ADAPTATION OF AN ASEXUAL POPULATION WITH ENVIRONMENTAL CHANGES*

FLORIAN LAVIGNE**

Abstract. Because of mutations and selection, pathogens can manage to resist to drugs. However, the evolution of an asexual population (e.g., viruses, bacteria and cancer cells) depends on some external factors (e.g., antibiotic concentrations), and so understanding the impact of the environmental changes is an important issue.

This paper is devoted to model this problem with a nonlocal diffusion PDE, describing the dynamics of such a phenotypically structured population, in a changing environment. The large-time behaviour of this model, with particular forms of environmental changes (linear or periodically fluctuations), has been previously developed. A new mathematical approach (limited to isotropic mutations) has been developed recently for this problem, considering a very general form of environmental variations, and giving an analytic description of the full trajectories of adaptation.

However, recent studies have shown that an anisotropic mutation kernel can change the evolutionary dynamics of the population: some evolutive plateaus can appear. Thus the aim of this paper is to mix the two previous studies, with an anisotropic mutation kernel, and a changing environment. The main idea is to study a multivariate distribution of (2^n) “fitness components”. Its generating function solves a transport equation, and describes the distribution of fitness at any time.

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1. Introduction

In this paper, I focus on a phenotypic structured population model. In such models, we study the evolution of the distribution of phenotype q(t,x) (normalized to 1 with respect to phenotypes), where each coordinate of x = (x_1, ..., x_n) ∈ R^n is a biological trait. More specifically, let us consider the parabolic equation:

$$ \partial_t q(t,x) = \sum_{i=1}^{n} \frac{\mu_i^2}{2} \partial_{x_i} q(t,x) + \left[ r(x) - \tau(t) \right] q(t,x), \ t > 0, \ x \in \mathbb{R}^n, $$

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Univ Rouen Normandie, LMRS, UMR6085, 76000 Rouen, France.

** Corresponding author: florian.lavigne@univ-rouen.fr

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where \( \mu_i^2 > 0 \) are some fixed real coefficients, \( r \in C^\infty(\mathbb{R}^n, \mathbb{R}^n) \) is a regular function, called fitness, and the mean fitness (or mean growth rate) of the population at time \( t > 0 \) is defined by:

\[
\tau(t) = \int_{\mathbb{R}^n} r(x) q(t,x) \, dx.
\]

The mean growth rate \( \tau(t) \) describes the evolution of the global population size \( N(t) \), by \( N'(t) = \tau(t) N(t) \) at all time \( t > 0 \). Because of genetic adaptation, \( \tau(t) \) can become positive, and so this pathogen can manage to resist to pesticides or antibiotics (e.g., [20] and [29]) or to produce antineoplastic resistance\(^1\) (see [24] for more details). In such cases, the pathogenic organisms population is self-sustaining in the environment.

This equation, called replicator-mutator equation, can model some complex asexual population (as viruses, bacteria or some plants), under mutations and selection for strong mutation parameters \( \mu_i^2 \) [19, 25, 31]. The first term \( \sum_{i=1}^{n} \mu_i^2 \partial_{x_i} q(t,x) /2 \) is an approximation of mutation effects, while the second \( [r(x) - \tau(t)] q(t,x) \) represents the selection: if \( r(x) > \tau(t) \), the subpopulation will grow, whereas if \( r(x) < \tau(t) \), the subpopulation will go to extinction. Let us note that more complex models, based on integro-differential equations, have been developed [11, 16–19, 28, 31].

In the case of a unique biological trait, id est, \( n = 1 \), the fitness can be the phenotype itself [2, 17, 31], and so extinction can occur in finite time. If the fitness function is a quadratic function [3], according to the sign of the convexity of \( r(x) \), the population becomes extinct in finite time or its distribution of phenotype converges to a stationary Gaussian one. In the multidimensional case \( n \in \mathbb{N} \), some new phenomena can occur, as the appearance of some evolutive plateaus [19]. Under the Fisher’s Geometric Model (FGM; a single peak phenotype-fitness landscape) – which has shown promising potential when compared to empirical measures of fitness epistasis (see [30] for example) – the fitness function admits a unique optimum \( \mathbf{O} \in \mathbb{R}^n \) and decreases quadratically away from \( \mathbf{O} \):

\[
\forall \mathbf{x} \in \mathbb{R}^n, r(\mathbf{x}) = r_{\max} - \frac{\| \mathbf{x} - \mathbf{O} \|^2}{2},
\]

with \( \| \mathbf{x} \| = \sqrt{x_1^2 + \cdots + x_n^2} \) the standard Euclidian norm of \( \mathbf{x} = (x_1, \ldots, x_n) \in \mathbb{R}^n \), and \( r_{\max} > 0 \) is a given constant. Thus we can define the (relative Malthusian) fitness \( m(\mathbf{x}) \) by:

\[
\forall \mathbf{x} \in \mathbb{R}^n, m(\mathbf{x}) = r(\mathbf{x}) - r_{\max},
\]

the mean (relative Malthusian) fitness \( \overline{m} \) by:

\[
\forall t \geq 0, \overline{m}(t) = \tau(t) - r_{\max},
\]

and so the distribution of phenotype is a solution of:

\[
\partial_t q(t, \mathbf{x}) = \sum_{i=1}^{n} \frac{\mu_i^2}{2} \partial_{x_i} q(t, \mathbf{x}) + [m(\mathbf{x}) - \overline{m}(t)] q(t, \mathbf{x}), \quad t > 0, \quad \mathbf{x} \in \mathbb{R}^n. \tag{1.1}
\]

Because of some fluctuating external factors (e.g., pesticides or antibiotics concentrations), environmental changes can have important consequences on the evolution of the population. Some particular form of fluctuating environments have already been concerned. Some models [6–8] are based on Fisher-KPP reaction-diffusion equations, without adaptation, with a constant shifting speed. [1] has considered a linear change in a one dimensional phenotype and a one dimensional space variable, studying a parabolic equation as \( (1.1) \) in \( \mathbb{R}^2 \). When the fluctuations are periodic, different models and different methods have been proposed: approximation

\(^1\)Ability of cancer cells to survive despite the chemiotherapeutic pressure.
by Gaussian solutions [22], principal eigenvalue of a time-periodic parabolic operator on a bounded phenotypic space [9], Hamilton-Jacobi equations on \( \mathbb{R}^n \), assuming a small mutation parameter [5, 12–15, 23, 26], etc. In each cases, when the environment shift is linear with a constant low speed \( c \), then \( r \) has more chance to have a nonnegative limit and so the population ends to be adapted to the environment. When \( c \) is large enough, small and large enough mutation parameters can destabilize this phenomenon, and let the population going to extinction [1, 6]. [7, 8] have focused their study to the existence of traveling wave, depending on the form of the environmental change and so on the principal eigenvalue of the associated parabolic equation.

This paper is focused on the extension of the replicator-mutator model, taking into account of environmental changes (e.g., due to pesticides or antibiotics concentrations). More precisely, the optimum \( O \) and the selection coefficients (previously equal to \( 1/2 \)) are considered as time-dependent functions. Thus the fitness \( m(x) \) in (1.1) has to be changed into:

\[
\forall t \geq 0, \forall x = (x_1, \ldots, x_n) \in \mathbb{R}^n, \quad m(t, x) = -\sum_{i=1}^{n} \frac{s_i^2(t)}{2} (x_i - O_i(t))^2, \tag{1.2}
\]

where \( O(t) = (O_1(t), \ldots, O_n(t)) \) and \( s(t) = (s_1(t), \ldots, s_n(t)) \) depend continuously on time, such that for all \( i \in \{1, \ldots, n\} \), and all time \( t \), \( 0 \leq s_i(t) \leq \sqrt{2} \). Eq. (1.1) becomes:

\[
\partial_t q(t, x) = \sum_{i=1}^{n} \frac{\mu_i^2}{2} \partial_{x_i} q(t, x) + [m(t, x) - \overline{m}(t)] q(t, x), \quad t > 0, \quad x \in \mathbb{R}^n, \tag{1.3}
\]

with:

\[
\overline{m}(t) = \int_{\mathbb{R}^n} m(t, x) q(t, x) \, dx.
\]

In a bounded phenotypic domain, the population goes to extinction if and only if the principal eigenvalue of the parabolic operator is positive (see [9] for more details of the influence of parameters on the eigenvalue, in periodic shift). The aim of this paper is:

(i) to consider very general impact of environmental variations (constant shifting speed, periodically, etc.) on parameters, while [27] assumes one directional variations of \( O \), and none variations of \( s \);

(ii) to consider unbounded phenotypic space, i.e., \( x \in \mathbb{R}^n \), while the bounded case can be solved thanks to principal eigenvalue method [9];

(iii) to make no assumption about the anisotropy of mutations effects, which can imply some evolutive plateaus (see [19] for the static optimum case);

(iv) to give an analytic description of the full trajectories of adaptation.

