

# Evolution of specialization in heterogeneous environments: equilibrium between selection, mutation and migration

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## Abstract

Adaptation in spatially heterogeneous environments results from the balance between local selection, mutation and migration. We study the interplay among these different evolutionary forces and demography in a classical two-habitat scenario with asexual reproduction. We develop a new theoretical approach that goes beyond the Adaptive Dynamics framework and allows us to explore the effect of high mutation rates on the stationary phenotypic distribution. We show that this approach improves the classical Gaussian approximation and captures accurately the shape of this equilibrium phenotypic distribution in one and two-population scenarios. We examine the evolutionary equilibrium under general conditions where demography and selection may be non-symmetric between the two habitats. In particular, we show how migration may increase differentiation in a source-sink scenario. We discuss the implications of these analytic results for the adaptation of organisms with large mutation rates such as RNA viruses.

**Key-Words:** local adaptation, migration-selection balance, gene flow, Adaptive Dynamics, Quantitative Genetics, skew.

## Introduction

Spatially heterogeneous selection is ubiquitous and constitutes a potent evolutionary force that promotes the emergence and the maintenance of biodiversity. Spatial variation in selection can yield adaptation to local environmental conditions, however, other evolutionary forces like migration and

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mutation tend to homogenize the spatial patterns of differentiation and thus to impede the build up of local adaptation. Understanding the balance between these contrasted evolutionary forces is a major objective of evolutionary biology theory (Slatkin 1978; Whitlock 2015; Savolainen et al. 2013) and could lead to a better understanding of the speciation process and the evolutionary response to global change (Doebeli and Dieckmann 2003; Leimar et al. 2008). In this article, we consider a two-habitat model with explicit demographic dynamics as in Meszéna et al. 1997; Day 2000; Ronce and Kirkpatrick 2001; Débarre et al. 2013. We assume that adaptation is governed by a single quantitative trait where individuals reproduce asexually. Maladapted populations have a reduced growth rate and, consequently, lower population size. In other words, selection is assumed to be 'hard' (Christiansen 1975; Débarre and Gandon 2010) as the population size in each habitat is affected by selection, mutation and migration. These effects are complex because, for instance, non-symmetric population sizes affect gene flow and adaptation feeds back on demography and population sizes (Nagylaki 1978; Lenormand 2002; Meszéna et al. 1997; Day 2000; Ronce and Kirkpatrick 2001; Débarre et al. 2013). To capture the complexity of these feed backs it is essential to keep track of both the local densities and the distributions of phenotypes in each habitat. Note that this complexity often led to the analysis of the simplest ecological scenarios where the strength of selection, migration and demographic constraints are assumed to be the same in the two habitats (we will refer to such situations as symmetric scenarios). See however Holt and Gaines 1992; García-Ramos and Kirkpatrick 1997; Gomulkiewicz et al. 1999; Holt et al. 2003 for the analysis of the effect of asymmetric migration from a source habitat on the dynamics of adaptation in a peripheral (i.e. sink) habitat. Three different approaches have been used to analyze these two-population models. Each of these approaches rely on a set of restrictive assumptions regarding the relative influence of the different evolutionary forces acting on the evolution of the population.

First, under the assumption that the rate of mutation is weak relative to selection, it is possible to use the Adaptive Dynamics framework (see Meszéna et al. 1997; Day 2000; Szilágyi and Meszéna 2009; Débarre et al. 2013; Fabre et al. 2012 but also the Results section for a presentation of this framework). This analysis captures the effect of migration and selection on the long-term evolutionary equilibrium. In particular, this approach shows that weak migration relative to selection promotes the coexistence of two specialist strategies (locally adapted on each habitat). In contrast, when migration is strong

relative to selection, a single generalist strategy is favored. The main limit of this approach is that it relies on the assumption that mutation rate is vanishingly small which results in a very limited amount of genetic variability. At most, 2 genotypes can coexist in this two-habitat model.

Second, Quantitative Genetics formalism, based on the computation of the moments of the phenotypic distribution, has been used to track evolutionary dynamics in heterogeneous habitats when there is substantial level of phenotypic diversity in each population Ronce and Kirkpatrick 2001. This model considers sexual reproduction with a quantitative trait (considering multiple loci with small effects Fisher 1919). However, similar types of equations, describing the dynamics of the moments of the phenotypic distribution, can also be derived in the case of asexual reproduction considering large mutation rates (see Débarre et al. 2013 and Section ). This formalism allows to recover classical migration thresholds below which specialization is feasible. But the analysis of Ronce and Kirkpatrick 2001 also reveals the existence of evolutionary bistability where transient perturbations of the demography can have long term evolutionary consequences on specialization. Yet, the assumption on the shape of the phenotypic distribution (assumed to be Gaussian in each habitat) is a major limit of this formalism.

Third, attempts to account for other shapes of the phenotypic distributions in heterogeneous environments have been developed recently Yeaman and Guillaume 2009; Débarre et al. 2013, 2015. These models highlight that calculations based on the Gaussian approximation which neglects the skewness of the equilibrium phenotypic distribution under-estimates the level of phenotypic divergence and local adaptation. Yet, there is currently no model able to accurately describe the build up of non-Gaussian distributions. The only attempt to model this distribution is to describe the phenotypic distributions in each habitat as the sum of two Gaussian distributions Yeaman and Guillaume 2009; Débarre et al. 2013. These models, however, only yield approximate predictions on long-term evolutionary equilibria.

Here we develop an alternative formalism that yields the population size and the phenotypic distribution in each habitat at the equilibrium between selection, mutation and migration. In the Materials and Methods section we present our two-population model. For heuristic reasons, we next provide the analysis of the equilibrium between selection and mutation in a single population. This provides an illustration of our approach in a simple scenario and shows how this analysis can go beyond the classical Gaussian approximation. Next, we extend this approach to a two-population scenario where migration

can also influence the phenotypic distribution, and we derive approximations for the level of adaptation under a migration-selection-mutation balance. We also explore the effects of non-symmetric constraints on selection, migration or demography between the two habitats. We evaluate the accuracy of these approximations by comparing them to numerical solutions of our deterministic model and we show that our approach improves previous attempts to study the interplay between adaptation and demography in heterogeneous environments. We contend that our results are particularly relevant for organisms with high mutation rates and may help to understand the within-host dynamics of chronic infections by RNA viruses Drake and Holland 1999; Sanjuán et al. 2010.

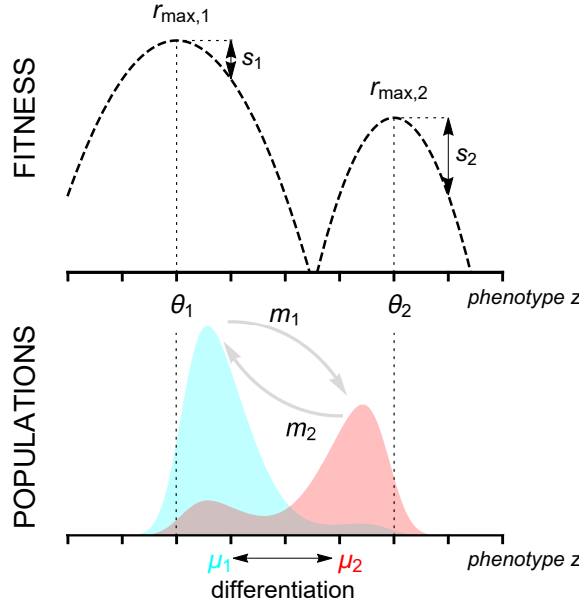
The present work has been prepared in parallel to the mathematical article Mirrahimi 2017 where we provide the mathematical basis and proofs for the method used here. See also Gandon and Mirrahimi 2016 where those mathematical results were announced. The aim of the present paper is to show how this approach can help to understand the balance between different evolutionary forces. We present several new biological scenarios and we derive new results that help grasp the interplay between different evolutionary forces and demography.

