, \frac{p}{D})$  or the survival state

$$P_x: \left(\sqrt{2}(\sqrt{2}-1)\frac{pk_u(r_x)r_x(\sqrt{2}-1)-D^2}{k_u(r_x)D}, (\sqrt{2}-1)\frac{pk_u(r_x)r_x(\sqrt{2}-1)-D^2}{k_u(r_x)D}, \frac{D}{k_u(r_x)r_x(\sqrt{2}-1)}\right)$$

is an attractor, *i.e.*, for  $k_u(r_x)r_x(\sqrt{2}-1) < D^2/p$  or  $k_u(r_x)r_x(\sqrt{2}-1) > D^2/p$ .

4.1.2. Resident-mutant model. For n = 2, the resident-mutant model in Equation (16) reduces to

(30a) 
$$\varepsilon \dot{x}_1 = u k_u (r_x) r_x (-x_1 + 2x_2) - x_1 D_1$$

(30b) 
$$\varepsilon \dot{x}_2 = uk_u(r_x)r_x(-x_2+x_1) - x_2D,$$

(30c) 
$$\dot{\tilde{y}}_1 = uk_u(r_y)r_y(-\tilde{y}_1 + 2\tilde{y}_2) - \tilde{y}_1D,$$

(30d) 
$$\tilde{y}_2 = uk_u(r_y)r_y(-\tilde{y}_2 + \tilde{y}_1) - \tilde{y}_2D,$$

(30e) 
$$\varepsilon \dot{u} = p - uD - uk_u(r_x)(x_1 + x_2) - \varepsilon uk_u(r_y)(\tilde{y}_1 + \tilde{y}_2),$$

where  $r_x, r_y \in (0, 1)$ . The relevant branch  $\mathcal{P}_x$  of the critical manifold  $\mathcal{S}_x$  is defined by  $x_1, x_2$ , and u taking their steady-state values  $x_1^*, x_2^*$ , and  $u_x^*$ , respectively, at  $P_x$ , as defined in (29), with  $\{\tilde{y}_1, \tilde{y}_2\}$ 



FIGURE 2. Dynamics of Equation (23) for  $r_x = 0.6$  and  $k_u(r_x) = 2$ : resident manifold  $\mathcal{M}_x$  (blue), representative orbit (red) with initial condition  $(x_1, x_2, u)(0) =$ (0.4, 0, 1), extinction state  $O_x$  (solid square), and survival state  $P_x$  (solid circle). We note that  $P_x$  is not shown in panel (a), as it is physiologically irrelevant there.

varying in a suitably defined compact subspace of  $\mathbb{R}^2_+$ . The reduced flow on  $\mathcal{P}_x$ , which is obtained for  $\varepsilon = 0$  in (30), reads

(31)  
$$\dot{\tilde{y}}_1 = u_x^* k_u(r_y) r_y(-\tilde{y}_1 + 2\tilde{y}_2) - \tilde{y}_1 D, \\ \dot{\tilde{y}}_2 = u_x^* k_u(r_y) r_y(-\tilde{y}_2 + \tilde{y}_1) - \tilde{y}_2 D.$$

In sum, it follows as in the proof of Corollary 3 that Equation (30) admits a globally attracting invariant manifold  $\mathcal{M}_{\tilde{y}}^*$ , the "invasion manifold". Furthermore, the stability of the steady state at the origin  $O_{\tilde{y}}$  on  $\mathcal{M}_{\tilde{y}}^*$  again depends on the relative magnitudes of  $k_u(r_y)r_y$  and  $k_u(r_x)r_x$ ; recall Proposition 4:

**Corollary 4.** The manifold  $\mathcal{M}^*_{\tilde{y}} \subset \mathcal{S}_x$  defined by

$$\tilde{y}_2 = 2^{-1/2} \tilde{y}_1,$$

with  $u = u_x^* \left( = D/\left[k_u(r_x)r_x(\sqrt{2}-1)\right] \right)$ , is invariant for the vector field in Equation (31). Moreover,  $\mathcal{M}^*_{\tilde{u}}$  is globally attracting under the flow of (31) for any  $r_x, r_y \in (0,1)$  and D > 0.

