# Influence of mutations in phenotypically-structured populations in time periodic environment

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**Abstract**

We study a parabolic Lotka-Volterra equation, with an integral term representing competition, and time periodic growth rate. This model represents a trait structured population in a time periodic environment. After showing the convergence of the solution to the unique positive and periodic solution of the problem, we study the influence of different factors on the mean limit population. As this quantity is the opposite of a certain eigenvalue, we are able to investigate the influence of the diffusion rate, the period length and the time variance of the environment fluctuations. We also give biological interpretation of the results in the framework of cancer, if the model represents a cancerous cells population under the influence of a periodic treatment. In this framework, we show that the population might benefit from a intermediate rate of mutation.

**Key-words: Parabolic integro-differential equations; Time-periodic coefficients; Evolution of mutation rates; Adaptive evolution; Principal eigenvalue of parabolic operators.**

**AMS classification: 35B10, 35K57, 35R09, 92D15**

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# 1 Introduction

## 1.1 Motivations

Evolution is a complex phenomenon, which intervenes in various scales of time and population sizes. In this article, we study an integro-differential model of a trait-structured population in a changing environment. This model aims at analysing the effect of environmental oscillations on the heterogeneity of a population. This question has emerged from the observation of

phenotypical and genetic diversity inside solid tumours [4, 31]. It is conjectured that this heterogeneity might be a consequence of the variations in the external conditions during tumour growth: oxygen and nutrients availability [13], immune system response and presence of chemotherapy [24] are varying during time. This phenomenon has been coined as *bet hedging* [18], in the sense that a large heterogeneity allows a tumour to better react to a non constant environment. The model we will study arises from more general models of adaptive evolution of phenotype-structured populations, however we will often come back to the cancer cells model to give biological insights on the theoretical results.

The study of evolving populations under constant environment has been carried out in several mathematical frameworks. Game theory and adaptive dynamics for example have been used in several studies [3, 15, 22, 23]. Replicator-mutator models [1] focus on the frequency of phenotypes in a group, without studying the actual size of the population. Stochastic models are relevant for small size populations, and integro-differential models can be derived from them in the limit of large size populations [9, 10]. The integro-differential equations framework has been studied especially in the case of small mutations [7, 12], to model the evolution of species on very large scales of time. Still in the case of constant environment, it has been studied with non local competition [11], or for specific growth terms [32].

We will study here an integro-differential model with a time-periodic environment, and investigate the role of mutations in the final outcome.

Consider $\Omega$ an open, connected bounded domain. We consider the following model:

$$\begin{cases} \partial_t n(t,x) &= D\Delta n(t,x) + n(t,x)\big(R(t,x) - \rho_n(t)\big) & \text{in } (0,\infty)\times\Omega, \\ \rho_n(t) &= \int_\Omega n(t,y)dy & \text{for all } t \geq 0, \\ \partial_\nu n(t,x) &= 0 & \text{on } (0,+\infty)\times\partial\Omega, \\ n(0,x) &= n_0(x) & \text{for all } x \in \Omega. \end{cases} \tag{1.1}$$

Here, $n(t,x)$ represents the density of individuals of trait $x$ at time $t$. We suppose that mutations occur randomly and are reversible, which is represented by the Laplace term of diffusion in the traits space, with a mutation rate coefficient $D$. The term $R(t,x)$ is a time-periodic function of period $T$, which represents the growth rate of individuals subject to a varying environment. The term $\partial_\nu n$ is the normal derivative of the function $n$ on the boundary $\partial\Omega$.

This model with periodic coefficients is very similar to models studied in [14, 26, 2]. However, the means and scopes of our article are different.