## Materials and Methods

We model an environment containing two habitats that we label 1 and 2 (Figure 1). The population is structured by a quantitative trait  $z$ . In each habitat  $i$  there is stabilizing selection on the trait  $z$  for an optimal value  $\theta_i$  (for habitat  $i = 1, 2$ ). The growth rate in habitat  $i$  is denoted by  $r_i(z)$  which has its maximum  $r_{\max,i}$  when  $z = \theta_i$ . In the following we will mainly focus on the following quadratic stabilizing selection function (Bürger 2000– pages 117-121 and chapter VI):

$$r_i(z) = r_{\max,i} - s_i (z - \theta_i)^2. \quad (1)$$

We denote by  $s_i$  the selection pressure in habitat  $i$ . Without loss of generality we assume that  $\theta_1 = -\theta_2 = -\theta$ . But our approach could be used with other stabilizing selection functions (see (12) below where another selection function is studied in the case of one population).



**Figure 1 – Schematic representation of the 2 habitat model.** The top figure shows the growth rate (fitness) in each habitat as a function of the phenotypic trait  $z$ . In habitat  $i$  the growth rate is assumed to be maximized at  $z = \theta_i$  and the strength of selection is governed by  $s_i$  (see equation (1)). Here we illustrate a scenario with non-symmetric fitness functions. The bottom figure shows the phenotypic density in each habitat (light blue and light red in habitats 1 and 2, respectively). Migration from population  $i$  is governed by the parameter  $m_i$  and tends to reduce the differentiation (i.e. the difference between the mean phenotypes) between populations.

Reproduction is assumed to be asexual. Offspring inherit the phenotype of their parent (i.e. no environmental variance) and we consider a continuum of alleles model Kimura 1965. Mutations occur with a constant rate  $U$  (i.e. mutations are not associated with reproduction) and add an increment  $y$  to the parents' phenotype; we assume that the distribution of these mutational effects is given by  $K(y)$ , with mean 0 and variance equal to  $2V_m$ . We also assume that individuals disperse out of habitat  $i$  with rate  $m_i$ . Rates of migration are assumed to be independent of individuals' phenotypes.

Let  $n_i(t, z)$  be the phenotypic density in habitat  $i$  at time  $t$ . The dynamics of this density in each

habitat is given by (for  $i = 1, 2$  and  $j = 2, 1$ ):

$$\begin{aligned} \frac{\partial n_i(t, z)}{\partial t} = & U \left( \underbrace{\int_{-\infty}^{+\infty} n_i(t, z - y) K(y) dy - n_i(t, z)}_{\text{mutation}} \right) \\ & + \underbrace{n_i(t, z) \left( r_i(z) - \kappa_i \int_{-\infty}^{+\infty} n_i(t, y) dy \right)}_{\text{growth}} + \underbrace{m_j n_j(t, z) - m_i n_i(t, z)}_{\text{migration}}. \end{aligned} \quad (2)$$

The first term in the right hand side of the above equation corresponds to the effect of mutations. The second term corresponds to logistic growth that results from the balance between reproduction given by (1) and density dependance where  $\kappa_i$  measures the intensity of competition within each habitat. The last term corresponds to the dispersal of individuals between habitats.

If we assume that the variance of the mutation distribution is small relative to the mutation rate  $U$ , we can consider an approximate model where we replace the mutation term in (2) by a diffusion (see Kimura 1965; Lande 1975 and the more recent article Champagnat et al. 2008 where the diffusion term has been derived directly from a stochastic individual based model). See also Bürger 2000–pages 239-241 for a discussion on the domain of the validity of such model. Our model then becomes:

$$\frac{\partial n_i(t, z)}{\partial t} = UV_m \frac{\partial^2 n_i(t, z)}{\partial z^2} + n_i(t, z) \left( r_i(z) - \kappa_i \int_{-\infty}^{+\infty} n_i(t, y) dy \right) + m_j n_j(t, z) - m_i n_i(t, z). \quad (3)$$

The total population sizes in each habitat is given by:

$$N_i(t) = \int_{-\infty}^{+\infty} n_i(t, z) dz, \quad \text{for } i = 1, 2. \quad (4)$$

In other words,  $n_i(t, z)$  refers to the density of individuals with phenotype  $z$  in habitat  $i$ , while  $N_i$  refers to the total density of the polymorphic population in habitat  $i$ .

## Data Availability Statement

No biological data is provided in this article.

## Results

### One population: the selection-mutation equilibrium

In this section we start by a simple scenario with no migration. This one-population example provides a good introduction to our method. The dynamics of the phenotypic density in a single habitat is given by:

$$\frac{\partial n_0(t, z)}{\partial t} = UV_m \frac{\partial^2 n_0(t, z)}{\partial z^2} + n_0(t, z) (r_0(z) - \kappa N_0(t)), \quad (5)$$

where  $N_0$  is the total population size:

$$N_0(t) = \int_{-\infty}^{+\infty} n_0(t, y) dy.$$

For this scenario we consider a more general form of growth rate  $r_0(z)$  than (1). We only suppose that  $r_0(z)$  is maximized for an optimal trait  $z_0$ . In the following we present our two-step approach. First, we analyse the evolutionary equilibria of the problem when the rate of mutation is small and we identify the evolutionary stable strategy (ESS). Second, we use this ESS to derive an approximation for the stationary solution of (5) when mutation is more frequent and maintains a standing variance at equilibrium.

### Adaptive dynamics and evolutionary stable strategies

In this section, we assume that the mutations are very rare such that a mutation is fixed or goes extinct before a new mutation arises in the population. The phenotypic distribution results from a collection of spikes. Such spikes are gradually replaced by others with the arrival of new mutations and through a competitive procedure. The theory of Adaptive Dynamics Geritz et al. 1998 is based on the study of the stable equilibrium distribution and the localization of the spikes of such equilibrium, known as evolutionary stable strategies (ESS). Note that in this first step we do not make any assumption regarding the effects of these mutations on the phenotype. We are interested in the identification of the global ESSs, i.e. when the resident population cannot be invaded by any mutation no matter its effect.

In absence of migration, the phenotype  $z_0$  constitutes a globally stable evolutionary strategy. Indeed, when such monomorphic population reaches its demographic equilibrium, the total population size is given by  $N_0^* = \frac{r(z_0)}{\kappa}$ . The fate of a mutant with phenotype  $z_m$  introduced in such a resident population is determined by its fitness given by (i.e. per capita growth rate minus density dependence):

$$w(z_m; N_0^*) = r_0(z_m) - \kappa_0 N_0^* < w(z_0; N_0^*) = 0. \quad (6)$$

No mutant trait  $z_m$  can indeed invade the population since  $r_0(z)$  takes its maximum at  $z_0$ .

### Equilibrium distribution with mutation

The ESS  $z_0$  corresponds to the long-term evolutionary outcome in a scenario where all phenotypic strategies are present initially but where mutation is absent. In the following we study the impact of mutation on the ultimate evolutionary equilibrium of the population.

We introduce a new parameter  $\varepsilon = \sqrt{V_m}$ . Hence we replace  $V_m$  by  $\varepsilon^2$  and we approximate the phenotypic density  $n_{\varepsilon,0}^*(z)$ , the equilibrium of (5), in terms of  $\varepsilon$  (where the subscript  $\varepsilon$  in  $n_{\varepsilon,0}^*$  indicates the dependence of the phenotypic density on the parameter  $\varepsilon$ ). Our objective is to provide an approximation of the phenotypic density when the effect of mutation (measured by  $\varepsilon$ ) is small while the mutation rate can be large.