Finally, the origin  $O_{\tilde{y}}$  is an asymptotically stable (unstable) steady state for Equation (31) when  $k_u(r_y)r_y < k_u(r_x)r_x$  ( $k_u(r_y)r_y > k_u(r_x)r_x$ ).

*Proof.* The first two statements follow verbatim as in the proof of Corollary 3.

The third statement is obtained as in the proof of Proposition 4: evaluating the Jacobian  $J_{\tilde{y}}$  for n = 2, we find

$$\left[\begin{array}{ccc} -u_x^*k_u(r_y)r_y-D & 2u_x^*k_u(r_y)r_y\\ u_x^*k_u(r_y)r_y & -u_x^*k_u(r_y)r_y-D \end{array}\right],$$

which has trace  $\operatorname{tr}(J_{\tilde{y}}) = -2[u_x^*k_y(r_y)r_y + D]$  and determinant  $\operatorname{det}(J_{\tilde{y}}) = D^2 + 2u_x^*k_u(r_y)r_yD - (u_x^*k_u(r_y)r_y)^2$ . Now, we recall that  $u_x^* = \frac{D}{k_u(r_x)r_x(\sqrt{2}-1)}$ ; then,  $\operatorname{tr}(J_{\tilde{y}}) = -2D\left[\frac{k_y(r_y)r_y}{k_u(r_x)r_x(\sqrt{2}-1)} + 1\right]$  is 14



(a) Extinction:  $r_y = 0.3$  and  $k_u(r_y) = 1$ .

(b) Invasion:  $r_y = 0.7$  and  $k_u(r_y) = 2$ .

FIGURE 3. Dynamics of Equation (30) for p = 0.2, D = 0.02,  $r_x = 0.6$ ,  $k_u(r_x) = 2$ , and  $\varepsilon = 0.05$ : critical manifold  $\mathcal{P}_x$  (blue), invasion manifold  $\mathcal{M}^*_{\tilde{y}}$  (yellow), and representative orbit (red) with initial condition  $(x_1, x_2, \tilde{y}_1, \tilde{y}_2, u)(0) = (0.4, 0, 1, 0, 1)$ .

clearly negative, while

$$\det(J_{\tilde{y}}) = -D^2 \left[ \frac{k_u(r_y)r_y}{k_u(r_x)r_x} - 1 \right] \cdot \left[ \frac{(\sqrt{2}+1)k_u(r_y)r_y}{(\sqrt{2}-1)k_u(r_x)r_x} + 1 \right]$$

is positive (negative) for  $k_u(r_y)r_y < k_u(r_x)r_x$  ( $k_u(r_y)r_y > k_u(r_x)r_x$ ). Hence, the origin  $O_{\tilde{y}}$  is asymptotically stable in the former case, whereas it is unstable in the latter, as claimed.

In accordance with Proposition 4, the invasion manifold  $\mathcal{M}_{\tilde{y}}^*$  for n = 2 corresponds to the weak stable manifold of the origin in (31) when  $k_u(r_y)r_y < k_u(r_x)r_x$ , whereas it equals the unstable manifold thereof for  $k_u(r_y)r_y > k_u(r_x)r_x$ ; one easily verifies that the eigenvector associated with the less negative of the two real eigenvalues of  $J_{\tilde{y}}$  is  $(\sqrt{2}, 1)^T$ . In Figure 3, we illustrate the dynamics of Equation (30) in these two scenarios, which result in extinction of mutant and successful invasion, respectively.

4.2. The case n = 3. Next, we consider both the resident model and the resident-mutant model for the three-class case where n = 3. Not unexpectedly, the analysis of the resulting dynamics is more involved algebraically than in the two-class case discussed in the previous subsection.