Section 2 is devoted to present main results: standard existence and uniqueness results and a general formula for \( \overline{m} \) (see Sect. 2.1), and different examples of the impact of environment on the optimum and on the selection coefficients. All proofs are postponed in Section 4.

Let us remark that the following results do not need assumption on the dimension (here, \( n \in \mathbb{N} \)), and Gaussian solution assumption. The method is based on the study of a multivariate distribution of a fitness components vector (e.g., [19, 27]) satisfying a degenerate parabolic equation. Its multidimensional cumulant generating function solves a transport equation, and so the explicit formula \( \overline{m} \) can be deduced.

2. MAIN RESULTS

This section is devoted to find an explicit formula for \( \overline{m}(t) \) at all time \( t \), and so find some criteria on biological parameters \( (\mu_i, s_i, O_i, \text{etc.}) \) for the persistence (case of \( r_{\text{max}} > -\overline{m}(\infty) \)) or extinction (case of \( r_{\text{max}} \leq -\overline{m}(\infty) \)).
2.1. The time-dependent problem

Well-posedness of the phenotypic Cauchy problem (1.3)

This differential problem admits a unique solution with the following assumptions on the initial distribution $q_0$:

(i) For some $\alpha \in (0, 1)$, $\|q_0\|_{C^{2+\alpha}(\mathbb{R}^n)} < +\infty$, i.e.:

$$q_0 \in C^{2+\alpha}(\mathbb{R}^n);$$

(ii) The function $q_0$ is a probability distribution:

$$\int_{\mathbb{R}^n} q_0(x) dx = 1;$$

(iii) There exists a function $g : \mathbb{R}_+ \to \mathbb{R}_+$ (with $\mathbb{R}_+ = [0, +\infty)$) such that:

$$g$$

is non-increasing, $0 \leq q_0 \leq g(\| \cdot \|)$ in $\mathbb{R}^n$,

$$\forall b > 0, x \mapsto \exp(b\|x\|)g(\|x\|)$$

is bounded in $\mathbb{R}^n$

and $\int_{\mathbb{R}^n} \exp(b\|x\|)g(\|x\|) dx < +\infty.$

These assumptions are made throughout the paper, and are therefore not repeated in the statements of the results below.

By the same arguments as in [19], the distribution of phenotype is well-defined: the Cauchy problem admits a unique solution.

Theorem 2.1. [4, 10] There exists a unique nonnegative solution $q \in C^{1,2}(\mathbb{R}_+ \times \mathbb{R}^n)$ of:

$$\begin{cases}
\partial_t q(t, x) &= \sum_{i=1}^n \mu_i^2 \partial_{x_i} q(t, x) + [m(t, x) - \overline{m}(t)] q(t, x), \quad t \geq 0, \ x \in \mathbb{R}^n, \\
q(0, x) &= q_0(x), \ x \in \mathbb{R}^n,
\end{cases}$$

such that $q \in L^\infty((0, T) \times \mathbb{R}^n)$ for all $T > 0$, and the function:

$$t \mapsto \overline{m}(t) = \int_{\mathbb{R}^n} m(t, x) q(t, x) dx,$$

is real-valued and continuous in $\mathbb{R}_+$. Moreover, for all $t \geq 0$, $q(t, \cdot)$ is a probability distribution, i.e.:

$$\int_{\mathbb{R}^n} q(t, x) dx = 1.$$

As in [19], we can find some explicit solutions under strong hypothesis on parameters and the initial condition of (2.4). An example is developed in the following corollary:
Corollary 2.2. Assume that the initial distribution of phenotype is Gaussian, that is,

$$\forall \mathbf{x} = (x_1, \ldots, x_n) \in \mathbb{R}^n, \quad q_0(\mathbf{x}) = (2\pi)^{-n/2} \left( \prod_{i=1}^{n} \sigma_i^0 \right)^{-1/2} \exp \left[ -\sum_{i=1}^{n} \frac{(x_i - \bar{x}_i^0)^2}{2\sigma_i^0} \right], \quad (2.5)$$

for some parameters $\bar{x}_i^0 \in \mathbb{R}$ and $\sigma_i^0 > 0$, for all $1 \leq i \leq n$ and that:

$$\forall t > 0, \forall i \in \{1, \ldots, n\}, s_i(t) = 1.$$

Then the solution $q(t, \mathbf{x})$ of the Cauchy problem (2.4) is Gaussian at all time:

$$\forall t \geq 0, \forall \mathbf{x} \in \mathbb{R}^n, \quad q(t, \mathbf{x}) = (2\pi)^{-n/2} \left( \prod_{i=1}^{n} \sigma_i(t) \right)^{-1/2} \exp \left[ -\sum_{i=1}^{n} \frac{(x_i - \bar{x}_i(t))^2}{2\sigma_i(t)} \right], \quad (2.6)$$

with:

$$\forall 1 \leq i \leq n, \quad \bar{x}_i(t) = \frac{\mu_i \bar{x}_i^0}{\mu_i \cosh(\mu_i t) + \sigma_i^0 \sinh(\mu_i t)} + \mu_i \int_{0}^{t} O_i(\tau) \frac{\mu_i \sinh(\mu_i \tau) + \sigma_i^0 \cosh(\mu_i \tau)}{\mu_i \cosh(\mu_i \tau) + \sigma_i^0 \sinh(\mu_i \tau)} \, d\tau,$$

and

$$\forall 1 \leq i \leq n, \quad \sigma_i(t) = \mu_i \frac{{\mu_i} \sinh(\mu_i t) + \sigma_i^0 \cosh(\mu_i t)}{{\mu_i} \cosh(\mu_i t) + \sigma_i^0 \sinh(\mu_i t)}, \quad (2.7)$$

Moreover, we have:

$$\bar{m}(t) = -\sum_{i=1}^{n} \frac{[\bar{x}_i(t) - O_i(t)]^2 + \sigma_i(t)}{2}.$$

The framework presented in [19] uses the fitness components vector $\mathbf{m}(\mathbf{x}) = (m_1(\mathbf{x}), \ldots, m_n(\mathbf{x}))$ with the component $m_i(\mathbf{x}) = -x_i^2/2$, to describe the adaptive evolution. As an important quantity is the mean fitness $\bar{m}(t)$, [19] have studied the distribution of the fitness components $p(t, \mathbf{m})$, which is the pushforward measure of the measure $q(t, \mathbf{x}) d\mathbf{x}$ by the function $\mathbf{x} \mapsto \mathbf{m}(\mathbf{x})$, and more explicitly by the relation:

$$\forall \mathbf{m} = (m_1, \ldots, m_n) \in \mathbb{R}^n, \quad p(t, \mathbf{m}) = \frac{2^{-n/2}}{\sqrt{|m_1 \cdots m_n|}} \sum_{\varepsilon = (\varepsilon_1, \ldots, \varepsilon_n) \in \{\pm 1\}^n} q(t, \mathbf{x}^\varepsilon(\mathbf{m})), \quad (2.8)$$

with $\mathbf{x}^\varepsilon(\mathbf{m}) = (\varepsilon_1 \sqrt{-2m_1}, \ldots, \varepsilon_n \sqrt{-2m_n}) \in \mathbb{R}^n$. While (1.1) is quadratic into the biological traits $x_1, \ldots, x_n$, the equation satisfied by $p(t, \mathbf{m})$ is linear with respect to the vector $\mathbf{m}$, and so the generating functions of $p$ are classical solutions of first order PDE. In the case of a mobile optimum, with anisotropic mutation effects, it seems impossible to find a closed PDE satisfied by $p$, because of the time-dependence of the term $m(t, \mathbf{x})$. This framework cannot be directly applied in this more general case and has to be adapted here.