To study  $n_{\varepsilon,0}^*(z)$  we will use a method based on Hamilton-Jacobi equations (see equation (A.5)) which has been developed by the mathematical community during the last decade to study selection-mutation models, when the effect of mutations is vanishingly small. This method was first suggested by Diekmann et al. 2005 and was developed for the case of homogeneous environments in Perthame and Barles 2008; Barles et al. 2009. However those works, which are addressed to the mathematical community, were mainly focused on the limit case where the effect of mutations  $\varepsilon$  is vanishingly small. Here, we go further than previous studies and characterize the phenotypic distribution when the mutations have non-negligible effects.

The method is based on the following transformation:

$$n_{\varepsilon,0}^*(z) = \frac{1}{\sqrt{2\pi\varepsilon}} \exp\left(\frac{u_{\varepsilon,0}(z)}{\varepsilon}\right). \quad (7)$$



The introduction of the function  $u_{\varepsilon,0}(z)$  is a mathematical trick. It is indeed easier to provide first an approximation of  $u_{\varepsilon,0}(z)$  rather than directly studying  $n_{\varepsilon,0}^*(z)$ .

Note that a first approximation of the population's phenotypic density which is commonly used in the theory of Quantitative Genetics is a Gaussian approximation of the following form around  $z^*$ :

$$n_{\varepsilon,0}^*(z) \approx N_{\varepsilon,0}^* \mathcal{N}(z^*, \varepsilon \sigma^2). \quad (8)$$

The Gaussian approximation, is as if we had imposed  $u_{\varepsilon,0}(z)$  to be a quadratic function of  $z$ , that is  $u_{\varepsilon,0}(z) = \varepsilon \log\left(\frac{N_{\varepsilon,0}^*}{\sigma}\right) - \frac{(z-z^*)^2}{2\sigma^2}$ . Our objective, however, is to obtain more accurate results than (8) and to approximate  $u_{\varepsilon,0}$  without making an a priori Gaussian assumption. To this end we postulate an expansion for  $u_{\varepsilon,0}(z)$  in terms of  $\varepsilon$ :

$$u_{\varepsilon,0}(z) = u_0(z) + \varepsilon v_0(z) + O(\varepsilon^2), \quad (9)$$

and we try to compute the coefficients  $u_0(z)$  and  $v_0(z)$ . These terms can indeed be explicitly computed and they lead to an approximation of the total population size  $N_{\varepsilon}^*$  and the phenotypic density  $n_{\varepsilon}^*(z)$  that we will call henceforth our *first approximation* (see the supplementary information A.1.1 for these derivations).

In order to provide more explicit formula for the moments of order  $k \geq 1$  of the population's distribution in terms of the parameters of the model, we also provide a *second approximation*. This *second approximation*, instead of using the values of  $u_0$  and  $v_0$  in the whole domain, is based on the Taylor expansions of  $u_0$  and  $v_0$  around the ESS points (see the supplementary information, Section A.1.2). Our *second approximation* is by definition less accurate than the first one. We illustrate below the quality of these different approximations under two different scenarios.

**Quadratic growth rate:** We first consider a quadratic growth rate as in (1):

$$r_0(z) = r_{\max,0} - s_0(z - \theta_0)^2. \quad (10)$$

In this case our *first approximation* yields the Gaussian distribution (8) with:

$$N_{\varepsilon,0}^* \approx \frac{1}{\kappa_0}(r_{\max,0} - \varepsilon\sqrt{s_0U}), \quad \sigma^2 \approx \frac{\sqrt{U}}{\sqrt{s_0}}. \quad (11)$$

Note that this Gaussian distribution is actually an exact equilibrium of (3) and the above  $\approx$  signs can indeed be replaced by equalities (see Kimura 1965 and Bürger 2000–Chapter IV). For the derivation of this result see the supplementary information–Section A.1.1.

**An asymmetric growth rate:** We next consider a growth rate which is not symmetric:

$$r_0(z) = r_{\max,0} - s_0(z - \theta_0)^2(a + (z - \theta_0 - b)^2). \quad (12)$$

In this case the phenotypic distribution does not have a Gaussian profile and our approximation yields:

$$N_{\varepsilon,0}^* \approx \frac{1}{\kappa_0}(r_{\max,0} - \sqrt{s_0U(a + b^2)}\varepsilon), \quad n_{\varepsilon,0}^*(z) \approx \frac{1}{\sqrt{2\pi\varepsilon}} \exp\left(\frac{u_0(z) + \varepsilon v_0(z)}{\varepsilon}\right),$$

where the values of  $u_0$  and  $v_0$  can be computed explicitly (see the supplementary information–Section A.1.1). In Figure 2 we plot this *first approximation* and compare it with the exact distribution that we derived numerically.

We can also use our *second approximation* to obtain analytic expressions for the mean phenotypic trait (see the supplementary information–Section A.1.2 for the derivation):

$$\mu_{\varepsilon,0}^* = \frac{1}{N_{\varepsilon,0}^*} \int zn_{\varepsilon,0}^*(z)dz = \theta_0 + \frac{2b\sqrt{U}\varepsilon}{\sqrt{s_0(a + b^2)^{3/2}}} + O(\varepsilon^2),$$

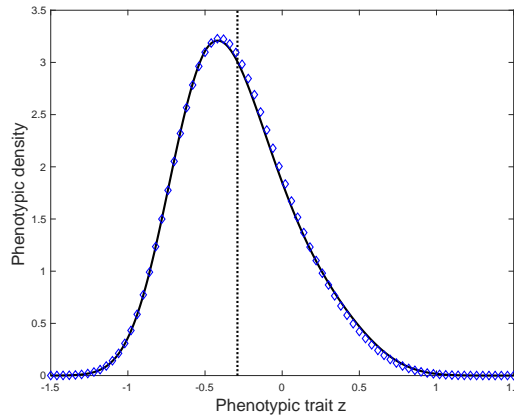
the mean variance:

$$\sigma_{\varepsilon,0}^{*2} = \frac{1}{N_{\varepsilon,0}^*} \int (z - \mu_{\varepsilon,0}^*)^2 n_{\varepsilon,0}^*(z)dz = \frac{\sqrt{U}\varepsilon}{\sqrt{s_0(a + b^2)}} + O(\varepsilon^2),$$

and the third central moment:

$$\psi_{\varepsilon,0}^* = \frac{1}{N_{\varepsilon,0}^*} \int (z - \mu_{\varepsilon,0}^*)^3 n_{\varepsilon,0}^*(z) dz = \frac{2bU\varepsilon^2}{s_0(a+b^2)^2} + O(\varepsilon^3).$$

In Table 1 we show that our two approximations capture accurately the first three moments of the equilibrium distribution using the parameters that we used in Figure 2. As expected, the *first approximation* is more accurate, but the analytic expressions of the *second approximation* given above allow us to capture the influence of the parameters of the model.



**Figure 2 – The selection-mutation equilibrium of the phenotypic density  $n_{\varepsilon,0}(z)$  in a single population.** We plot the exact phenotypic density at equilibrium obtained from numerical computations of the equilibrium of (5) (blue dots) together with our *first approximation* (full black line) with the growth rate given in (12). The vertical dotted line indicates the mean of the phenotypic distribution. Note the skewness of the equilibrium distribution that is accurately captured with our approximation (see also Table 1). In this figure, to compute numerically the equilibrium, we have solved numerically the dynamic problem (5) and kept the solution obtained after long time when the equilibrium has been reached. Parameter values:  $r_{\max} = 3$ ,  $s_0 = 1$ ;  $\theta = -0.5$ ,  $\kappa = 1$ ,  $a = 0.2$ ,  $b = 1$ ,  $U = 1$ ,  $\varepsilon = 0.1$ .