In [14], the authors consider a general growth rate which is periodic in $t$. They prove similar existence and large-time behaviour results for the solutions of (1.1), but their approach is slightly different since they consider traits belonging to the full space $x \in \mathbb{R}^k$ (as in [2, 26]), while we consider traits in a bounded domain $x \in \Omega$, but this is mostly a small technical difference. But our approach diverges after this first step, since the authors of [14] are mostly interested in the asymptotic $D \to 0$, and investigate the influence of the time-heterogeneity for the asymptotic problem they derive. In the present paper, one of our aims is to show that, in time-periodic media, it is sometimes more advantageous for the population to keep a positive mutation rate $D > 0$, in the sense that it could give a larger mean population

than $D \simeq 0$. As an application of our results, we for example derive from [25] that time-heterogeneity always increases the mean population, while such a positive dependence is not clear when $D \simeq 0$.

The authors of [26] do consider large mutations, but for a specific growth term $R$ of Gaussian type, where only the position of the maximum of $R$ varies over time. They focus on the fact that, $R$ being there unimodal, the population $n$ is also unimodal and is shifting over time to follow the maximum of $R$. Our results derive from a more general model, and we give a theoretical result on the effects of the mutation coefficient on the final population density.

In [2], the authors carry calculations that are very similar to what we perform in Section 4, however once again for a particular choice of $R$, in this case quadratic in $x$. They demonstrate that, for a certain range of parameters, a more plastic population can invade a less plastic one. We show in Section 4 that in general, a species achieving alone a larger mean population will invade a species less performing when alone.

The different results we will present in this article arise from the study of principal eigenvalues of periodic parabolic operators. To find references on such problems, we refer the reader mainly to [8, 17, 20, 21], and for more recent works to [5, 6, 25, 27, 28, 29], and references therein.

## 1.2 Assumptions and application framework

In the model (1.1), the domain $\Omega \subset \mathbb{R}^k$ is the set of all possible traits for the population, we consider it to be connected, bounded and smooth.

We make very few assumptions on the growth rate $R$, except that it is $T-$periodic with respect to time and that it belongs to $L^\infty\big((0,T)\times\Omega\big)$. This will guarantee the regularity of solutions, without imposing a particular term.

We consider initial data $n_0 \in L^\infty(\Omega)$ that are non-negative and non null.

As announced in the introduction, we will often consider the framework of tumour growth to put the theoretical results in a biological perspective. For this, we will consider $\Omega = (0,1)$ and $R$ of the following form:

$$R(t,x) = p(x) - \alpha(x)C(t) \quad \text{for all } (t,x) \text{ in } (0,\infty)\times\Omega. \tag{1.2}$$

In this case, the phenotype $x$ will denote a proliferation trait and a trait of resistance to a certain chemotherapy. The function $p(x)$ is then the proliferation rate of the cells of phenotype $x$, $\alpha(x)$ the efficiency of the treatment on those cells, and $C$ the concentration of the treatment.

The question we will ask then, is how one should allocate a dose of treatment during each period of time? In particular, if one can give a quantity $M$ of treatment during each period, we want to investigate the influence of $\tau$ on the outcome, where

$$C(t) = \begin{cases} \frac{TM}{\tau} \text{ if } 0 \le t < \tau, \\ 0 \text{ if } \tau \le t < T. \end{cases}$$

A treatment schedule with a small time of drug administration $\tau$ can be linked to MTD (maximal tolerated dose) protocols, where drugs are given at a very high dose for short

periods of time. A time of administration $\tau$ close to the time period $T$ can be linked to metronomic treatments, where smaller doses of drugs are used but for longer periods of time.

## 1.3 Main results and their biological interpretation

We first state a proposition on the regularity of solutions of (1.1).

**Theorem 1.1** (Regularity). *There exists a unique weak solution $n$ of (1.1), with $\rho_n \in L^\infty(0,\infty)$.*

This theorem is obtained from classical analysis arguments, see for example [11, 17].

Before stating the next theorem, we define $\lambda_1(R,D)$ as the first eigenvalue of the linear time-periodic operator $L$ defined by:

$$L\phi = \partial_t\phi - D\Delta\phi - R(t,x)\phi, \tag{1.3}$$

with Neumann boundary condition on $(0,\infty)\times\partial\Omega$. The existence of $\lambda_1(R,D)$ is demonstrated in Lemma 14.3 of [17], in which useful properties of $\lambda_1(R,D)$ can be found.