4.2.1. Resident model. For n = 3, the system of equations in (1) evaluates to

(32a) 
$$\dot{x}_1 = uk_u(r_x)r_x(-x_1+2x_3) - x_1D_1$$

(32b) 
$$\dot{x}_2 = uk_u(r_x)r_x(-x_2+x_1)-x_2D,$$

(32c) 
$$\dot{x}_3 = uk_u(r_x)r_x(-x_3+x_2) - x_3D,$$

(32d) 
$$\dot{u} = p - uD - uk_u(r_x)(x_1 + x_2 + x_3).$$

Propositions 1 and 2 then imply the following result:

Corollary 5. Let  $r_x \in (0,1)$ . Then, the invariant manifold  $\mathcal{M}_x$  for Equation (32) is defined by (33)  $x_2 = 2^{-1/3}x_1$  and  $x_3 = 2^{-2/3}x_1$ .

Moreover,  $\mathcal{M}_x$  is globally attracting under the flow of (32) for any D > 0.

*Proof.* The first statement is immediate from Proposition 1.

The second statement can be shown by making the procedure in the proof of Proposition 2 explicit for n = 3. To that end, we note that

$$\begin{aligned} \frac{1}{2} \frac{d}{dt} \|\Phi\|^2 &= (\phi_2, \phi_3) \begin{bmatrix} -uk_u(r_x)r_x - D & -2^{2/3}uk_u(r_x)r_x \\ uk_u(r_x)r_x & -uk_u(r_x)r_x(1+2^{1/3}) - D \end{bmatrix} \begin{pmatrix} \phi_2 \\ \phi_3 \end{pmatrix} \\ &= -\left[ uk_u(r_x)r_x(1+2^{1/3}) + D \right] \|\Phi\|^2 + uk_u(r_x)r_x \left[ 2^{1/3}\phi_2^2 + (1-2^{2/3})\phi_2\phi_3 \right] \\ &\leq -\left[ uk_u(r_x)r_x(1+2^{1/3}) + D \right] \|\Phi\|^2 + uk_u(r_x)r_x \left[ \left( 2^{1/3} + \frac{2^{2/3} - 1}{2\delta} \right) \phi_2^2 + \frac{2^{2/3} - 1}{2}\delta \phi_3^2 \right], \end{aligned}$$

where we have again used the estimate  $|uv| \leq \frac{1}{2}(\frac{u^2}{\delta} + \delta v^2)$ , with  $\delta > 0$ . Fixing  $\delta$  in the last line above so that  $2^{1/3} + \frac{2^{2/3}-1}{2\delta} = \frac{2^{2/3}-1}{2}\delta$ , we find the unique (positive) solution

$$\delta = \frac{2^{1/3} + \sqrt{2^{4/3} + 1 - 2^{2/3}}}{2^{2/3} - 1}$$

which implies

$$\frac{2^{2/3}-1}{2}\delta = 2^{1/3} + \frac{\left(2^{2/3}-1\right)^2}{2\left(2^{1/3}+\sqrt{2^{4/3}+1-2^{2/3}}\right)} =:\nu$$

in the notation of Proposition 2; hence,

$$\frac{1}{2}\frac{d}{dt}\|\Phi(t)\|^2 \le -\left[u(t)k_u(r_x)r_x\left(1+2^{1/3}-\nu\right)+D\right]\|\Phi(t)\|^2.$$

Since  $1 + 2^{1/3} - \nu = 1 - (2^{2/3} - 1)^2 / [2(2^{1/3} + \sqrt{2^{4/3} + 1 - 2^{2/3}})] \approx 0.9349 > 0$ , while  $0 < u(t)k_u(r_x)r_x < \infty$  for all t > 0, see Lemma 1, it follows that  $\|\Phi(t)\|^2$  decays to zero exponentially for any initial value  $\|\Phi(t_0)\|^2$  and any D > 0, which implies global asymptotic stability of  $\mathcal{M}_x$ , as claimed.