## Two populations: the selection-mutation-migration equilibrium

Next we return to the analysis of the stationary solution of (3), which results from the equilibrium between selection, mutation and migration in each habitat. Using (1) and (3) one can derive dynamical

	Exact value	First approximation	Second approximation
Mean: $\mu_{\varepsilon,0}^*$	-0.29	-0.29	-0.35
Variance: $\sigma_{\varepsilon,0}^{*2}$	0.13	0.14	0.09
Third central moment: $\psi_{\varepsilon,0}^*$	0.02	0.02	0.01

**Table 1 – First three moments of the phenotypic distribution at mutation-selection equilibrium in a single population.** We compare the values from the exact numerical resolution of (5) and our two approximations using the growth rate given in (12) (see also Figure 2). Parameter values:  $r_{\max} = 3$ ,  $s_0 = 1$ ;  $\theta = -0.5$ ,  $\kappa = 1$ ,  $a = 0.2$ ,  $b = 1$ ,  $U = 1$ ,  $\varepsilon = 0.1$ .

equations for the size of the population and the mean phenotype ( $\mu_i = \frac{1}{N_i} \int z n_i(t, z) dz$ ):

$$\frac{d}{dt} N_i = N_i(r_{\max,i} - \kappa_i N_i) - s_i N_i((\mu_i - \theta_i)^2 + \sigma_i^2) + m_j N_j - m_i N_i,$$

$$\frac{d}{dt} \mu_i = -s_i(2(\mu_i - \theta_i)\sigma_i^2 + \psi_i) + m_j \frac{N_j}{N_i}(\mu_j - \mu_i),$$

where  $\sigma_i^2$  and  $\psi_i$  are the variance and the third central moment of the phenotypic distribution, respectively. These two quantities are also dynamical variables and their dynamics are governed by higher moments of the phenotypic distribution. But this dynamical system is not closed and these higher moments are also dynamical variables that depend on additional moments. Various approximations, however, have been used to capture its behavior. Typically, many results are based on the Gaussian approximation that focuses on the dynamics of the mean and the variance and discards all higher cumulants of the distribution Bürger 2000; Rice 2004. Yet several authors pointed out that neglecting the skewness of the distribution can underestimate the amount of differentiation and local adaptation Yeaman and Guillaume 2009; Débarre et al. 2013, 2015. Indeed, in the case of symmetric habitats, that is when  $m_1 = m_2 = m$ ,  $\kappa_1 = \kappa_2 = \kappa$ ,  $s_1 = s_2 = s$ ,  $r_{\max,1} = r_{\max,2} = r_{\max}$ , one can readily obtain the size and the mean trait of the population at equilibrium (the equilibrium is indicated by a superscript \*). Using the fact that  $N_1^* = N_2^* = N^*$ ,  $\mu_1^* = -\mu_2^*$ ,  $\sigma_1^* = \sigma_2^* = \sigma^*$  and  $\psi_1^* = -\psi_2^* = \psi^*$ , we obtain:

$$N^* = \frac{1}{\kappa} \left( r_{\max} - s \left( \frac{(2m\theta - s\psi^*)^2}{4(m + g\sigma^{*2})^2} + \sigma^{*2} \right) \right),$$

$$\mu_1^* = \frac{-s(\psi^* + 2\theta\sigma^{*2})}{2(m + s\sigma^{*2})}.$$

The differentiation between the two habitats is thus (Figure 1):

$$\mu_2^* - \mu_1^* = \frac{s(\psi^* + 2\theta\sigma^{*2})}{m + s\sigma^{*2}}. \quad (13)$$

There is, however, no analytic predictions on the magnitude of the different moments of the phenotypic distribution except in the limit when the mutation rate is extremely low Débarre et al. 2013.

Next, we follow the two-step approach we used to obtain the stationary phenotypic distribution in a single population. First, we analyse the evolutionary equilibria of the system when mutations are rare using the Adaptive Dynamics framework. We identify monomorphic or dimorphic globally evolutionary stable strategies (ESS). Second, we use these ESSs to derive approximations of the stationary solution of (3) when mutation is more frequent and maintains a standing variance at equilibrium.

### Adaptive dynamics and evolutionary stable strategies

We consider a resident population at a demographic equilibrium set by the phenotypic densities of the resident in both habitats (see the supplementary information, Section A.2.1). We want to determine the fate of a mutant with phenotype  $z_m$  introduced in this resident population. The ability of the mutant to invade is determined by its fitness given by:

$$w_i(z_m; N_i) = r_i(z_m) - \kappa_i N_i, \quad \text{for } i = 1, 2. \quad (14)$$

To take into account migration between habitats we introduce an effective fitness which corresponds to the growth rate of a trait in the whole environment (see Caswell 1989; Metz et al. 1992; Meszéna et al. 1997). The effective fitness  $W(z_m; N_1, N_2)$ , which corresponds to the *effective* growth rate associated

with trait  $z_m$  in the resident population  $(n_1, n_2)$ , is the largest eigenvalue of the following matrix:

$$\mathcal{A}(z_m; N_1, N_2) = \begin{pmatrix} w_1(z_m; N_1) - m_1 & m_2 \\ m_1 & w_2(z_m; N_2) - m_2 \end{pmatrix}. \quad (15)$$

After some time, the dynamical system will reach a globally stable demographic equilibrium. Because there are two habitats, we expect that at most two distinct traits can coexist. With an analysis of the effective fitness  $W$ , we characterize such equilibrium corresponding to the evolutionary stable strategy (see the supplementary information, Section A.2.1.1). This equilibrium is indeed either monomorphic (with phenotype  $z^{M*}$  and the total population size  $N_i^{M*}$ ) or dimorphic (with phenotypes  $z_I^{D*}$  and  $z_{II}^{D*}$  and the total population sizes  $N_i^{D*}$ , where the subscripts I and II indicate that the phenotype is best adapted to habitat 1 and 2, respectively).

### Equilibrium distribution with mutation

In the following we allow mutation rate to increase and we study the impact of mutations on the ultimate evolutionary equilibrium of the phenotypic densities, i.e. the stationary solution of (3). We present below the general principle of the approach before examining specific case studies.

As above we introduce the parameter  $\varepsilon = \sqrt{V_m}$  and we approximate the phenotypic density  $n_{\varepsilon,i}^*(z)$ , the equilibrium of (3) with  $V_m = \varepsilon^2$ , in terms of  $\varepsilon$ . Our objective is to provide an approximation of the phenotypic density in each habitat when the effect of mutation (measured by  $\varepsilon$ ) is small while the mutation rate can be large.

We use analogous transformation to (7):

$$n_{\varepsilon,i}^*(z) = \frac{1}{\sqrt{2\pi\varepsilon}} \exp\left(\frac{u_{\varepsilon,i}(z)}{\varepsilon}\right). \quad (16)$$

Our objective is then to estimate  $u_{\varepsilon,i}(z)$ . We proceed as in the one population scenario and we

postulate an expansion for  $u_{\varepsilon,i}$  in terms of  $\varepsilon$ :

$$u_{\varepsilon,i}(z) = u_i(z) + \varepsilon v_i(z) + O(\varepsilon^2), \quad (17)$$

and we try to compute the coefficients  $u_i(z)$  and  $v_i(z)$ . First we can show that, when there is migration in both directions (i.e.  $m_i > 0$  for  $i = 1, 2$ ), the zero order terms are the same in both habitats:  $u_1(z) = u_2(z) = u(z)$  (see the supplementary information, Section A.2.1.2). We can indeed compute explicitly  $u(z)$  which is given by (A.23) in the monomorphic case and by (A.24) in the dimorphic case. As we observe in the formula (A.23) and (A.24),  $u(z)$  attains its maximum (which is equal to 0) at the ESS points identified in the previous subsection. This means that the peaks of the population's distribution are around the ESS points ( $z^{M*}$  in the case of the monomorphic ESS and  $(z_I^{D*}, z_{II}^{D*})$  for the dimorphic ESS). Note that the fact that  $u_1(z) = u_2(z) = u(z)$  means that the peaks of the population distribution are placed approximately at the same points (ESS points) in both habitats. However, the size of the peaks may be different since  $v_1(z)$  is not necessarily equal to  $v_2(z)$ .