**A fitness vector and a degenerate parabolic PDE satisfied by $\mathbf{u}(t, \mathbf{v})$**

I define a new transformed fitness components vector $\mathbf{v} = (v_1, v_2, \ldots, v_{2n}) \in \mathbb{R}^{2n}$ by:

$$\forall i \in \{1, \ldots, n\}, \forall \mathbf{x} = (x_1, \ldots, x_n) \in \mathbb{R}^n, \quad v_{2i-1}(\mathbf{x}) = x_i \in \mathbb{R}, \quad \text{and} \quad v_{2i}(\mathbf{x}) = -\frac{x_i^2}{2} \in \mathbb{R}_-, \quad (2.9)$$
such that its joint distribution $u(t, v)$ is the pushforward measure of the measure $q(t, x) \, dx$ by the map $x \mapsto (x_1, -x_1^2/2, x_2, \ldots, -x_n^2/2) \in \Gamma_{2n}$ where $\Gamma_{2n}$ is a submanifold of $\mathbb{R}^{2n}$ defined by:

$$\Gamma_{2n} = \{(y_1, \ldots, y_{2n}) \in \mathbb{R}^{2n}, \forall i \in \{1, \ldots, n\}, y_{2i} = -\frac{y_{2i-1}^2}{2}\}.$$

**Proposition 2.3.** For all $t \geq 0$ and $v = (v_1, \ldots, v_{2n}) \in \Gamma_{2n}$, there holds:

$$u(t, v) = q(t, x(v)), \quad (2.8)$$

where the variable change $x(v)$ is defined by $x(v) = (v_1, v_3, \ldots, v_{2n-1})$. Furthermore, we have:

$$\forall t \geq 0, \int_{\Gamma_{2n}} u(t, v) \, dv = 1 \quad \text{and} \quad \overline{m}(t) = -\sum_{i=1}^{n} \frac{s_i^2(t)O_i^2(t)}{2} + \int_{\Gamma_{2n}} \alpha(t) \cdot v \, u(t, v) \, dv, \quad (2.9)$$

where all above integrals are convergent, and with:

$$\alpha = (s_1^2O_1, s_1^2O_2, s_2^2O_2, \ldots, s_n^2O_n, s_n^2) \in C(\mathbb{R}_+, \mathbb{R}^{2n}).$$

As $p$ in the static environment case, the distribution $u$ satisfies a nonlocal degenerate parabolic equation on the submanifold $\Gamma_{2n}$:

**Theorem 2.4.** The distribution function of the fitness components $u$ is a classical $C^{1,2}(\Gamma_{2n})$ solution of:

$$\partial_t u(t, v) = \sum_{i=1}^{n} \frac{\mu_i^2}{2} \left[ \partial_{v_{2i-1}v_{2i-1}} u(t, v) - \partial_{v_{2i}} u(t, v) - 2v_{2i-1} \partial_{v_{2i-1}v_{2i}} u(t, v) + v_{2i-1}^2 \partial_{v_{2i}v_{2i}} u(t, v) \right] + \left[ \alpha(t) \cdot v - \tau(t) \right] u(t, v), \quad (2.10)$$

for $t \geq 0$ and $v \in \Gamma_{2n}$, with initial condition:

$$u_0(v) = q_0(x(v)), \quad (2.11)$$

and:

$$\forall t \geq 0, \quad \tau(t) = \overline{m}(t) + \sum_{i=1}^{n} \frac{s_i^2(t)O_i^2(t)}{2} = \int_{\Gamma_{2n}} \alpha(t) \cdot v \, u(t, v) \, dv. \quad (2.12)$$

Let us note that the partial derivatives of $u$, appearing in (2.10), are defined thanks to the Lie derivative. More precisely, each term of the right hand side sum is the second derivative with respect to the tangent direction of the function $u$, where all $v_j$ with $j \notin \{2i-1, 2i\}$ are fixed.

**Generating functions**

I define the moment generating functions (MGFs) $M_u$ of $u$ and its logarithm – the cumulant generating function (CGF) – $C_u$ by:

$$M_u(t, z) = \int_{\Gamma_{2n}} e^{z \cdot v} u(t, v) \, dv, \quad \text{and} \quad C_u(t, z) = \log M_u(t, z), \quad (2.13)$$
for $t \geq 0$, $z \in \mathbb{R}_+^n$. The aim of using $C_u$, instead of $u$ (or $q$), is finding a transport equation, which has explicit solutions at all time $t$, whereas the previous equations are second order equations:

**Theorem 2.5.** The cumulant generating function $C_u$ of $u$ is well-defined, and a classical $C^{1,1}(\mathbb{R}_+ \times \mathbb{R}_+^n)^2$ solution of:

$$
\begin{cases}
\partial_t C_u(t, z) = [\alpha(t) + V(z)] \cdot \nabla C_u(t, z) - \nu(t) + \gamma(z), & t \geq 0, \ z \in \mathbb{R}_+^n, \\
C_u(0, z) = C_{u_0}(z), & z \in \mathbb{R}_+^n,
\end{cases}
$$  \tag{2.14}

where:

$$
\alpha(t) = (s_1^2(t)O_1(t), s_2^2(t), \ldots, s_n^2(t)O_n(t), s_n^2(t)), \quad V(t) = \alpha(t) \cdot \nabla C_u(t, 0),
$$

$$
\nu(t)(z) = \left(-\mu_1^2z_{21} - \mu_1^2z_{22} - \mu_1^2z_{34}, \ldots, -\mu_1^2z_{22n-1}z_{2n}, -\mu_1^2z_{2n}^2\right),
$$

$$
\text{and } \gamma(z) = \sum_{i=1}^n \frac{\mu_i^2}{2} (z_{2i-1} - z_{2i}),
$$  \tag{2.15}

and $\nabla C_u(t, z)$ denotes the gradient of $C_u$ with respect to the variable $z$.

Classic methods yield an explicit formula for the solution $C_u$ of (2.14), and so for $m(t)$ at all time $t > 0$, for all kind of smooth initial distribution $\varphi_0$. Let us define $\varphi[\cdot; f, \tau_0]$ the smooth solution of the Riccati equation:

$$
\begin{cases}
\varphi'(\tau) = -f(\tau) + \varphi^2(\tau), & \tau \in \mathbb{R}, \\
\varphi(\tau_0) = 0,
\end{cases}
$$

for $f$ a continuous function and $\tau_0 \in \mathbb{R}$ an initial condition.

**Proposition 2.6.** I define for all $i \in \{1, \ldots, n\}$:

$$
\forall t > 0, \ z = (z_1, \ldots, z_{2n}) \in \mathbb{R}_+^n, \ y_{2i}(t, z) = \frac{1}{\mu_i^2} \varphi\left[t; \mu_i^2 s_i^2, t + z_{2i}\right] \quad \text{and}
$$

$$
y_{2i-1}(t, z) = \Phi(t, z) \left[z_{2i} - z_{2i-1} + \int_t^{t+z_{2i}} \frac{s_i^2(\tau)O_i(\tau)}{\Phi(\tau, t, z)} \ d\tau \right],
$$

where:

$$
\Phi(\tau, t, z) = \exp\left[\mu_i^2 \int_0^\tau y_{2i}[\zeta, z + (t - \zeta)1] \ d\zeta\right],
$$

and $1 = (1, \ldots, 1) \in \mathbb{R}_+^{2n}$. Then the mean fitness at time $t \geq 0$ is equal to:

$$
\bar{m}(t) = -\sum_{i=1}^n \frac{s_i^2(t)O_i^2(t)}{2} + \int_0^t \sum_{i=1}^{2n} \partial_{\tau_i} y(t - \tau, 1) \cdot \nabla \gamma[\Psi(\tau, t)]d\tau + \sum_{i=1}^{2n} \partial_{\tau_i} y(0, 1) \cdot \nabla C_{u_0}[\Psi(t, t)],
$$  \tag{2.16}

with $\Psi(\tau, t) = y(t - \tau, \tau 1)$, for all $0 \leq \tau \leq t$.

Because of the complexity of the formula, I have chosen to develop two subcases (constant selection coefficients and constant optimum) in the following sections.