The long time behaviour of solutions is described by the following theorem:

**Theorem 1.2** (Existence, Uniqueness and attractiveness).

- *If $\lambda_1(R,D) \geq 0$ then all solutions of the Cauchy problem for equation (1.1) converge towards 0.*
- *If $\lambda_1(R,D) < 0$, then there exists a unique positive periodic solution $N$ of (1.1). Moreover, this solution attracts all the solutions of the Cauchy problem with non-negative bounded initial data, and $\frac{1}{T}\int_t^{t+T}\rho_n(s)ds$ converges to $-\lambda_1(R,D)$ as $t\to+\infty$.*

To study the long time behaviour of solutions of (1.1), we thus have to study the periodic solution $N$ in the case $\lambda_1(R,D) < 0$. Especially, we are interested in the variation of $\bar\rho_N = \frac{1}{T}\int_0^T\int_\Omega N(t,x)dxdt$, the mean limit total population, with respect to the different parameters of (1.1). As Theorem 1.2 yields that

$$\bar\rho_N = \lim_{t\to+\infty}\frac{1}{T}\int_t^{t+T}\rho_n(s)ds = -\lambda_1(R,D),$$

we have to study the influence of $D$, $R$ and other parameters on $\lambda_1(R,D)$.

We then derive from earlier works on the optimization of principal eigenvalues the following results.

**Proposition 1.3** (Minimization of $\bar\rho_N$). *The mean limit population $\bar\rho_N$ is a convex function of $R$. Consecutively, for a given $\bar R(x) = \frac{1}{T}\int_0^T R(t,x)dt$, $\bar\rho_N$ is minimal for a constant in time $R$.*

The proof of this proposition is a direct application of Proposition 2.10 in [27].

**Remark 1.** In the framework of cancer treatment, *i.e.* if $R$ is as described in (1.2), this proposition gives us a method of minimization of the final mean tumour burden. Indeed, for a given quantity of drug $M$ to be delivered during each treatment period, the protocol minimizing $\bar{\rho}_N$ is $C(t) \equiv \frac{M}{T}$. Moreover, if two treatments $C_1$, $C_2$ are of the form:

$$C_1(t) = \begin{cases} \frac{M}{\tau} \text{ if } 0 < t \leq \tau, \\ 0 \text{ if } \tau < t \leq T \end{cases} \quad , \quad C_2(t) = \begin{cases} \frac{M}{2\tau} \text{ if } 0 < t \leq 2\tau, \\ 0 \text{ if } 2\tau < t \leq T \end{cases}$$

then by convexity of $\bar{\rho}_N$, since $C_2(t) = \frac{C_1(t)+C_1(t+\tau)}{2}$, the mean final total population $\bar{\rho}_{N,2}$ associated to $C_2$ is smaller than the mean final total population $\bar{\rho}_{N,1}$ associated to $C_1$. In other words, concentrating the same quantity of treatment on half the time of administration will make the final mean population of cells higher. It is also true for a concentration on an administration time of $\tau/n$, for any $n \in \mathbb{N}$. We conjecture it to be true for any real factor of concentration.

**Theorem 1.4** (Influence of mutations)**.** *Decompose $R$ in the following way:*

$$R(t,x) = r(x) + \gamma S(t,x) \text{ where } \int_0^T R(t,x)dt = r(x) \text{ for all } x \in \Omega.$$

*Then if $S$ is not zero and $R$ is not spatially uniform, for $\gamma$ large enough, there exists $D_0 > 0$ such that, in the neighbourhood of $D_0$, the mean limit population $\bar{\rho}_N$ is an increasing function of the mutation rate $D$.*

**Remark 2.** A biological interpretation of this theorem is that bet hedging tumours are more successful in some conditions. Indeed, if $R$ satisfies the conditions of Theorem 1.4, then a tumour with a higher mutation rate $D$ will have a higher mean final population. We identify here the heterogeneity with a high plasticity.