We are also able to compute the first order term  $v_i(z)$  (see the supplementary information, Section A.2.1.2). This allows us to obtain a *first approximation* of the phenotypic density  $n_{\varepsilon,i}^*(z)$ . This approximation of the stationary distribution is very accurate (see for instance Figure 4).

As in the one population scenario we derive more explicit formula for the moments of order  $k \geq 1$  of the stationary phenotypic distribution. This *second approximation*, instead of using the values of  $u(z)$  and  $v_i(z)$  in the whole domain, is based on the computation of the Taylor expansions of  $u(z)$  and  $v_i(z)$  around the ESS points (see the supplementary information, Section A.2.1.3).

## Case studies

### *Symmetric fitness landscapes*

We focus first on a symmetric scenario where, apart from the position of the optimum, the two habitats are identical:  $m_1 = m_2 = m, \kappa_1 = \kappa_2 = \kappa, s_1 = s_2 = s, r_{\max,1} = r_{\max,2} = r_{\max}$ . In this special

case it is possible to fully characterize the evolutionary equilibrium.

When migration rate is higher than critical migration threshold:

$$m > m_c = 2s\theta^2 \quad (18)$$

migration prevents the differentiation of the trait between the two habitats (see the supplementary information- Subsection A.2.1.1). The only evolutionary equilibrium, when the mutation rate is vanishingly small, is monomorphic and satisfies  $z^{M^*} = 0$  and  $n_1^{M^*}(z) = n_2^{M^*}(z) = N^{M^*}\delta(z)$ , where  $\delta(\cdot)$  is the dirac delta function and  $N^{M^*} = \frac{1}{\kappa} (r_{\max} - s\theta^2)$ .

**Monomorphic case:** Let's suppose that  $m_c = 2s\theta^2 \leq m$ . Then  $z^{M^*} = 0$  is the only ESS and  $N^{M^*} = \frac{1}{\kappa} (r_{\max} - s\theta^2)$ . Then, we can provide our *first approximation* of the phenotypic density  $n_{\varepsilon,i}(z)$  following the method introduced above (Figure 3). Moreover, defining  $\phi = \sqrt{1 - 2s\theta^2/m}$ , we can use the *second approximation* to obtain analytic formula for the moments of the stationary state:

$$\left\{ \begin{array}{l} N_{\varepsilon,1}^{M^*} = N_{\varepsilon,2}^{M^*} = \int n_{\varepsilon,i}^{M^*}(z)dz = \frac{1}{\kappa} (r_{\max} - s\theta^2) - \varepsilon \frac{\sqrt{Us}\phi}{\kappa} + O(\varepsilon^2), \\ \mu_{\varepsilon,1}^{M^*} = \frac{1}{N_{\varepsilon,1}^{M^*}} \int zn_{\varepsilon,1}^{M^*}(z)dz = -\varepsilon \frac{\sqrt{Us}\theta}{m\phi} + O(\varepsilon^2), \\ \mu_{\varepsilon,2}^{M^*} = \frac{1}{N_{\varepsilon,2}^{M^*}} \int zn_{\varepsilon,2}^{M^*}(z)dz = \varepsilon \frac{\sqrt{Us}\theta}{m\phi} + O(\varepsilon^2), \\ \sigma_{\varepsilon,1}^{M^*2} = \sigma_{\varepsilon,2}^{M^*2} = \frac{1}{N_{\varepsilon,i}^{M^*}} \int (z - \mu_{\varepsilon,i}^{M^*})^2 n_{\varepsilon,i}^{M^*}(z)dz = \frac{\varepsilon\sqrt{U}}{\sqrt{s}\phi} + O(\varepsilon^2), \\ \psi_{\varepsilon,i}^{M^*} = \frac{1}{N_{\varepsilon,i}^{M^*}} \int (z - \mu_{\varepsilon,i}^{M^*})^3 n_{\varepsilon,i}^{M^*}(z)dz = O(\varepsilon^3). \end{array} \right. \quad (19)$$

These results are consistent with (13). Note that the equilibrium variance in each habitat  $\sigma_{\varepsilon,i}^{M^*2} \approx \frac{\varepsilon\sqrt{U}}{\sqrt{s}\phi}$  is larger than the equilibrium variance maintained in the absence of heterogeneity between the habitats (compare with (11)). This increase in the equilibrium variance comes from  $\phi$  which depends on dispersion and the heterogeneity between the two habitats. The variance of the distribution increases as  $\phi$  decreases. When  $\phi = 0$  the approximation for the variance becomes infinitely large. Indeed, this corresponds to the threshold value of migration below which the above approximation collapses

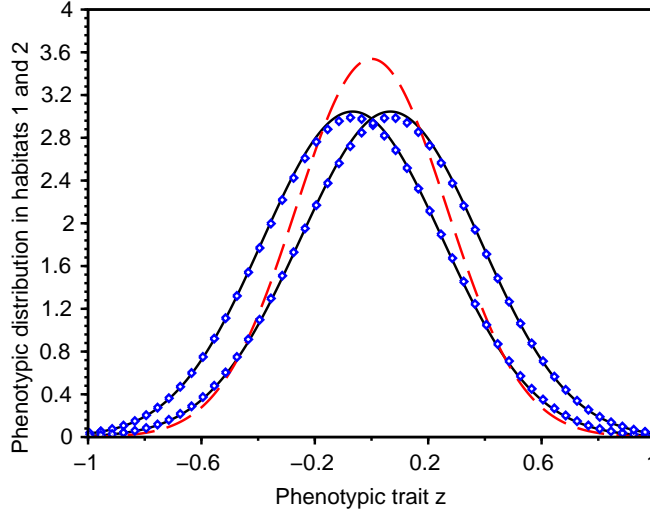


because the distribution becomes bimodal. In this case we have to switch to the analysis of the dimorphic case. Note that the differentiation between habitats depends also on  $\phi$ . Some differentiation emerges even when the migration rate is above the critical migration rate,  $m_c$  (Figures 3 and 4). In Figure 4 we provide a comparison of the results from the *first* and the *second approximations*. Our *second approximation* yields convincing results when the parameters are such that we are far from the transition zone from monomorphic to dimorphic distribution. This approximation is indeed based on an integral approximation which is relevant only when the population's distribution is relatively sharp around the ESS points. This is not the case in the transition zone unless the effect of the mutations, i.e.  $\varepsilon$ , is very small.

**Dimorphic case:** When  $m < m_c$ , the only globally stable evolutionary equilibrium is dimorphic which yields the following ESS:  $\{z_I^{D*}, z_{II}^{D*}\}$  with  $z_I^{D*} = -z_{II}^{D*} = -z^{D*}$  and  $z^{D*} = \frac{\sqrt{4s^2\theta^4 - m^2}}{2s\theta}$ . When  $\varepsilon = 0$  this yields the following phenotypic densities at equilibrium:  $n_i^{D*}(z) = \nu_{I,i}\delta(z - z_I^{D*}) + \nu_{II,i}\delta(z - z_{II}^{D*})$  (analytic expressions for  $\nu_{I,j}$  and  $\nu_{II,j}$  are given in the supplementary information, Section B.1). When  $\varepsilon > 0$  we can use our *first* and *second approximations* to obtain convincing approximations of the phenotypic distribution and its moments (see Figure 4). Our *first approximation* improves the Adaptive Dynamics predictions in a broad range of the parameter space and, as pointed above, our *second approximation* is pertinent when the parameters are such that we are far from the transition zone from dimorphic to monomorphic distribution. The analytic expressions for the local moments of the stationary distribution in each habitat, obtained from our *second approximation*, are given in the supplementary information, Section B.3.