**Remark 11.** The estimate in Corollary 5 is sharper than the general one resulting from Proposition 2, as the expression for  $\delta_{2n}$  therein combines with that for  $\delta_{n-1,n}$  to yield  $\delta$ ; regardless, both estimates imply exponential decay of  $\|\Phi(t)\|^2$  as  $t \to \infty$ .

The dynamics of Equation (32) is illustrated in Figure 4; again, we consider both the scenario where resident goes extinct  $(k_u(r_x)r_x(2^{1/3}-1) < D^2/p)$  and the one where it survives  $(k_u(r_x)r_x(2^{1/3}-1) > D^2/p)$ .

4.2.2. Resident-mutant model. When n = 3, the resident-mutant model in (16) reads

(34a) 
$$\varepsilon \dot{x}_1 = u k_u(r_x) r_x(-x_1 + 2x_3) - x_1 D,$$

(34b) 
$$\varepsilon \dot{x}_2 = uk_u(r_x)r_x(-x_2+x_1) - x_2D,$$

(34c) 
$$\varepsilon \dot{x}_3 = u k_u (r_x) r_x (-x_3 + x_2) - x_3 D$$

(34d) 
$$\dot{\tilde{y}}_1 = uk_u(r_y)r_y(-\tilde{y}_1 + 2\tilde{y}_3) - \tilde{y}_1D_y$$

(34e) 
$$\tilde{y}_2 = uk_u(r_y)r_y(-\tilde{y}_2 + \tilde{y}_1) - \tilde{y}_2D,$$

(34f) 
$$\dot{\tilde{y}}_3 = uk_u(r_y)r_y(-\tilde{y}_3 + \tilde{y}_2) - \tilde{y}_3D,$$

(34g) 
$$\varepsilon \dot{u} = p - uD - uk_u(r_x)(x_1 + x_2 + x_3) - \varepsilon uk_u(r_y)(\tilde{y}_1 + \tilde{y}_2 + \tilde{y}_3),$$



(a) Extinction: p = 0.1 and D = 0.3.

(b) Survival: p = 0.2 and D = 0.02.

FIGURE 4. Dynamics of Equation (32) for  $r_x = 0.6$  and  $k_u(r_x) = 2$ : resident manifold  $\mathcal{M}_x$  (blue), representative orbit (red) with initial condition  $(x_1, x_2, x_3, u)(0) = (0.4, 0, 0, 0)$ , extinction state  $O_x$  (solid cube), and survival state  $P_x$  (solid sphere). We note that  $P_x$  is not shown in panel (a), as it is physiologically irrelevant there.

with  $r_x, r_y \in (0, 1)$ , as before. In analogy to the case where n = 2, we consider the singular limit as  $\varepsilon \to 0$  in (34), which yields the reduced flow

(35)  
$$\begin{aligned} \dot{\tilde{y}}_1 &= u_x^* k_u(r_y) r_y(-\tilde{y}_1 + 2\tilde{y}_3) - \tilde{y}_1 D, \\ \dot{\tilde{y}}_2 &= u_x^* k_u(r_y) r_y(-\tilde{y}_2 + \tilde{y}_1) - \tilde{y}_2 D, \\ \dot{\tilde{y}}_3 &= u_x^* k_u(r_y) r_y(-\tilde{y}_3 + \tilde{y}_2) - \tilde{y}_3 D \end{aligned}$$

on the branch  $\mathcal{P}_x$  of the critical manifold  $\mathcal{S}_x$  that is obtained by evaluating  $x_1, x_2, x_3$ , and u at the survival steady state  $P_x$  defined in Proposition 3; in particular,  $u_x^* = D/[k_u(r_x)r_x(2^{1/3}-1)]$  in that case.

**Corollary 6.** The manifold  $\mathcal{M}^*_{\tilde{u}}$  defined by

$$\tilde{y}_2 = 2^{-1/3} \tilde{y}_1$$
 and  $\tilde{y}_3 = 2^{-2/3} \tilde{y}_1$ 

with  $u = u_x^* \left( = D/\left[k_u(r_x)r_x(2^{1/3}-1)\right] \right)$ , is invariant for the vector field in Equation (35). Moreover,  $\mathcal{M}_{\tilde{u}}^*$  is globally attracting under the flow of (35) for any  $r_x, r_y \in (0,1)$  and D > 0.