**Proposition 1.5** (The case of a non-increasing growth rate)**.** *Let $k = 1$ and $\Omega = (0,1)$. Assume that $x \in (0,1) \mapsto R(t,x)$ is non-increasing for all $t \in (0,T)$, and that $\partial_x R$ is defined for a.e. $x \in (0,1)$ and bounded over $(0,1) \times (0,T)$. Lastly, assume that $R(t,\cdot)$ is not constant with respect to $x$ for a non-negligible set of $t \in (0,T)$.*

*Then $D > 0 \mapsto \bar{\rho}_N(R,D)$ is decreasing.*

**Remark 3.** Proposition 1.5 presents some conditions in which the result presented in Theorem 1.4 does not hold. Theorem 1.5 in [29] presents a similar result: their proof follows the same type of reasonning. We will provide here our own proof for sake of completeness.

**Proposition 1.6** (Minimization of the minimal size among time)**.** *Assume that*

$$R(t,x) = p(x) - \alpha(x)C(t) \quad \text{for all } (t,x) \in (0,\infty) \times \Omega.$$

*Let $C_{max} > 0$, $T > 0$ and $0 < \sigma < 1$. Consider the solution $n_{hom}$ of (1.1) associated with the constant function $C(t) = C_{max}\sigma$ for all $t \in (0,+\infty)$ and the solution $n_{het}$ of (1.1) associated with the $T-$periodic function*

$$C(t) = \begin{cases} C_{max} \text{ if } 0 \leq t < \sigma T, \\ 0 \text{ if } \sigma T \leq t < T. \end{cases}$$

*Assume that* $\max_{x\in\Omega}\left(p(x)-\alpha(x)C_{max}\right)<0$ *and* $\min_{x\in\Omega}\left(p(x)-\alpha(x)C_{max}\sigma\right)>0$. *Then if* $T$ *is large enough, one has*

$$\liminf_{t\to+\infty}\rho_{n_{het}}(t)<\liminf_{t\to+\infty}\rho_{n_{hom}}(t).$$

**Remark 4.** Proposition 1.6 gives, in the framework of cancer treatment, an interesting comparison between constant and "bang-bang" treatments. Indeed, it demonstrates that in some situations, the population $\rho_n(t)$ will reach regularly a smaller size if subjected to a "bang-bang" protocol than if the same amount of treatment is given constantly, even if the mean limit population $\bar{\rho}_N$ is higher, as demonstrated by Proposition 1.3. Biologically, if $\rho_n(t)$ reaches a very small size, it is very likely that the population is in fact extinct, and thus $\rho_n(t)=0$ afterwards. Thus, while the constant treatment reduces the global mean tumoural charge, the "bang-bang" treatments increases the chances of eradicating the tumour.

The next Proposition is indeed an immediate corollary of Theorem 1.1 of [25], but we state it here since its biological interpretation is meaningful.

**Proposition 1.7** (Influence of the period)**.** *Assume that* $R$ *is* $1-$*periodic in* $t$ *and cannot be written as* $R(t,x)=R_1(t)+R_2(x)$. *Define* $R_T(t,x):=R(t/T,x)$. *Then* $T>0\mapsto\overline{\rho}_N(R_T,D)$ *is increasing.*

We refer to [25] for the proof of their theorem, but will not present here the proof of this proposition, since it is a very straightforward corollary.

**Remark 5.** The condition for this theorem to hold does not have a straightforward biological interpretation, but the outcome is interesting. Indeed, if $T$ is large, the environment $R_T$ is changing slowly, allowing the population $n$ to approach equilibrium values if $R$ is constant in time on some interval. On the contrary, if $T$ is short, the population faces a fast changing environment, which does not give it time to adapt to any new situation. Hence, $n$ achieves a smaller total mean population $\bar{\rho}_N$ if $T$ is short than if $T$ is large.