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2This means that the partial derivatives of $C_u$ with respect to the variables $t$ and $z$ exist and are continuous in $\mathbb{R}_+ \times \mathbb{R}_+^n$. 
2.2. Examples of environmental impact on the optimum

In this Section, I make the hypothesis that the functions $s_i$ are all constant. As for constant $f$:

$$g(t; f, \tau_0) = \sqrt{f} \tanh[\sqrt{f}(\tau_0 - \tau)]$$

let the function $y = (y_1, \ldots, y_{2n})$ defined by:

$$\forall i \leq n, \forall t > 0, \forall z \in \mathbb{R}^{2n},$$

$$y_{2i-1}(t, z) = \frac{\cosh[\mu_i s_i (t + z_{2i})]}{\cosh[\mu_i s_i z_{2i}]} \left[ z_{2i} - z_{2i-1} + s_i^2 \int_0^{t+z_{2i}} O_i(\tau) \frac{\cosh[\mu_i s_i (t - \tau + z_{2i})]}{\cosh[\mu_i s_i (t + z_{2i})]} d\tau \right],$$

$$y_{2i}(t, z) = \frac{s_i \tanh[\mu_i s_i z_{2i}]}{\mu_i}.$$  

As for all $0 \leq \tau \leq t$ and $z \in \mathbb{R}^{2n}$, we get that:

$$\partial_{z_{2i}} y_{2i}(t, \tau, 1) = s_i^2 [1 - \tanh^2[\mu_i s_i \tau]]$$

and:

$$(\partial_{z_{2i}} + \partial_{z_{2i-1}}) y_{2i-1}(t, \tau, 1) = \frac{s_i^2 O_i(t)}{\cosh[\mu_i s_i \tau]} + \mu_i s_i^3 \int_{t-\tau}^t O_i(\zeta) \frac{\sinh[\mu_i s_i (t - \zeta)]}{\cosh^2[\mu_i s_i \tau]} d\zeta,$$

Proposition 2.6 yields that:

**Proposition 2.7** (Mean fitness with constant selection coefficients $s_i$). The mean fitness is given by, for all $t \geq 0$:

$$\bar{m}(t) = -\sum_{i=1}^n \frac{s_i^2}{2} \left[ O_i(t) - \mu_i s_i \int_0^t O_i(\tau) \frac{\sinh[\mu_i s_i \tau]}{\cosh[\mu_i s_i \tau]} d\tau \right]^2 - \sum_{i=1}^n \frac{\mu_i s_i}{2} \tanh[\mu_i s_i t]$$

$$+ \sum_{i=1}^n s_i^2 \left[ O_i(t) - \mu_i s_i \int_0^t O_i(\tau) \frac{\sinh[\mu_i s_i \tau]}{\cosh[\mu_i s_i \tau]} d\tau \right] \frac{\partial_{z_{2i-1}} C_{\bar{u}_0}(\psi(t))}{\cosh[\mu_i s_i \tau]}$$

$$+ \sum_{i=1}^n s_i^2 \left[ 1 - \tanh^2[\mu_i s_i t] \right] \partial_{z_{2i}} C_{\bar{u}_0}(\psi(t)), \quad (2.17)$$

with:

$$\psi(t) = \left( s_1 \int_0^t O_1(\tau) \frac{\cosh[\mu_1 s_1 (t - \tau)]}{\cosh[\mu_1 s_1 t]} d\tau, s_1 \tanh[\mu_1 s_1 t], \ldots, s_n \int_0^t O_n(\tau) \frac{\cosh[\mu_n s_n (t - \tau)]}{\cosh[\mu_n s_n t]} d\tau, s_n \tanh[\mu_n s_n t] \right) \in \mathbb{R}^{2n}.$$  

Because of the form of the formula (2.17), the long time behaviour of the mean fitness $\bar{m}$ is clearly equal to the sum of the long time behaviour of each mean fitness component $\bar{m}_i$ defined by:

$$\forall t \geq 0, \forall i \in \{1, \ldots, n\}, \quad \bar{m}_i(t) := -\frac{s_i^2}{2} \left[ O_i(t) - \mu_i s_i \int_0^t O_i(\tau) \frac{\sinh[\mu_i s_i \tau]}{\cosh[\mu_i s_i \tau]} d\tau \right]^2 - \frac{\mu_i s_i}{2} \tanh[\mu_i s_i t].$$

Let us develop different examples of $\bar{m}_i$ (which is equivalent to study the unidimensional case):

**Proposition 2.8.** Let $i \in \{1, \ldots, n\}$.  

1. If $O_i$ shifts slowly, i.e., either $O_i$ converges to $O_i(\infty)$ or $O_i$ is increasing and concave (but not linear), then:

$$m_i(\infty) := \lim_{t \to +\infty} m_i(t) = -\frac{\mu_i s_i}{2}.$$ 

2. If $O_i$ is time linear, i.e., there exists $c_i \in \mathbb{R}$ such that $O_i = c_i t$, $m_i$ converges with:

$$m_i(\infty) := \lim_{t \to +\infty} m_i(t) = -\frac{c_i^2}{2\mu_i^2} - \frac{\mu_i s_i}{2}.$$ 

3. If the variations of $O_i$ are too strong – more precisely if $O_i$ is increasing and convex (but not linear) – then the function $m_i$ diverges to $-\infty$ as $t$ tends to $+\infty$.

We retrieve the results presented by [27], where the mutation is isotropic, and the selection coefficients are all equal to 1. More specifically, when $O_i(t) = t^\alpha$, $\alpha > 1$ implies that the adaptation can never occur, whereas $\alpha < 1$ yields that the persistence condition is the same as in the static case.

**Remark 2.9.** As the population growth rate $r(t)$ is equal to $r(t) = r_{\text{max}} + m(t)$, for $r_{\text{max}} > 0$ a fixed constant corresponding of the growth rate at the phenotypic optimum, given by the Fisher’s Geometric Model. The population will go to resist of the biological pressure (antibiotics, pesticides, etc.), if $r(\infty) := \lim_{t \to +\infty} r(t) > 0$. Therefore Proposition 2.8 yields that:

1. If each $O_i$ shifts slowly, then the mean growth rate converges to the same limit as in the static case:

$$r(\infty) = r_{\text{max}} - \sum_{i=1}^{n} \frac{\mu_i s_i}{2}.$$ 

In this case, the evolutionary rescue occurs if and only if:

$$r_{\text{max}} \geq \sum_{i=1}^{n} \frac{\mu_i s_i}{2}.$$ 

When the mutation parameters are too strong, then the population goes to extinction because of strong mutations: this well-known phenomenon is called *lethal mutagenesis* (e.g., [19, 21, 25, 27]).

2. If $O_i$ shifts slowly for $i \in I \subset \{1, \ldots, n\}$, and linearly for $i \in J := \{1, \ldots, n\} \setminus I$, then the mean growth rate tends to:

$$r(\infty) = r_{\text{max}} - \sum_{j \in J} \frac{c_j^2}{2\mu_j^2} - \sum_{i=1}^{n} \frac{\mu_i s_i}{2},$$ 

and so the population can survive if and only if:

$$r_{\text{max}} \geq \sum_{j \in J} \frac{c_j^2}{2\mu_j^2} + \sum_{i=1}^{n} \frac{\mu_i s_i}{2}.$$ 

Here, an additional term appears compared to the static case, because of the optimum movement: this term is called "lag load" [27]. It depends only on the shifting vector $(c_j)_{j \in J}$ and the mutation parameters $(\mu_j)_{j \in J}$, but not on the selection coefficients $(s_i)_{1 \leq i \leq n}$. Thus the linear environmental changes penalize
the rescue criterion, but the mutation parameters can help the distribution of phenotype to follow the optimum shifting.

3. If one $O_i$ is increasing and convex (but not linear), then the population is maladapted to the environment at each time $t \geq 0$, and goes to extinction.