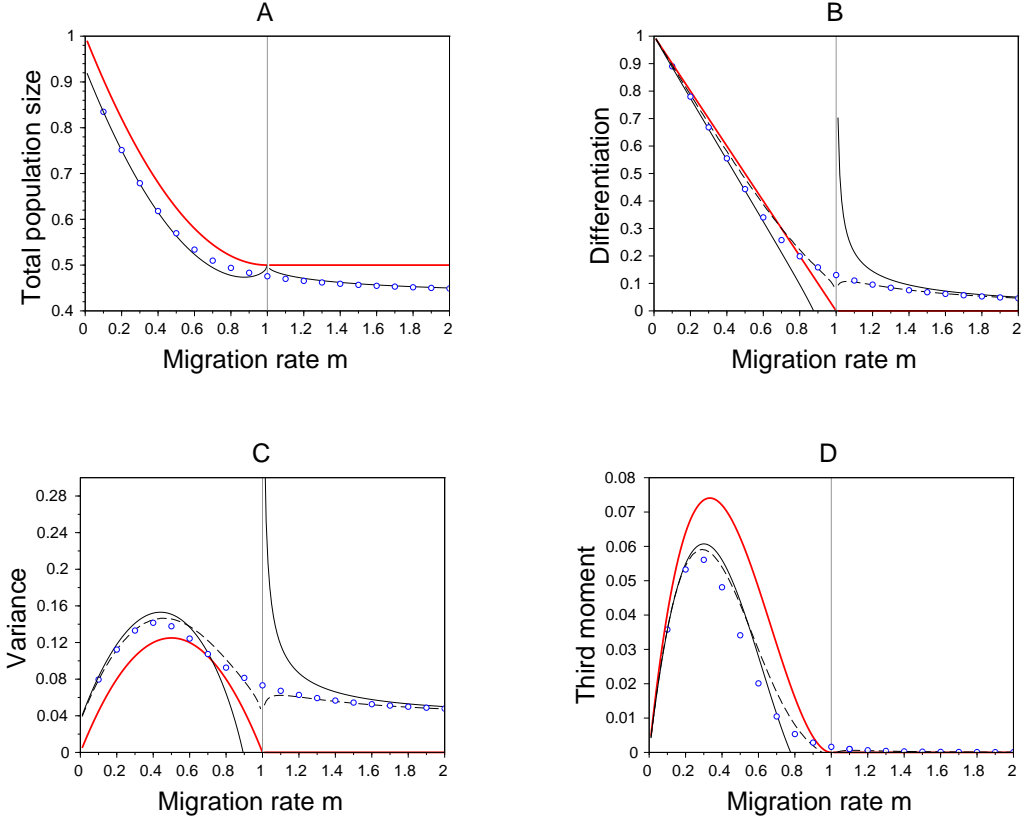
### *Non-symmetric scenarios*

**A general non-symmetric scenario:** In a non-symmetric scenario, there is also a unique globally stable evolutionary strategy which is either monomorphic or dimorphic. There is still a threshold value of migration above which the maintenance of a dimorphic polymorphism is impossible:  $\Delta = \frac{m_1 m_2}{4s_1 s_2 \theta^4} \geq 1$ . Note that this condition generalizes the condition in the symmetric case (i.e. when  $m_1 = m_2$  and  $s_1 = s_2$ ). However, for the ESS to be dimorphic, the condition  $\Delta < 1$  is not enough



**Figure 3 – Selection-mutation-migration equilibrium of the phenotypic densities  $n_{\varepsilon,i}(z)$  in the two habitats in a symmetric scenario.** We plot the exact phenotypic densities at equilibrium obtained from numerical computations of the equilibrium of (3) (blue dots) together with our *first approximation* (full black line) in a case where the distribution is unimodal in each habitat. We also plot the approximation given in Débarre et al. 2013 (red dashed line). Note that our approximation captures the emergence of some differentiation even though we are above the critical migration rate leading to the evolution of a dimorphic population. In the presence of large mutation rates, the population’s distribution is indeed shifted to the left (respectively right) in the first (respectively second) habitat, while Débarre et al. 2013 provided the same approximation for both habitats. Our calculation yields also better approximations for the variance of the distribution in each habitat (Débarre et al. 2013 underestimates this variance). In this figure and in the following ones, to compute numerically the equilibrium, we have solved numerically the dynamic problem (3) and kept the solution obtained after long time when the equilibrium has been reached. Parameter values:  $m = 1.5$ ,  $r_{\max} = 3$ ,  $s = 2$ ;  $\theta = 0.5$ ,  $\kappa = 1$ ,  $U = 1$ ,  $\varepsilon = 0.1$ .

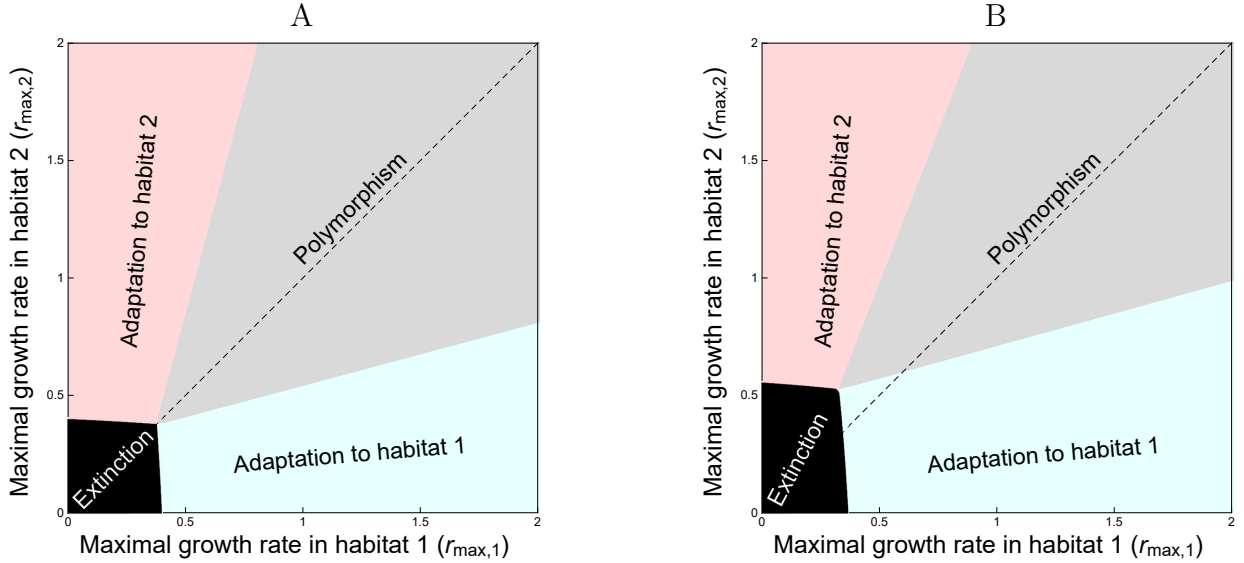
and two other conditions should also be satisfied. These conditions (i.e.  $\eta_1 < \beta_2 r_{\max,2} - \alpha_1 r_{\max,1}$  and  $\eta_2 < \beta_1 r_{\max,1} - \alpha_2 r_{\max,2}$  with the constants  $\alpha_i, \beta_i$  and  $\eta_i$  depending on the parameters  $m_1, m_2, s_1, s_2, \kappa_1, \kappa_2$  and  $\theta$ , see the supplementary information, Section B.2), guarantee that the qualities of the habitats are not very different. Indeed, if one habitat has a higher quality it is likely to overwhelm the dynamics of adaptation in the other habitat. This will yield a monomorphic equilibrium biased toward the high-quality habitat. Figure 5 illustrates that a polymorphism is only maintained in a range of parameter values where the two habitats are relatively similar. Interestingly, in spite of the asymmetry of the two habitats, the locations of the two peaks of the phenotypic distribution are al-