**Theorem 1.8** (Competition)**.** *Let* $(n,m)$ *be a solution of:*

$$\begin{cases}\partial_t n(t,x)-D_1\Delta n(t,x)=n(t,x)(R(t,x)-\rho_n(t)-\rho_m(t)),\\ \partial_t m(t,x)-D_2\Delta m(t,x)=m(t,x)(R(t,x)-\rho_n(t)-\rho_m(t)),\\ \rho_n(t)=\int_\Omega n(t,x)dx,\ \rho_m(t)=\int_\Omega m(t,x)dx,\\ n(0,x)=n_0(x),\ m(0,x)=m_0(x),\\ \textit{Neumann conditions for both functions on the border of }\Omega.\end{cases}\tag{1.4}$$

*We consider that* $n_0\not\equiv 0$ *and* $m_0\not\equiv 0$ *are non-negative functions on* $\Omega$. *Suppose that* $D_1$, $D_2$ *are such that* $0>\lambda_1(R,D_1)>\lambda_1(R,D_2)$. *Then*

$$n(t,\cdot)\underset{t\to\infty}{\longrightarrow}0\quad\textit{and}\quad m(t,\cdot)-M(t,\cdot)\underset{t\to\infty}{\longrightarrow}0,$$

*where* $M$ *is the* $T$*-periodic solution of* (1.1) *with* $D=D_2$.

**Remark 6.** This theorem ensures that, if two populations with different plasticities are in competition, the one with the largest equilibrium population will dominate.

This article is divided as follows: section 2 is devoted to the demonstration of results of existence, *i.e.* Theorems 1.1 and 1.2, and Proposition 1.5, which proof is closely linked to these theorems. Theorem 1.4 is demonstrated in section 3, along with Proposition 1.6, as both results give interesting insight on treatment protocol choice, when $R$ is of the form (1.2). Section 4 is devoted to the demonstration of Theorem 1.8 on competing species. Finally, section 5 presents numerical simulations of the model, illustrating different phenomenons described earlier.

# 2 Existence of a $T$-periodic solution and treatment optimization

*Proof of Theorem 1.1.* Consider the operator $\mathcal{T}$ that associates with $\rho \in L^\infty(0,\infty)$ the function $t \mapsto \int_\Omega n(t,x)dx$, where $n$ is the solution of

$$\begin{cases} \partial_t n(t,x) &= D\Delta n(t,x) + n(t,x)\big(R(t,x) - \rho(t)\big) & \text{in } (0,\infty)\times\Omega, \\ \partial_\nu n(t,x) &= 0 & \text{for all } (t,x) \in \mathbb{R}\times\partial\Omega, \\ n(0,x) &= n_0(x) & \text{for all } x \in \Omega. \end{cases} \tag{2.5}$$

Clearly, as $n_0 \geq 0$ by hypothesis, one has $n \geq 0$. Moreover, it follows from classical $L^p$ regularity for parabolic equations that the operator $\mathcal{T} : \rho \mapsto \rho_n$ is compact over $L^\infty(0,\infty)$.

Assume that there exist $\sigma \in (0,1)$ and $\rho \in L^\infty(0,\infty)$ such that $\rho = \sigma\mathcal{T}(\rho) = \sigma\rho_n$, with $\rho_n(t) := \int_\Omega n(t,x)dx \geq 0$. Integrating the equation satisfied by $n$, one gets

$$\rho_n'(t) \leq \rho_n(t)\big(R_{max} - \rho(t)\big) = \rho_n(t)\big(R_{max} - \sigma\rho_n(t)\big) \quad \text{ on } (0,\infty),$$

from which we easily derive $\sigma\rho_n(t) \leq \max\{R_{max}, \sigma\int_\Omega n_0\}$ for all $t > 0$. Hence, $0 \leq \rho \leq \max\{R_{max}, \sigma\int_\Omega n_0\}$ and the set of all such $\rho$ is bounded. We can thus apply the Shaefer fixed point theorem and get the existence of solution $n$ of (1.1), with $\rho_n \in L^\infty(0,\infty)$.