Previously, the environmental shift is assumed monotonic. Let us turn to the case of a $p$-periodic function $O$ (with $p > 0$), because of periodic external factors (antibiotics concentration, temperature, light, etc.). Let us remark that for all time $t = pN + \varepsilon$, with $N \in \mathbb{N}$ and $0 \leq \varepsilon < p$:

\[
\int_0^t O_i(\tau) \frac{\sinh[\mu_i s_i (\tau + \varepsilon)]}{\cosh[\mu_i s_i \varepsilon]} d\tau = \int_0^\varepsilon O_i(\tau) \frac{\sinh[\mu_i s_i (\tau + pN)]}{\cosh[\mu_i s_i t]} d\tau + \sum_{j=0}^{N-1} \int_0^p O_i(\tau) \frac{\sinh[\mu_i s_i (\tau + pj)]}{\cosh[\mu_i s_i t]} d\tau,
\]

which converges as $N \to +\infty$. Thus the large time behaviour of the mean fitness is:

**Proposition 2.10.** If $O$ is $p$-periodic, for some $p \in \mathbb{R}_+^*$, the mean fitness $\overline{m}(t)$ is asymptotically equivalent to the $p$-periodic function defined by:

\[
\forall t \in [0, p],
\overline{m}_\infty(t) = -\sum_{i=1}^n \frac{s_i^2}{2} \left[ O_i(t) - \mu_i s_i \int_0^t O_i(\tau)e^{\mu_i s_i (\tau - t)} d\tau - \frac{\mu_i s_i \exp[-\mu_i s_i p/2]}{2\sinh[\mu_i s_i p/2]} \int_0^p O_i(\tau)e^{\mu_i s_i (\tau - t)} d\tau \right]^2 - \sum_{i=1}^n \frac{\mu_i s_i}{2},
\]

as $t \to +\infty$. The average value over a period tends to:

\[
\langle \overline{m}_\infty \rangle := \frac{1}{p} \lim_{t \to +\infty} \int_t^{t+p} \overline{m}(\tau) d\tau = -\sum_{i=1}^n \frac{s_i^2}{2p} \int_0^p \left[ \int_0^\tau O_i'(\tau) \cosh[\mu_i s_i \tau] d\tau \right]^2 d\tau - \sum_{i=1}^n \frac{\mu_i s_i}{2},
\]

if $O \in C^1(\mathbb{R}_+, \mathbb{R}^n)$.

When the shift is periodic, the “lag load” is more complex than the previous cases. It is null if and only if for all $i \in \{1, \ldots, n\}$:

\[
\forall t \in [0, p], \quad \int_0^t O_i'(\tau) \cosh[\mu_i s_i \tau] d\tau = 0,
\]

which is equivalent to $O'_i(t) = 0$ for all $t$, and so to the static case. Even a little periodic disturbance of the static case will imply a decrease of the mean asymptotic average of $\overline{m}$ over a period.
Case of an elliptic movement

Let us see an explicit example of periodic function $O$, with $n = 2$. I assume that the optimum moves on an ellipsoid $p$-periodically:

$$\forall t > 0, \quad O(t) = \left[ a \cos \left( \frac{2\pi t}{p} \right), b \sin \left( \frac{2\pi t}{p} \right) \right],$$

with $p > 0$. Proposition 2.10 implies that $m$ is asymptotically equivalent to:

$$m_\infty(t) = -2s_1^2a^2\pi^2 \left[ \frac{2\pi \cos[2\pi t/p] - \mu_1 s_1 p \sin[2\pi t/p]}{4\pi^2 + \mu_1^2 s_1^2 p^2} \right]^2 - 2s_2^2b^2\pi^2 \left[ \frac{2\pi \sin[2\pi t/p] + \mu_2 s_2 p \cos[2\pi t/p]}{4\pi^2 + \mu_2^2 s_2^2 p^2} \right]^2 - \frac{\mu_1 s_1 + \mu_2 s_2}{2},$$

and the average mean fitness over a period tends to:

$$\langle m_\infty \rangle = -a^2 \frac{s_1^2 \pi^2 p}{4\pi^2 + \mu_1^2 s_1^2 p^2} - b^2 \frac{s_2^2 \pi^2 p}{4\pi^2 + \mu_2^2 s_2^2 p^2} - \frac{\mu_1 s_1 + \mu_2 s_2}{2}.$$

If $a$ is fixed, the value $\langle m_\infty \rangle$ is maximal when $b$ is null: the population has more chance to survive to the environmental changes when the optimum is shifting on only one direction, and so oscillate on a segment. I conclude this example remarking that $\langle m_\infty \rangle$ is constant according to $(a, b)$ on the ellipsoid:

$$\mathcal{E}_R := \left\{ (a, b) \in \mathbb{R}^2, \quad a^2 \frac{s_1^2 \pi^2 p}{4\pi^2 + \mu_1^2 s_1^2 p^2} + b^2 \frac{s_2^2 \pi^2 p}{4\pi^2 + \mu_2^2 s_2^2 p^2} = R^2 \right\},$$

for $R > 0$.

2.3. Examples of environmental impact on selection coefficients

Let us turn to study the consequences of variations of the selection coefficients $s_1, \ldots, s_n$, and so I make the assumption that $O$ is constant (and so equal to $(0, \ldots, 0) \in \mathbb{R}^n$). Therefore, the terms $y_{2i-1}(t, \tau)$ for $i \in \{1, \ldots, n\}$ and for all $t > \tau > 0$ are all null, and (2.16) yields that:

**Proposition 2.11.** If the optimum is constant over time, then the mean fitness is equal to:

$$\overline{m}(t) = -\sum_{i=1}^{n} \mu_i^2 s_i^2(t) \left[ \frac{1}{2} e^2 f_{i0}^t e_{i}(\zeta) d\zeta \right] + \sum_{i=1}^{n} \left[ e^2 f_{i0}^t e_{i}(\zeta) d\zeta \right]^{\mu_i^2 s_i^2(t)} \partial_{\zeta^2} C_{u_i} \psi(t),$$

with $\psi(t) = \phi[\zeta; \mu_i^2 s_i^2, -1]$ and:

$$\psi(t) = \left( 0, \frac{\phi_t(0)}{\mu_1^2} - \frac{\phi_t(t)}{\mu_1^2} e^2 f_{i0}^t e_{i}(\zeta) d\zeta, \ldots, 0, \frac{\phi_n(0)}{\mu_n^2} - \frac{\phi_n(t)}{\mu_n^2} e^2 f_{n0}^t e_{n}(\zeta) d\zeta \right) \in \mathbb{R}^n.$$
Proof. This is a direct consequence of the form of the Riccati equation solution and so:

\[ \mu_i^2 y_{21}(t, z) = g_i(t) - \frac{g_i(t + z_{2i}) \exp \left[ 2 \int_0^t g_i(\tau) d\tau \right]}{\exp \left[ 2 \int_0^{t + z_{2i}} g_i(\tau) d\tau \right] - g_i(t + z_{2i}) \int_t^{t + z_{2i}} \exp \left[ 2 \int_0^\tau g_i(\zeta) d\zeta \right] d\tau}. \]

The choice of \( \varrho_i \) can be relaxed: any solution of \( \varrho_i'(\tau) = \varrho_i^2(\tau) - \mu_i^2 \), such that for all \( t \geq 0 \):

\[ e^{2 \int_0^t \varrho_i(\tau) d\tau} \neq \varrho_i(t) \int_0^t e^{2 \int_0^\tau \varrho_i(\zeta) d\zeta} d\tau, \]

can be used. Let us illustrate the previous result with an example of selection coefficient variations:

**Proposition 2.12** (Monotonic selection coefficients). Let \( s_i \) nonnegative monotonic functions, for all \( i \in \{1, \ldots, n\} \), and converging to \( s_{\infty,i} \in (0, \sqrt{2}] \). The mean fitness converges to:

\[ m_{\infty} = - \sum_{i=1}^n \frac{\mu_i s_{\infty,i}}{2}, \]

as \( t \) tends to \( +\infty \).

Proposition 2.12 means that when the environment “tends to” a static state, then the mean fitness tends to the same limit value as in the case of constant coefficients \( (s_{\infty,1}, \ldots, s_{\infty,n}) \in (0, \sqrt{2}]^n \). For example, when for all \( i \in \{1, \ldots, n\} \) the selection coefficients and mutation parameters satisfy:

\[ \forall t > 0, \quad s_i(t) = \frac{1}{\mu_i} \sqrt{C^2 + \frac{2C}{(t + K)}}, \]

with \( C \in (0, \sqrt{2} \mu_i] \) and \( K = 1 - \frac{2}{C} \), the mean fitness \( m(t) \) at time \( t \) is given by:

\[ m(t) = - \sum_{i=1}^n \frac{1}{2} \left[ C^2 + \frac{2C}{t + K} \right] \int_0^t \frac{e^{2C\tau}}{(K + \tau)^2} d\tau + \int_0^t \frac{e^{2C\tau}}{(K + \tau)^2} \left( C + \frac{1}{K + \tau} \right) \int_0^t \frac{e^{2C\tau}}{(K + \tau)^2} d\tau \]

\[ + \sum_{i=1}^n \left[ C^2 + \frac{2C}{t + K} \right] \int_0^t \frac{e^{2C\tau}}{(K + \tau)^2} d\tau \]

\[ \left[ \frac{e^{2Ct}}{(K + t)^2} + \left( C + \frac{1}{K + t} \right) \int_0^t \frac{e^{2C\tau}}{(K + \tau)^2} d\tau \right]^2 \frac{\partial_{z_{2i}} C_{u_0[\psi(t)]}}{2}, \]

with \( \psi \) given by Proposition 2.11. This function converges to \(-nC/2\).

\[ ^3 \]This a direct consequence of the choice of \( \varrho_i(t) = -s_{\infty} + 1/[K + t] \).
3. Discussion

In this paper, I have proposed a model taking into account of anisotropic mutations and environmental changes, based on a nonlocal diffusion equation. Anisotropy can have important impacts on the evolution of the mean fitness (appearance of evolutive plateaus, see [19]). Environmental changes can have different impact on Fisher Geometric Model hypotheses: the optimum can shift on the phenotypic space (more general trajectories than in [27], considering only a shift on one direction), and the selection strength can also change (with a variation of the selection coefficients). By the way, the n-dimensional case can be seen as the sum of unidimensional cases, which have already been studied. However, this model does not include some interaction with others species (e.g., host/parasite), nor pharmacodynamics description (e.g., drugs effects).