**Figure 4 – Effects of migration in a symmetric scenario on (A) the total population size ( $N_{\varepsilon,1}^*$ ) in habitat 1, (B) the differentiation between habitats ( $\mu_{\varepsilon,2}^* - \mu_{\varepsilon,1}^*$ ), (C) the variance ( $\sigma_{\varepsilon,1}^{*2}$ ) and (D) the third central moment of the phenotypic distribution ( $\psi_{\varepsilon,1}^*$ ) in habitat 1** (see (19) and Section B.3 for the definition of these quantities and the analytic formula obtained from our *second approximation*). The dots refer to the numerical resolutions of the problem with  $\varepsilon = 0.05$ , the red line indicates the case where  $\varepsilon = 0$ , while the lines in black refer to our two approximations when  $\varepsilon = 0.05$  (the dashed line for the *first approximation* and the full line for the *second approximation*). The vertical gray line indicates the critical migration rate below which dimorphism can evolve in the Adaptive Dynamics scenario. Note that both approximations predict the same total population size. Other parameter values:  $r_{\max} = 1$ ,  $s = 2$ ,  $\theta = 0.5$ ,  $\kappa = 1$ ,  $U = 1$ .

ways symmetric and consequently:  $z_1^{D*} = -z_2^{D*} = -z^{D*}$  where:  $z^{D*} = \sqrt{\theta^2(1 - \Delta)}$ . The symmetric locations of the peaks is indeed a consequence of the choice of the quadratic stabilizing selection (1). See the supplementary information, Section B.1 for the expressions of the densities in each habitat and Section A.2.1.1 for the conditions leading to this stable equilibrium.

**A source-sink scenario:** An extreme case of asymmetry occurs when one population (the source)



**Figure 5 – Maintenance of polymorphism and non-symmetric adaptation as a function of the maximal growth rates  $r_{max,1}$  and  $r_{max,2}$  in the two habitats.** In (A) we examine a symmetric situation where all the parameters are identical in the two habitats:  $m_1 = m_2 = 0.5$ ,  $s_1 = s_2 = 2$ ,  $\kappa_1 = \kappa_2 = 1$ . In (B) we show a non-symmetric case with the same parameters as in (A) except  $m_1 = 0.5$  and  $m_2 = 0.7$ . The black area indicates the parameter space where the population is driven to extinction because the maximal growth rates are too low. In the grey area some polymorphism can be maintained in the two-habitat population as long as the difference in the maximal growth rates are not too high. When this difference reaches a threshold polymorphism cannot be maintained and the single type that is maintained is more adapted to the good-quality habitat (the habitat with the highest maximal growth rate).

does not receive any migrant from the second population (the sink). For instance, when  $m_1 > 0$  and  $m_2 = 0$  there is no immigration in habitat 1. Note that this is a degenerate case. In contrast with the above analysis where both  $m_1$  and  $m_2$  are positive, we have to provide an analysis of ESS for each habitat separately. Moreover, the computation of the equilibrium in presence of mutations is slightly different because of this degeneracy (see the supplementary information Section A.2.2).

The evolutionary outcome in the first habitat is obvious because it depends only on selection acting in habitat 1: the ESS is  $-\theta$  and

$$N_1^* = \frac{r_{max,1} - m_1}{\kappa_1}. \quad (20)$$

Moreover, the population's phenotypic density  $n_{\varepsilon,1}^*$  can be computed explicitly:  $n_{\varepsilon,1}^* = N_{\varepsilon,1}^* f_\varepsilon$ , where  $N_{\varepsilon,1}^* = \frac{r_{max,1} - m_1 - \varepsilon \sqrt{U s_1}}{\kappa_1}$  and  $f_\varepsilon$  is the probability density of a normal distribution  $\mathcal{N}(-\theta, \frac{\varepsilon \sqrt{U}}{\sqrt{s_1}})$ .

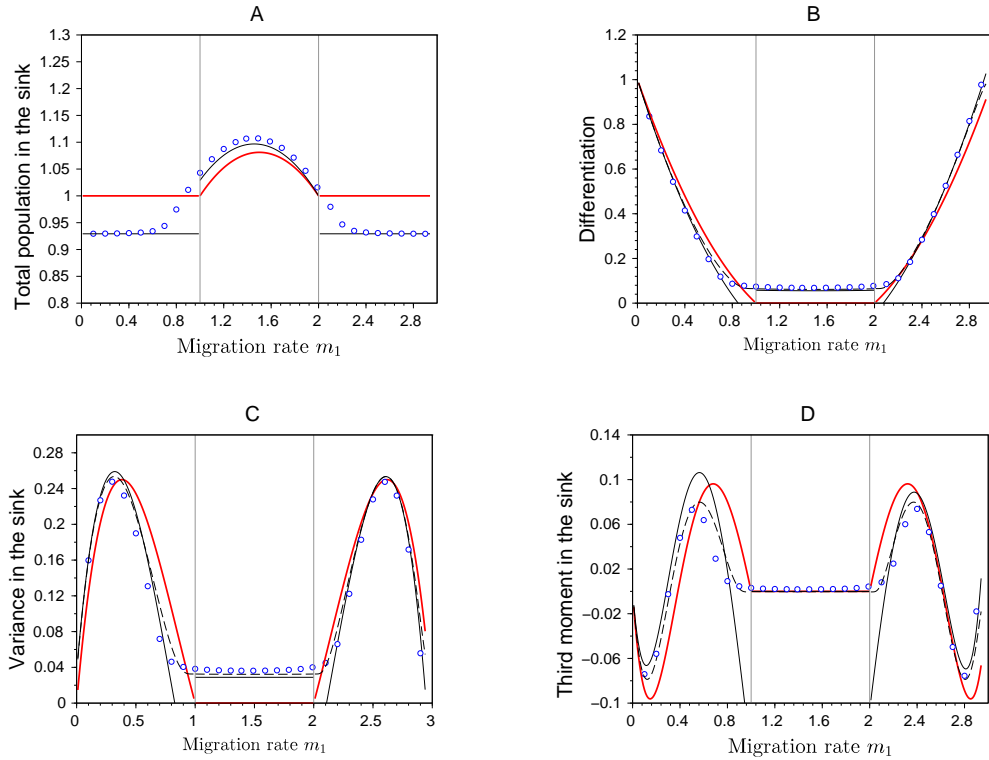
In habitat 2, the evolutionary outcome results from the balance between migration from habitat 1 and local selection. Interestingly, migration has a non-monotonic effect on adaptation in the sink (See Figure 6). Indeed, Figure 6A shows that the population size in the sink is maximized for intermediate values of migration. More migration from the source has a beneficial effect on the demography of the sink but it prevents local adaptation. Yet, when migration from the source becomes very large it limits the size of the population in the source (see (20)). This limits the influence of the source on the sink and can even promote adaptation to the sink. In fact, it is worth noting that differentiation between the two habitats can actually increase with migration (Figure 6B). The level of migration from the source that prevents local adaptation in the sink is given by the condition:

$$\frac{4s_2\theta^2 r_{\max,2}}{\kappa_2} \leq \frac{m_1(r_{\max,1} - m_1)}{\kappa_1}. \quad (21)$$

Indeed, when condition (21) is verified, the migration from the source overwhelms local selection and the evolutionary stable strategy in the sink is  $z^* = -\theta$ . In contrast, when condition (21) does not hold, the effective growth rate of the optimal trait  $\theta$  in the sink habitat is high enough to compete with the trait  $-\theta$  coming from the source, allowing coexistence between the two strategies. Note again that our two approximations (see supplementary information sections A.2.2.2 for the derivation of the *first approximation* and B.4 for the analytic formula for the moments of the phenotypic distribution derived from our *second approximation*) provide very good predictions for the moments of the phenotypic distribution in the sink (Figure 6).