We now prove the uniqueness of such a solution. Let $n_1$, $n_2$ be two solutions of the system (1.1) with the same initial condition $n_0$. Then the function

$$\widetilde{n}(t,x) = n_1(t,x)\exp(\int_0^t \rho_{n_1}(s)ds)$$

satisfies the following equation:

$$\begin{cases} \partial_t\widetilde{n}(t,x) = D\Delta\widetilde{n}(t,x) + \widetilde{n}(t,x)R(t,x) \text{ in } (0,\infty)\times\Omega, \\ \partial_\nu\widetilde{n}(t,x) = 0 \text{ for all } (t,x) \in \mathbb{R}\times\partial\Omega, \\ \widetilde{n}(0,x) = n_0(x) \text{ for all } x \in \Omega. \end{cases} \tag{2.6}$$

By uniqueness of the solution of (2.6), we deduce that:

$$n_1(t,x)\exp(\int_0^t \rho_{n_1}(s)ds) = n_2(t,x)\exp(\int_0^t \rho_{n_2}(s)ds). \tag{2.7}$$

Moreover, $\int_\Omega \widetilde{n}(t,x)dx > 0$ for all $t \geq 0$ since $n_0 \not\equiv 0$, thus $\rho_{n_i} > 0$. By integrating (2.7) on $\Omega$ and derivating in time, we get that $\rho_{n_1}$ satisfies the following differential equation:

$$y'(t) = y(t)(\frac{\rho'_{n_2}(t)}{\rho_{n_2}(t)} + \rho_{n_2}(t) - y(t)). \tag{2.8}$$

Since $\rho_{n_2}$ also satisfies (2.8) with the same initial condition, we deduce that $\rho_{n_1} = \rho_{n_2}$, and thus that $n_1 = n_2$ on $[0, +\infty) \times \Omega$ by (2.7).

□

*Proof of Theorem 1.2.* We first prove Theorem 1.2 in the case $\lambda_1(R, D) < 0$. The proof is organized in three parts: we first prove the existence of a periodic solution, then its uniqueness, and finally its attractiveness.

**Existence** Let $\phi$ be the eigenfunction of (1.3) associated to $\lambda_1(R, D)$, with normalization $\int_\Omega \phi(0, x)dx = 1$. By definition, $\phi > 0$. We define:

$$\rho_\phi(t) = \int_\Omega \phi(t, x)dx > 0 \quad \text{for all } t \in \mathbb{R}$$

Consider the following differential equation:

$$y' = y(\frac{\rho'_\phi}{\rho_\phi} + (-\lambda_1(R, D)) - y). \tag{2.9}$$

Since $\frac{\rho'_\phi}{\rho_\phi}$ is a $T$-periodic function, equation (2.9) admits a single $T$-periodic solution, namely

$$\rho(t) = \frac{\rho_\phi(t)e^{-\lambda_1(R,D)t}(e^{-\lambda_1(R,D)T} - 1)}{\int_0^T \rho_\phi(s)e^{-\lambda_1(R,D)s}ds + (e^{-\lambda_1(R,D)T} - 1)\int_0^t \rho_\phi(s)e^{-\lambda_1(R,D)s}ds}$$

Notice that this function does not depend on our choice of normalization for the eigenfunction $\phi$. We define the following functions:

$$\widetilde{N}(t, x) = \rho(0)\phi(t, x) \quad \text{for all } (t, x) \in \mathbb{R}^+ \times \Omega,$$
$$N(t, x) = \widetilde{N}(t, x) \exp(-\int_0^t \rho(s)ds - \lambda_1(R, D)t).$$

By direct calculations one sees that $N$ is a $T$-periodic in time solution of (1.1), with

$$\rho(t) = \int_\Omega N(t, x)dx \quad \text{for all } t \in \mathbb{R}^+.$$

This concludes the proof of existence of a periodic solution to problem (1.1).

**Uniqueness** Let $N_1$ and $N_2$ be two $T$-periodic solutions of (1.1). We define the following functions:

$$\widetilde{N}_1(t,x) = N_1(t,x)\exp(\int_0^t \rho_{N_1}(s)ds - \overline{\rho}_{N_1}t),$$
$$\widetilde{N}_2(t,x) = N_2(t,x)\exp(\int_0^t \rho_{N_2}(s)ds - \overline{\rho}_{N_2}t)$$

where $\overline{\rho}_{N_i} = \frac{1}{T}\int_0^T \rho_{N_i}(s)ds$ for $i = 1,2$. Then $\widetilde{N}_i$ are positive eigenfunctions of $\partial_t\phi - D\Delta\phi - R(t,x)\phi$ associated with the eigenvalues $-\overline{\rho}_{N_i}$ respectively. Thus we have $\overline{\rho}_{N_1} = \overline{\rho}_{N_2} = -\lambda_1(R,D)$, and there exists $\lambda > 0$ such that $\widetilde{N}_1 = \lambda\widetilde{N}_2$.