Methodology Thanks to generating functions (see [17, 19, 25, 27] for other applications of this method), I have found an analytic formula for the mean fitness associated to (1.3), without assumption either on the initial distribution of phenotype or on environmental changes. This framework leads us to a total description of the evolution of an asexual population across time, while traditional approaches – “traveling waves”, Hamilton-Jacobi, “moment closure” (as “Gaussian solution”) or spectral analysis – focus on the asymptotic behaviour. The replicator-mutator equation can give the asymptotic behaviour and the evolution of the mean fitness across time, and so we can check the monotonicity, the existence of some evolutionary plateaus, etc. which can be compared with some experimental data (e.g., [19]). Because of the mobility of the environment, the traditional fitness (or the fitness components vector \((-x_i^2/2, \ldots, -x_n^2/2)\), as in [19]) had to be extended into the transformed fitness components vector:

\[ \mathbf{v} = (x_1, -x_1^2/2, \ldots, x_n, -x_n^2/2) \in \mathbb{R}^{2n}. \]

Additivity of the effects of anisotropic mutations The form of Eq. (2.16) yields that the mean fitness is the sum of each mean fitness components:

\[
\overline{m}_i(t) := -\frac{\mu_i^2}{2} \int_0^t (\partial_{z_{2i-1}} + \partial_{z_{2i}})y_{2i-1}(t - \tau, \tau \mathbf{1})y_{2i-1}(t - \tau, \tau \mathbf{1})d\tau + \mathbf{1}^T \partial_{z_{2i-1}} \partial_{z_{2i}} \mathbf{C}_{u_0}[\Psi(t; t)]
\]

where \(\partial_{z_{2i-1}} \mathbf{C}_{u_0}[\mathbf{z}]\) and \(\partial_{z_{2i}} \mathbf{C}_{u_0}[\mathbf{z}]\) depend only on \(z_{2i-1}\) and \(z_{2i}\). This remark yields that evolutionary plateaus can appear during the population evolution (see [19]). Furthermore, understanding the case \(n = 1\) implies the general case \(n \geq 2\).

Impact on the optimum shifting Formula (2.17) can be seen as the sum of an anisotropic mutations term (see [19]):

\[
\overline{m}_s(t) = \sum_{i=1}^n \left[ 1 - \tanh^2[\mu_i s_i t] \right] \partial_{z_{2i}} \mathbf{C}_{u_0}(\psi(t)) - \frac{\mu_i s_i}{2} \tanh[\mu_i s_i t],
\]

and a moving term (see [27]):

\[
\overline{m}_m(t) = \sum_{i=1}^n s_i^2 \left[ O_i(t) - \mu_i s_i \int_0^t O_i(\tau) \frac{\sinh[\mu_i s_i \tau]}{\cosh[\mu_i s_i t]} d\tau \right] \frac{\partial_{z_{2i-1}} \mathbf{C}_{u_0}(\psi(t))}{\cosh[\mu_i s_i t]} + \frac{1}{2} \sum_{i=1}^n s_i^2 \left[ O_i(t) - \mu_i s_i \int_0^t O_i(\tau) \frac{\sinh[\mu_i s_i \tau]}{\cosh[\mu_i s_i t]} d\tau \right]^2.
\]
Thus the shift of the phenotypic optimum has an additive impact on the evolution of the mean fitness, compared to the classic anisotropy. However, this impact depends on the mutation and selection coefficients. Therefore the interaction between both phenomena seems more complex, according to the form of the optimum movement:

1. If the optimum moves slowly (i.e., either converging or sublinear), the mean fitness \( \mathbf{m} \) converges to the same value as for the static optimum case:

\[
\lim_{t \to +\infty} \mathbf{m}(t) = -\sum_{i=1}^{n} \frac{\mu_i s_i}{2}.
\]

Thus a slow environment change will not change (drastically) the comportment of the population adaptation.

2. When the optimum shift is linear, then the mean fitness converges to a limit strictly lower than the previous case:

\[
\lim_{t \to +\infty} \mathbf{m}(t) < -\sum_{i=1}^{n} \frac{\mu_i s_i}{2}.
\]

The difference between the two terms depends on the optimum speed and on the mutation parameters. The choice of \( \mu_i \) to minimise this load is the same as in [27]. These two previous strategies can be used to control some population.

3. When the environment change is too harsh (e.g., convex), then \( \mathbf{m} \) diverges to \(-\infty\) as \( t \) tends \(+\infty\): the population goes to extinction.

4. Periodic changes will make the mean fitness periodic also.

**Impact of varying selection coefficients** In this paper, I have proposed to focus only to the case of monotonic selection coefficients, converging to a vector \( \mathbf{s}_\infty \). Here, the mean fitness tends to the same value as in the case with non varying selection coefficients equals to the coordinates of \( \mathbf{s}_\infty \). However, thanks to the formula given by Proposition (2.11), we can also describe the evolution of \( \mathbf{m} \). The main difficulty is to solve the associated Riccati equations:

\[
q'_i(t) = q_i^2(t) - \mu_i^2 s_i^2(t).
\]

4. **Proofs**

This section is devoted to the proofs of the results announced in Section 2. Section 4.1 is concerned with the PDE satisfied by the distribution of the fitness vector \( \mathbf{v} \). This study yields a description of the generating functions of this distribution, developed in Section 4.2.

**4.1. Study of the distribution \( u(t, \mathbf{v}) \) of the fitness vector**

The aim of this section is to describe the distribution \( u(t, \mathbf{v}) \), which is the pushforward measure of the measure \( q(t, \mathbf{x}) \, d\mathbf{x} \) by the map \( \varphi : \mathbf{x} \in \mathbb{R}^n \mapsto (x_1, -x_1^2/2, x_2, \ldots, -x_n^2/2) \in \mathbb{R}^{2n} \).

**Proof of Proposition 2.3.** This is a direct consequence of the definition of the fitness components vector \( \mathbf{v} \), and of the integration of the pushforward measure on a submanifold. \( \square \)
### 4.2. Generating functions

**Proof of Theorem 2.5.** A classic change of variable yields that:

\[
M_u(t, z) = \int_{\mathbb{R}^n} \exp \left[ \sum_{i=1}^{n} z_{2i-1} x_i - z_{2i} \frac{x_i^2}{2} \right] q(t, x) dx.
\]