## Discussion

The balance between selection, migration and mutation drives the dynamics of local adaptation in heterogeneous environments. Here we present a new theoretical approach to obtain accurate approximations for the equilibrium phenotypic densities in a two-habitat environment. This analysis goes beyond the Adaptive Dynamics framework because it allows us to account for the effect of large mutation rates. This analysis does not rely on the Gaussian approximation which underlies many



**Figure 6 – Effects of migration in a source-sink scenario on (A) the total population size in the sink habitat, (B) the differentiation between habitats, (C) the variance and (D) the third central moment of the phenotypic distribution in sink.** The dots refer to exact numerical computations when  $\varepsilon = 0.05$ , the red line indicates the case where  $\varepsilon = 0$  while the lines in black refer to our two approximations when  $\varepsilon = 0.05$  (dashed line for the *first approximation* and the full line for the *second approximation*). The vertical gray lines, at  $m_1 = 1$  and  $m_1 = 2$ , indicate the critical migration rates where transition occurs between monomorphism and dimorphism in the Adaptive Dynamics framework (see condition (21)). Note that both approximations predict the same total population size. Other parameter values:  $r_{\max,1} = 3$ ,  $r_{\max,2} = 1$ ,  $s_1 = 3$ ,  $s_2 = 2$ ,  $\kappa_1 = \kappa_2 = 1$ ,  $\theta = 0.5$ ,  $U = 1$ .

Quantitative Genetics models. Our analysis yields analytic approximations that help provide a good understanding of the balance between the different evolutionary forces in both *symmetric* and *non-symmetric* scenarios.

In the *symmetric* scenario we recover the classical results from Quantitative Genetics in a single population Lande 1975; Bürger 2000; Rice 2004 but expand this to spatially heterogeneous scenarios. In particular, we capture the emergence of differentiation between habitats when the migration rate

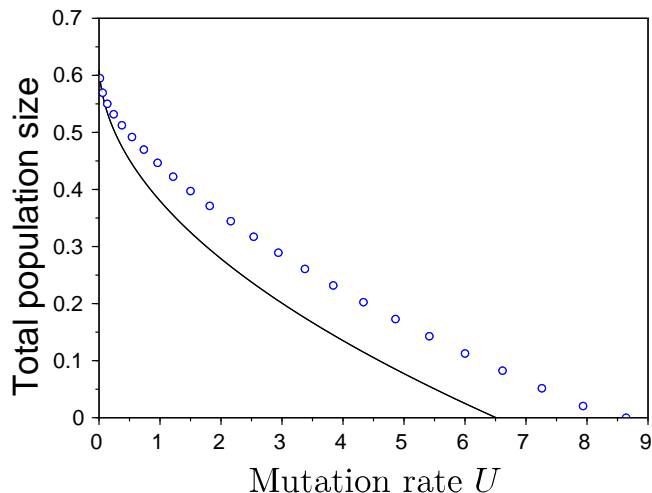
decreases. When migration is strong relative to selection, the stationary phenotypic density is unimodal in each habitat but heterogeneous selection increases phenotypic variance and differentiation (see (19) and Figure 4). When migration is close to the critical migration rate  $m_c$  (see condition (18)) we observe a shift between the phenotypic distributions of the two habitats. This pattern was not detected in previous studies but our method captures this shift and improves the approximation of the variance of the phenotypic distributions (see Débarre et al. 2013 and Figure 3). When the migration rate is much smaller than  $m_c$  and selection is sufficiently strong between habitats, the equilibrium distribution in each habitat can be well approximated as the sum of two distributions. But unlike previous approximations Yeaman and Guillaume 2009; Débarre et al. 2013 these two distributions are non-gaussian. We derive approximations for the moments of these distributions. In other words, this work generalises previous attempts to derive the distribution of a phenotypic trait at the mutation-selection-migration equilibrium. Our results confirm the importance of the skewness in the phenotypic distribution and improve predictions of measures of local adaptation in a heterogeneous environment.

In the *non-symmetric* scenario we show that the condition for the maintenance of two specialized strategies are more restrictive (Figure 5). Indeed, asymmetries promote a single strategy that is more locally adapted to the habitat with larger population size and/or lower immigration rate. The impact of biased migration rates from a source population into the adaptation of peripheral populations has been discussed before Holt and Gaines 1992; García-Ramos and Kirkpatrick 1997; Gomulkiewicz et al. 1999; Holt et al. 2003; Akerman and Bürger 2014. Our approach, however, yields a quantitative description of the shape of the phenotypic distributions in both the source and the sink habitats. These accurate predictions are key to understand the effect of different evolutionary forces on the level of adaptation in the two habitats. For instance, the analysis of an extreme case with source-sink dynamics reveals the complex interplay between migration, demography and local selection. The maintenance of a polymorphic equilibrium is possible when migration from the source is either very weak or very strong. This result challenges the classical prediction where migration is always an homogenizing force reducing the differentiation among populations (Figure 6).

Our work illustrates the potential of a new mathematical tool in the field of evolutionary biology. In this work, we use an approach based on Hamilton-Jacobi equations (see (A.22)) which has been developed, mostly by the mathematical community, during the last decade to describe the asymptotic solutions of the selection-mutation models, as the effect of mutation vanishes. We refer to Diekmann et al. 2005; Perthame and Barles 2008; Mirrahimi 2011 for the establishment of the basis of this approach. Note, however, that previous studies were mainly focused on the limit case where the effects of mutations are vanishingly small. In particular, they do not provide approximations of the phenotypic density and its moments when the effect of mutations,  $\varepsilon$ , is nonzero. In the present work we go further than the previous studies and characterize the phenotypic distributions when the influx of mutations can alter significantly the shape of the stationary distribution. Understanding the build up of this distribution is particularly important to study the effect of mutation on adaptation. Although mutation is the ultimate source of adaptive variation, the accumulation of deleterious mutations generates a load on the average fitness of populations. This is particularly relevant in organisms like RNA viruses which are characterized by very large mutation rates Drake and Holland 1999; Sanjuán et al. 2010. In fact, the mutation loads of RNA virus is so high that it may even lead some populations to extinction Bull et al. 2007; Martin and Gandon 2010. Our model can be used to accurately capture the effect of increasing mutation rates on the mutation load of a population living in a heterogeneous environment (Figure 7). This heterogeneity may be particularly relevant in chronic infections by pathogenic virus that can adapt to different organs Kemal et al. 2003; Sanjuán et al. 2004; Ducoulombier et al. 2004; Jridi et al. 2006. A better understanding of the phenotypic distribution at equilibrium in heterogeneous environments may thus provide more accurate prediction on the critical mutation rates that can ultimately lead within-host dynamics to pathogen extinction.

Our analysis of the equilibrium between selection, migration and mutation could be extended in several new directions. More than 2 habitats could be considered, or different growth rates and/or mutation kernels could be used (see Mirrahimi 2013 and the supplementary information, Section (A.3)). The approach could also be used to analyze situations away from the equilibrium. For instance, it would be possible to track the dynamics of the distribution as the population adapts to a new environment





**Figure 7** – Effect of increasing the mutation rate  $U$  on the total population size in the symmetric scenario used in Figure 3 with  $m = 0.5$ . The full line indicates the approximation and the dots are the results of exact numerical computations. This figure illustrates that our approximation given by the first line of (19) captures reasonably well the effect of large mutation rates on the mutation load in a two-habitat scenario where there is differentiation and some local adaptation.

or to a time-varying environment Lande and Shannon 1996. Hamilton-Jacobi equations have indeed also been used to study time-varying (but space homogeneous) environments (see for instance Mirrahimi et al. 2015; Figueroa Iglesias and Mirrahimi 2018). Finally, it is interesting to note that the generalization of the present ecological scenario to model the adaptation of sexual species in heterogeneous environments remains to be carried out. Our method could be extended to allow for sexual reproduction within the framework of the infinitesimal model (see Fisher 1919; Calvez et al. 2019). But this analysis falls beyond the scope of the present paper.

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