We denote $f(t) = \lambda\exp(\int_0^t(\rho_{N_2}(s) - \rho_{N_1}(s))ds)$. Then $f$ is $T$-periodic and $N_1 = f(t)N_2$. Moreover $f$ satisfies $f'(t) = \rho_{N_2}(t)f(t)(1-f(t))$. Thus $f(t) \equiv 1$, and $N_1 = N_2$.

**Attractiveness** Let $n_0 \geq 0$ be non null, and $n$ be the solution to the Cauchy problem (1.1).

Let $\widetilde{n}(t,x) := n(t,x)e^{\int_0^t \rho_n(s)ds + \lambda_1(R,D)t}$.

Then $\widetilde{n}$ satisfies:

$$\partial_t\widetilde{n} - D\Delta\widetilde{n} = \widetilde{n}(R(t,x) + \lambda_1(R,D)). \tag{2.10}$$

Let $\phi_0$ an eigenvector of operator $L$ associated to the eigenvalue $\lambda_1(R,D)$, and $\widetilde{\phi_0}$ a principal eigenvector of the adjoint operator. The same computations as in Lemma 6.4 of [30], with $H(x) = x^2$, yield for all $\alpha > 0$:

$$\frac{d}{dt}\int_\Omega \frac{\widetilde{\phi}_0(t,x)}{\phi_0(t,x)}\left|\widetilde{n}(t,x) - \alpha\phi_0(t,x)\right|^2 dx = -2\int_\Omega \widetilde{\phi}_0(t,x)\phi_0(t,x)\left|\nabla(\frac{\widetilde{n}(t,x)}{\phi_0(t,x)})\right|^2 dx.$$

Let $\alpha := \frac{1}{|\Omega|}\int_\Omega \widetilde{n}(0,x)\widetilde{\phi}_0(0,x)dx$, so that, by Lemma 6.4 of [30], with $H(x) = x$, one has $\frac{1}{|\Omega|}\int_\Omega \widetilde{n}(t,x)\widetilde{\phi}_0(t,x)dx = \alpha$ for all $t > 0$. Now, the positivity and boundedness of $\widetilde{\phi}_0$ and $\phi_0$ and the Poincaré-Wirtinger inequality yield the existence of a constant $C > 0$ such that:

$$\begin{aligned}\frac{d}{dt}\int_\Omega \frac{\widetilde{\phi}_0(t,x)}{\phi_0(t,x)}\left|\widetilde{n}(t,x) - \alpha\phi_0(t,x)\right|^2 dx &\leq -2C\int_\Omega \frac{\widetilde{\phi}_0(t,x)}{\phi_0(t,x)}\left|\widetilde{n}(t,x) - \phi_0(t,x)\times\frac{1}{|\Omega|}\int_\Omega \frac{\widetilde{n}(t,y)}{\phi_0(t,y)}dy\right|^2 dx \\ &\leq -2C\int_\Omega \frac{\widetilde{\phi}_0(t,x)}{\phi_0(t,x)}\left|\widetilde{n}(t,x) - \alpha\phi_0(t,x)\right|^2 dx\end{aligned}$$

since $\widetilde{n}(t,\cdot) - \alpha\phi_0(t,\cdot)$ is the projection of $\widetilde{n}(t,\cdot)$ on $\mathbb{R}\phi_0(t,\cdot)$ with respect to the $L^2(\Omega)$ scalar product with weight $\frac{\widetilde{\phi}_0(t,\cdot)}{\phi_0(t,\cdot)}$. It follows from the Gronwall inequality, the boundedness of $\phi_0$ and the positivity of $\widetilde{\phi}_0$ that, for some constant that we still denote $C > 0$, one has:

$$\int_\Omega \left|\widetilde{n}(t,x) - \alpha\phi_0(t,x)\right|^2 dx \leq Ce^{-2Ct}$$

Hence, $\widetilde{n}(t,x) - \alpha\phi_0(t,x) \longrightarrow 0$ as $t \to +\infty$.