Therefore the same arguments as in [19] prove that \( M_u \) is well-posed and smooth. Furthermore, a direct generalization of the proof of Theorem 2.6 in [19] justifies the following formal computations:

\[
\int_{\mathbb{R}^n} \exp \left[ \sum_{i=1}^{n} z_{2i-1} x_i - z_{2i} \frac{x_i^2}{2} \right] \partial_{x, x_i} q(t, x) dx = \int_{\mathbb{R}^n} \partial_{x, x_i} \left[ \exp \left[ \sum_{i=1}^{n} z_{2i-1} x_i - z_{2i} \frac{x_i^2}{2} \right] \right] q(t, x) dx,
\]

integrating by parts twice,

\[
= \int_{\mathbb{R}^n} \left[ z_{2i-1}^2 - 2 z_{2i-1} z_{2i} x_i + z_{2i}^2 x_i^2 - z_{2i} \right] \exp \left[ \sum_{i=1}^{n} z_{2i-1} x_i - z_{2i} \frac{x_i^2}{2} \right] q(t, x) dx,
\]

\[
= (z_{2i-1}^2 - z_{2i}) M_u(t, z) - 2 z_{2i-1} z_{2i} \partial_{z_{2i-1}} M_u(t, z) - 2 z_{2i}^2 \partial_{z_{2i}} M_u(t, z),
\]
and:

\[
\int_{\mathbb{R}^n} \exp \left[ \sum_{i=1}^{n} z_{2i-1} x_i - z_{2i} \frac{x_i^2}{2} \right] [m(t, x) - \overline{m}(t)] q(t, x) \, dx
\]

\[
= \int_{\mathbb{R}^n} \exp \left[ \sum_{i=1}^{n} z_{2i-1} x_i - z_{2i} \frac{x_i^2}{2} \right] \left[ \sum_{i=1}^{n} s_i^2(t) O_i(t) x_i - \frac{s_i^2(t) x_i^2}{2} - \overline{\sigma}(t) \right] q(t, x) \, dx,
\]

\[
= \sum_{i=1}^{n} s_i^2(t) O_i(t) \partial_{z_{2i-1}} M_u(t, z) + s_i^2(t) \partial_{z_{2i}} M_u(t, z) - \overline{\sigma}(t) M_u(t, z),
\]

\[
= \alpha(t) \cdot \nabla M_u(t, z) - \overline{\sigma}(t) M_u(t, z).
\]

Therefore we formally have that:

\[
\partial_t M_u(t, z) = \int_{\mathbb{R}^n} \exp \left[ \sum_{i=1}^{n} z_{2i-1} x_i - z_{2i} \frac{x_i^2}{2} \right] \partial_t q(t, x) \, dx,
\]

\[
= \sum_{i=1}^{n} \frac{\mu_i^2}{2} \int_{\mathbb{R}^n} \exp \left[ \sum_{i=1}^{n} z_{2i-1} x_i - z_{2i} \frac{x_i^2}{2} \right] \partial_{x_i x_i} q(t, x) \, dx
\]

\[
+ \int_{\mathbb{R}^n} \exp \left[ \sum_{i=1}^{n} z_{2i-1} x_i - z_{2i} \frac{x_i^2}{2} \right] [m(t, x) - \overline{m}(t)] q(t, x) \, dx,
\]

which implies that:

\[
\partial_t M_u(t, z) = -\sum_{i=1}^{n} \mu_i^2 z_{2i-1} \partial_{z_{2i-1}} M_u(t, z) - \sum_{i=1}^{n} \mu_i^2 \partial_{z_{2i}} M_u(t, z)
\]

\[
+ \sum_{i=1}^{n} \frac{\mu_i^2}{2} (z_{2i-1} - z_{2i}) M_u(t, z) + \alpha(t) \cdot \nabla M_u(t, z) - \overline{\sigma}(t) M_u(t, z), \tag{4.1}
\]

for every \((t, z) \in \mathbb{R}_+ \times \mathbb{R}_{2n}^2\). The continuity of the right-hand side terms of the above equation lets us infer that the function \(\partial_t M_u\) is extendable by continuity in \(\mathbb{R}_+ \times \mathbb{R}_{2n}^2\) and (4.1) holds in \(\mathbb{R}_+ \times \mathbb{R}_{2n}^2\). Owing to the definition \(C_u = \log M_u\), the function \(\partial_t C_u\) is continuous on \(\mathbb{R}_+ \times \mathbb{R}_{2n}^2\) and:

\[
\partial_t C_u(t, z) = -\sum_{i=1}^{n} \mu_i^2 z_{2i-1} \partial_{z_{2i-1}} C_u(t, z) - \sum_{i=1}^{n} \mu_i^2 \partial_{z_{2i}} C_u(t, z) + \sum_{i=1}^{n} \frac{\mu_i^2}{2} (z_{2i-1} - z_{2i})
\]

\[
+ \alpha(t) \cdot \nabla C_u(t, z) - \overline{\sigma}(t),
\]

for all \((t, z) \in \mathbb{R}_+ \times \mathbb{R}_{2n}^2\). Therefore, Eq. (2.14) holds in \(\mathbb{R}_+ \times \mathbb{R}_{2n}^2\) and the proof of Theorem 2.5 is thereby complete. □

I have proven that \(C_u\) is a smooth solution of a nonlocal first order equation. The explicit formula given by (2.16) is a consequence of the following lemma:
Lemma 4.1. [19] The Cauchy problem:

\[
\begin{aligned}
\partial_t Q(t, z) &= 1 \cdot (\nabla Q(t, z) - \nabla Q(t, 0)) - \tilde{b}(t, z), \quad t \geq 0, \quad z \in \mathbb{R}^{2n}_+,
Q(0, z) &= Q_0(z), \quad z \in \mathbb{R}^{2n}_+,
Q(t, 0) &= 0, \quad t \geq 0,
\end{aligned}
\tag{4.2}
\]

with \( \tilde{b} \in \mathbb{R}^{2n}_+ \) and \( Q_0 \in C^1(\mathbb{R}_+ \times \mathbb{R}^{2n}_+) \) such that \( \tilde{b}(t, 0) = Q_0(0) = 0 \), admits a unique \( C^{1,1}(\mathbb{R}_+ \times \mathbb{R}^{2n}_+) \) solution, which is given by the expression:

\[
\forall t \geq 0, \forall z \in \mathbb{R}^{2n}_+, \quad Q(t, z) = \int_0^t \left[ b(t - \tau, \tau 1) - \tilde{b}(t - \tau, z + \tau 1) \right] d\tau + Q_0(z + t 1) - Q_0(1),
\tag{4.3}
\]

where \( 1 = (1, \ldots, 1) \in \mathbb{R}^n \).

Proof of Proposition 2.6. Let us fix an index \( i \in \{1, \ldots, n\} \). By classic arguments on ODEs, we know that \( (\tau, \tau_0) \mapsto \varrho[\tau; f, \tau_0] \) is a smooth function, implying that:

\[
\forall t > 0, \forall z = (z_1, \ldots, z_{2n}) \in \mathbb{R}^{2n}_+, \quad \partial_t y_{2i}(t, z) = \frac{1}{\mu_1^2} \left[ \partial_t \varrho[t; \mu_1^2 s_1^2, t + z_{2i}] + \partial_{\tau_0} \varrho[t; \mu_1^2 s_1^2, t + z_{2i}] \right], \quad \text{and}\n\end{aligned}
\]

\[
\partial_{z_i, y_{2i}}(t, z) = \frac{1}{\mu_1^2} \partial_{\tau_0} \varrho[t; \mu_1^2 s_1^2, t + z_{2i}].
\]

Thus the function \( y_{2i} \) satisfies:

\[
\forall t > 0, \forall z = (z_1, \ldots, z_{2n}), \quad \partial_t y_{2i}(t, z) - \partial_{z_i, y_{2i}}(t, z) = -s_1^2(t) + \frac{1}{\mu_1^2} \rho^2[t; \mu_1^2 s_1^2, t + z_{2i}] = -\alpha_{2i}(t) - V_{2i}(y(t, z)).
\]

Furthermore, differentiating \( y_{2i-1} \) with respect to \( t \):

\[
\partial_t y_{2i-1}(t, z) = \mu_1^2 \left[ y_{2i}(t, z) + \int_0^t 1 \cdot \nabla y_{2i}[\zeta, z + (t - \zeta) 1] d\zeta \right] y_{2i-1}(t, z)
+ \Phi(t, t, z) \left[ \frac{s_1^2(t + z_{2i}) O_i(t + z_{2i})}{\Phi(t + z_{2i}, t, z)} - \frac{s_1^2(t) O_i(t)}{\Phi(t, t, z)} - \int_t^{t + z_{2i}} \frac{s_1^2(\tau) O_i(\tau)}{\Phi^2(\tau, t, z)} \partial_t \Phi(\tau, t, z) d\tau \right],
\]

and also to \( z \):

\[
\sum_{j=1}^{2n} \partial_{z_j} y_{2i-1}(t, z) = \mu_1^2 \int_0^t 1 \cdot \nabla y_{2i}[\zeta, z + (t - \zeta) 1] d\zeta y_{2i-1}(t, z)
+ \Phi(t, t, z) \left[ \frac{s_1(t + z_{2i}) O_i(t + z_{2i})}{\Phi(t + z_{2i}, t, z)} - \int_t^{t + z_{2i}} \frac{s_1^2(\tau) O_i(\tau)}{\Phi^2(\tau, t, z)} \nabla \Phi(\tau, t, z) \cdot 1 d\tau \right],
\]

yields that:

\[
\partial_t y_{2i-1}(t, z) - \sum_{j=1}^{2n} \partial_{z_j} y_{2i-1}(t, z) = \mu_1^2 y_{2i}(t, z) y_{2i-1}(t, z) - s_1^2(t) O_i(t) = -V_{2i-1}(y(t, z)) - \alpha_{2i-1}(t).
\]
Therefore the vector-valued function $y = (y_1, \ldots, y_{2n})$ is a smooth solution of:

\[
\begin{cases}
\partial_t y(t, z) - 2n \sum_{i=1}^{2n} \partial_{z_i} y(t, z) = -\alpha(t) - \mathbf{V}(y(t, z)), \ t \geq 0, \ z \in \mathbb{R}_{+}^{2n}, \\
y(t, 0) = 0, \ t \geq 0.
\end{cases}
\]