Finally, the origin  $O_{\tilde{y}}$  is an asymptotically stable (unstable) steady state for Equation (35) when  $k_u(r_y)r_y < k_u(r_x)r_x$  ( $k_u(r_y)r_y > k_u(r_x)r_x$ ).

*Proof.* The first statement again follows from Proposition 1, while the second statement is obtained as in the proof of Corollary 5, with u(t) replaced by  $u_x^*$ .

The third statement follows by evaluating the Jacobian  $J_{\tilde{y}}$  of (35) about the origin  $O_{\tilde{y}}$ ,

$$\begin{bmatrix} -u_x^* k_u(r_y) r_y - D & 0 & 2u_x^* k_u(r_y) r_y \\ u_x^* k_u(r_y) r_y & -u_x^* k_u(r_y) r_y - D & 0 \\ 0 & u_x^* k_u(r_y) r_y & -u_x^* k_u(r_y) r_y - D \end{bmatrix}$$

where  $u_x^*$  is defined as above. One easily finds that  $\operatorname{tr}(J_{\tilde{y}}) = -3D\left[\frac{k_u(r_y)r_y}{k_u(r_x)r_x(2^{1/3}-1)} + 1\right]$  is always negative, while

$$\det(J_{\tilde{y}}) = D^3 \left[ \frac{k_u(r_y)r_y}{k_u(r_x)r_x} - 1 \right] \cdot \left[ \frac{k_u^2(r_y)r_y^2}{k_u^2(r_x)r_x^2} \frac{1}{(2^{1/3} - 1)^3} + \frac{k_u(r_y)r_y}{k_u(r_x)r_x} \frac{4 - 3 \cdot 2^{1/3}}{(2^{1/3} - 1)^3} + 1 \right].$$

Since the second factor in square brackets in the above expression is always positive, it follows that  $\det(J_{\tilde{y}})$  is positive (negative) for  $k_u(r_y)r_y > k_u(r_x)r_x$  ( $k_u(r_y)r_y < k_u(r_x)r_x$ ). Now, since  $\operatorname{tr}(J_{\tilde{y}})$  is always negative,  $J_{\tilde{y}}$  has precisely one eigenvalue with positive real part and two eigenvalues with negative real part in the former case, which implies that  $O_{\tilde{y}}$  is unstable then; it remains to show that all three eigenvalues have strictly negative real part in the latter case, which implies stability. To that end, we note that the maximum of the real parts of the eigenvalues of  $J_{\tilde{y}}$  is given by  $D\left(\frac{k_u(r_y)r_y}{k_u(r_x)r_x}-1\right)$ ; recall the proof of Proposition 4. Since that expression becomes negative when  $k_u(r_y)r_y < k_u(r_x)r_x$ , the assertion follows.

As before, the proof of Corollary 6 implies that the invasion manifold  $\mathcal{M}_{\tilde{y}}^*$  for n = 3 coincides with the eigendirection  $(2^{2/3}, 2^{1/3}, 1)^T$  at the origin in (35), which is stable when  $k_u(r_y)r_y < k_u(r_x)r_x$ , whereas it is unstable for  $k_u(r_y)r_y > k_u(r_x)r_x$ ; in fact, one can show explicitly that the corresponding eigenvalue is real, as well as that  $J_{\tilde{y}}$  additionally admits a pair of complex-conjugate eigenvalues with negative real part now.

# 5. DISCUSSION

In this article, we have studied invariant manifolds in a family of class-structured models from adaptive dynamics. Under the simplifying assumption that the mortality rate (D) is independent of class, *i.e.*, of i = 1, ..., n, we have shown that the resident-only model defined in Equation (1) admits a "resident" manifold  $\mathcal{M}_x$  that is globally attracting under the corresponding flow, and on which the system converges to a steady state  $(x_1^*, ..., x_n^*, u_x^*)$  which may be either the extinction state or a survival state at which all classes coexist. In particular, we have shown that the survival state is only physiologically relevant, with the steady-state values  $\{x_i^*\}$  of all classes being positive, when it is an attractor, and we have derived a corresponding condition on the model parameters  $p, D, r_x$ , and  $k_u(r_x)$ . Our analysis implies, in particular, that the significance of the manifold  $\mathcal{M}_x$ for the dynamics of (1) decreases with increasing number of classes (n), given that  $\mathcal{M}_x$  is always a line in an *n*-dimensional phase space – neglecting the dynamics of u – and, hence, that trajectories will generically approach steady state directly for n large.

While we have not studied the augmented resident-mutant model, Equation (16), in full generality, we have considered the regime where mutant is scarce, and we have recovered a condition for when it may invade the resident population that is based on a scale separation in the governing equations. Specifically, we have assumed that resident has reached quasi-steady state at  $(x_1^*, \ldots, x_n^*, u_x^*)$ ; under that assumption, we have identified a transient regime on a critical manifold in the resulting "reduced problem", with mutant evolving along an invasion manifold  $\mathcal{M}_{\tilde{y}}^*$ , while the resident population is fixed in a first approximation. The manifold  $\mathcal{M}_{\tilde{y}}^*$  is again globally attracting within the ambient critical manifold and, hence, determines the dynamics of mutant after an initial transient. In that sense, we have obtained a dynamical and highly intuitive interpretation of invasion into an established cell population. As Fenichel's Theorem [3, 6] a priori only guarantees the persistence of compact submanifolds of  $\mathcal{M}_{\tilde{y}}^*$ , our analysis does not describe the long-term evolution of the mutant population; by interpreting our rescaling of  $\{y_i\}$  with  $\varepsilon$  as the "rescaling chart" in an appropriately defined geometric "blow-up" [8], one may be able to establish a connection with the regime where  $y_i = \mathcal{O}(1)$  as  $\varepsilon \to 0$ .

**Remark 12.** As an aside, we note that the invasion manifold is equal, in  $\{y_i\}$ , to the mutant manifold  $\mathcal{M}_y$  that exists for the mutant-only model, *i.e.*, for  $x_i$  replaced by  $y_i$  (i = 1, ..., n) in Equation (1). (The corresponding *u*-value will differ, of course, with *u* fixed to  $u_x^*$  in the former case, but varying in some compact subinterval of  $(0, \infty)$  in the latter; however, that difference is inconsequential to our proofs of Proposition 1 and Corollary 2, respectively.)

Finally, we have illustrated our results for the two-class case and the three-class case, with n = 2 and n = 3, respectively, in which much of the underlying analysis simplifies.

While our study hence provides rigorous insight into the phase space geometry of the resident model and the resident-mutant model in Equations (1) and (16), respectively, various generalisations naturally suggest themselves.

Thus, we have assumed throughout that mortality is independent of class. If the mortality rates in Equation (1) are allowed to differ, our proofs are no longer valid as they stand. However, numerical simulation suggests that globally attracting invariant manifolds will continue to exist in that scenario and, in particular, that invasion manifolds can be defined on normally hyperbolic critical manifolds. Preliminary analysis indicates that our proofs can be adapted accordingly; the persistence of critical manifolds as slow manifolds will again follow by standard theory provided the defining steady states can be shown to be globally asymptotically stable. Interestingly, we expect that the resulting invasion manifolds will differ from the corresponding mutant manifolds when mortality rates are different between classes.

Similarly, when considering the invasion of mutant, it may be reasonable to introduce two distinct perturbation parameters in Equation (16), with  $\varepsilon$  denoting the timescale separation between resident and mutant, as before, and a separate small parameter scaling the mutant population to reflect the initial scarcity of mutant.