The function defined for $t \geq 0$ and $z \in \mathbb{R}_{+}^{2n}$ by:

\[
Q(t, z) = C_u(t, y(t, z)),
\]

is a $C^{1,1}(\mathbb{R}_{+} \times \mathbb{R}_{+}^{2n})$ solution of:

\[
\begin{cases}
\partial_t Q(t, z) = 1 \cdot (\nabla Q(t, z) - \nabla Q(t, 0)) + \gamma(y(t, z)), \ t \geq 0, \ z \in \mathbb{R}_{+}^{2n}, \\
Q(t, 0) = C_u(t, 0) = 0, \ t \geq 0,
\end{cases}
\]

as $\overline{v}(t) = \alpha(t) \cdot \nabla C_u(t, 0) = 1 \cdot \nabla Q(t, 0)$ for all time $t$. It is clear that the functions $Q(0, \cdot) = C_u(0, y(0, \cdot))$ and $b = -\gamma \circ y$ are $C^{1}(\mathbb{R}_{+} \times \mathbb{R}_{+}^{2n})$ and that:

\[
C_u(0, y(0, 0)) = \tilde{b}(t, 0) = 0.
\]

As $\overline{v}(t) = \alpha(t) \cdot \nabla C_u(t, 0) = 1 \cdot \nabla Q(t, 0)$, Lemma 4.1 yields that:

\[
\overline{v}(t) = \sum_{i=1}^{2n} \int_0^t \partial_{z_i} \tilde{b}(t - \tau, \tau \mathbf{1}) d\tau + \partial_{z_i} Q_0(t \mathbf{1}),
\]

\[
= - \int_0^t [\partial_t \tilde{b}(t - \tau, \tau \mathbf{1}) + \partial_{\tau} \tilde{b}(t - \tau, \tau \mathbf{1})] d\tau + 1 \cdot \nabla Q_0(t \mathbf{1}),
\]

\[
= \tilde{b}(t, 0) - \tilde{b}(0, t \mathbf{1}) - \int_0^t \partial_{\tau} \tilde{b}(t - \tau, \tau \mathbf{1}) d\tau + 1 \cdot \nabla Q_0(t \mathbf{1}).
\]

The definitions of $\tilde{b}$, $y$ and $Q_0$ let us end the proof.

\[\square\]

### 4.3. Different forms of environmental impacts on the optimum

**Proof of Proposition 2.8.** Let us begin by the convergent case, i.e., let us assume that $O_i(t)$ tends to $O_i(\infty) \in \mathbb{R}$. By translation, we can make the hypothesis that $O_i(\infty) \neq 0$, which implies that:

\[
O_i(t) - \mu_i s_i \int_0^t O_i(\tau) \frac{\sinh[\mu_i s_i \tau]}{\cosh[\mu_i s_i t]} d\tau \underset{t \to +\infty}{\sim} \frac{O_i(\infty)}{\cosh[\mu_i s_i t]},
\]

which converges to 0.
Now make the hypothesis that $O_i$ is increasing and concave (but not linear). Thus we get:

$$O_i(t) - \mu_is_i \int_0^t O_i(\tau) \frac{\sinh[\mu_is_i\tau]}{\cosh[\mu_is_i\tau]} d\tau \geq O_i(t) \left[ 1 - \mu_is_i \int_0^t \frac{\sinh[\mu_is_i\tau]}{\cosh[\mu_is_i\tau]} d\tau \right] = \frac{O_i(t)}{\cosh[\mu_it]} \geq 0,$$

and:

$$O_i(t) - \mu_is_i \int_0^t O_i(\tau) \frac{\sinh[\mu_is_i\tau]}{\cosh[\mu_is_i\tau]} d\tau = \frac{O_i(t)}{\cosh[\mu_is_i\tau]} + \mu_is_i \int_0^t \left[ O_i(t) - O_i(\tau) \right] \frac{\sinh[\mu_is_i\tau]}{\cosh[\mu_is_i\tau]} d\tau,$$

where:

$$\leq \frac{O_i(t)}{\cosh[\mu_is_i\tau]} + \frac{\mu_is_i O_i(t)}{t} \int_0^t \left[ t - \tau \right] \frac{\sinh[\mu_is_i\tau]}{\cosh[\mu_is_i\tau]} d\tau,$$

$$\leq \frac{O_i(t)}{\mu_is_i t} \tanh[\mu_is_i\tau].$$

Therefore $\mathcal{m}_s$ tends to 0, when $O_i$ shifts slowly.

The limit when $O_i(t) = c_it$ is a direct computation. Let us end the proof when $O_i$ is an increasing convex function:

$$O_i(t) - \mu_is_i \int_0^t O_i(\tau) \frac{\sinh[\mu_is_i\tau]}{\cosh[\mu_is_i\tau]} d\tau = \frac{O_i(t)}{\cosh[\mu_is_i\tau]} + \mu_is_i \int_0^t \left[ O_i(t) - O_i(\tau) \right] \frac{\sinh[\mu_is_i\tau]}{\cosh[\mu_is_i\tau]} d\tau,$$

$$\geq \frac{O_i(t)}{\cosh[\mu_is_i\tau]} + \frac{\mu_is_i O_i(t)}{t} \int_0^t \left[ t - \tau \right] \frac{\sinh[\mu_is_i\tau]}{\cosh[\mu_is_i\tau]} d\tau,$$

$$\geq \frac{O_i(t)}{\mu_is_i t} \tanh[\mu_is_i\tau],$$

which tends to $+\infty$, by convexity of $O_i$.

\[\square\]

### 4.4. Monotonic Selection Coefficients

**Proof of Proposition 2.12.** We have to study the solution $g_i$ of the Riccati equation. This function is nonpositive on $(-1, +\infty)$: if $g_i(T) = 0$ for $T \geq 1$, then $g_i(T) = -\mu_i^2 s_i^2(T) < 0$ implies that $g_i$ is decreasing in a neighborhood of $T$, and so $T = 1$.

Now, let us focus on the convergence of $g_i$. First, if $t_c$ is a critical point of $g_i$, then $g_i''(t) = -\mu_i^2 s_i(t) + 2\mu_i s_i(t) t_c$. Therefore, if $s_i$ is increasing, then $t_c$ is a local maximum, which is impossible: $g_i$ is not nonincreasing. If $s_i$ is decreasing, then $t_c$ would be a local minimum. Therefore, in all cases, the function $g_i$ is either decreasing, or decreasing on $(-1, t_c)$ and then increasing on $(t_c, +\infty)$. This remark, added to the Riccati equation $g_i'(t) = g_i''(t) - \mu_i^2 s_i^2(t)$ and to the boundedness of the function $s_i$, imply that $g_i$ is always bounded below: if $g_i$ diverges to $-\infty$, then $g_i(t) \to +\infty$ as $t \to +\infty$, which is absurd. Therefore $g_i$ converges to $g_{\infty,i} := -\mu_i s_{\infty,i}$.

As $s_{\infty,i} > 0$, the integral $\int_0^t g_i(\tau)d\tau$ is equivalent to $-\mu_i s_{\infty,i} t$, and so the mean fitness is equivalent to:

$$\mathcal{m}(t) \sim \frac{\sum_{i=1}^n \mu_i^2 s_{\infty,i}^2}{2 g_{\infty,i}} = \frac{\sum_{i=1}^n \mu_i s_{\infty,i}}{2},$$

as $t \to +\infty$. \[\square\]

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