In the case where n = 2, we provided an alternative proof for the existence and global stability of the resident manifold  $\mathcal{M}_x$  by transformation of the  $(x_1, x_2)$ -subsystem in Equation (23) to an equivalent Riccati equation. It would be interesting to investigate whether that analysis can be extended to the general *n*-class scenario.

We have not considered the "open" system corresponding to Equation (1) in which the "boundary" class n has been removed. We expect that, in the limit as  $n \to \infty$ , the "closed" system studied here will converge to its open counterpart, in the sense that higher classes will become insignificant in that limit. In the steady-state regime, our expectation is supported by the observation that  $x_n^* \to 0$  as  $n \to \infty$ ; recall Proposition 3. However, as much of the analysis presented in Sections 2 and 3 seems to degenerate then, we have opted not to consider the "open" counterpart to (1) further here.

Finally, it would be interesting to study extensions of the simplistic models in Equations (1) and (15) that allow for alternative metabolic pathways and multiple nutrients, as discussed in Sections 2.5 and 4.3 of [7], respectively. Given the algebraically involved structure of the resulting equations, the general theory of normally hyperbolic invariant manifolds developed, for instance, in [9] may prove beneficial in that context.

Acknowledgment. The author acknowledges Chris Josephides for extensive discussions of a precursor of the family of models studied here and in [7]. Furthermore, the author is grateful to two anonymous reviewers whose comments and suggestions greatly improved the original manuscript.

**Declarations of Interest.** None.

#### References

- G.S. Christensen, Uniform asymptotic stability of linear non-autonomous systems, Can. J. Elect. Comput. Eng. 28(3-4), 173-176, 2003.
- [2] F. Dercole and S. Rinaldi, Analysis of evolutionary processes: the adaptive dynamics approach and its applications, Princeton University Press, Princeton, 2008.
- [3] N. Fenichel, Geometric singular perturbation theory for ordinary differential equations. J. Differential Equations 31(1), 53–98, 1979.
- [4] J. Hofbauer and K. Sigmund, Adaptive dynamics and evolutionary stability, Appl. Math. Lett. 3(4), 75–79, 1990.
- [5] J. Hofbauer and K. Sigmund, Evolutionary games and population dynamics. Cambridge University Press, Cambridge, 1998.
- [6] C.K.R.T. Jones, Geometric singular perturbation theory. Dynamical systems (Montecatini Terme, 1994), 44–118, Lecture Notes in Math. 1609, Springer-Verlag, Berlin, 1995.
- [7] C. Josephides, Modeling adaptive dynamics in microbial populations with applications to the evolution of cellular resource allocation trade-offs, PhD Thesis, The University of Edinburgh, 2016.
- [8] M. Krupa and P. Szmolyan, Extending geometric singular perturbation theory to nonhyperbolic points—fold and canard points in two dimensions, SIAM J. Math. Anal. 33(2), 286–314, 2001.
- [9] K. Nipp and D. Stoffer, Invariant manifolds in discrete and continuous dynamical systems, European Mathematical Society, Zürich, 2013.
- [10] M.A. Nowak, What is a quasispecies?, Trends Ecol. Evol. 7(4), 118–121, 1992.
- [11] K. Sigmund and M.A. Nowak, Evolutionary game theory, Curr. Biol. 9(14), R503–R505, 1999.
- [12] H.L. Smith and P.E. Waltman, The theory of the chemostat: dynamics of microbial competition, Cambridge University Press, Cambridge, 1995.
- [13] V.F. Zaitsev and A.D. Polyanin. Handbook of exact solutions for ordinary differential equations. Chapman and Hall/CRC, New York, 2002.

UNIVERSITY OF EDINBURGH, SCHOOL OF MATHEMATICS AND MAXWELL INSTITUTE FOR MATHEMATICAL SCI-ENCES, JAMES CLERK MAXWELL BUILDING, KING'S BUILDINGS, PETER GUTHRIE TAIT ROAD, EDINBURGH, EH9 3FD, UNITED KINGDOM

Email address: Nikola.Popovic@ed.ac.uk