Next, we will show that $\rho_n(t) - \rho_N(t) \longrightarrow 0$ as $t \to +\infty$.

By derivating the logarithm of the integral of the definition of $\widetilde{n}$, we see that $\rho_{\widetilde{n}}$ satisfies

$$\rho_n'(t) = \rho_n(t)(\frac{\rho_{\widetilde{n}}'(t)}{\rho_{\widetilde{n}}(t)} - \rho_n(t) - \lambda_1(R,D)).$$

Thus, since $\rho_n(0) > 0$, there exists $A_0 > 0$ such that

$$\rho_n(t) = \frac{\rho_{\widetilde{n}}(t)e^{-\lambda_1(R,D)t}}{A_0 + \int_0^t \rho_{\widetilde{n}}(s)e^{-\lambda_1(R,D)s}ds}.$$

Similarly, there exists $B_0 > 0$ such that

$$\rho_N(t) = \frac{\rho_{\phi_0}(t)e^{-\lambda_1(R,D)t}}{B_0 + \int_0^t \rho_{\phi_0}(s)e^{-\lambda_1(R,D)s}ds}.$$

Thus:

$$\begin{aligned}\rho_n(t) - \rho_N(t) &= \frac{\rho_{\widetilde{n}}(t)e^{-\lambda_1(R,D)t}}{A_0 + \int_0^t \rho_{\widetilde{n}}(s)e^{-\lambda_1(R,D)s}ds} - \frac{\rho_{\phi_0}(t)e^{-\lambda_1(R,D)t}}{B_0 + \int_0^t \rho_{\phi_0}(s)e^{-\lambda_1(R,D)s}ds} \\ &= \frac{B_0\rho_{\widetilde{n}}(t) - A_0\rho_{\phi_0}(t) + \rho_{\widetilde{n}}(t)\int_0^t \rho_{\phi_0}(s)e^{-\lambda_1(R,D)s}ds - \rho_{\phi_0}(t)\int_0^t \rho_{\widetilde{n}}(s)e^{-\lambda_1(R,D)s}ds}{(A_0 + \int_0^t \rho_{\widetilde{n}}(s)e^{-\lambda_1(R,D)s}ds)(B_0 + \int_0^t \rho_{\phi_0}(s)e^{-\lambda_1(R,D)s}ds)}e^{-\lambda_1(R,D)t}\end{aligned}$$

Since there exists $a > 0$ such that $\rho_{\phi_0}(t) \geq a$ and $\rho_{\widetilde{n}}(t) \geq a$ for all $t \geq 0$, we can see that:

$$(A_0+\int_0^t \rho_{\widetilde{n}}(s)e^{-\lambda_1(R,D)s}ds)(B_0+\int_0^t \rho_{\phi_0}(s)e^{-\lambda_1(R,D)s}ds) \geq \frac{a^2}{\lambda_1(R,D)^2}e^{-2\lambda_1(R,D)t}+O(e^{-\lambda_1(R,D)t})$$

as $t \to +\infty$.

We now treat the numerator: we will show that

$$A(t) := \rho_{\widetilde{n}}(t)\int_0^t \rho_{\phi_0}(s)e^{-\lambda_1(R,D)s}ds - \rho_{\phi_0}(t)\int_0^t \rho_{\widetilde{n}}(s)e^{-\lambda_1(R,D)s}ds = o(e^{-\lambda_1(R,D)t}).$$

We first decompose $A$: set $\mu > 0$ such that $\mu < -\lambda_1(R,D)$, and write:

$$\begin{aligned}A(t) = \rho_{\widetilde{n}}(t)&\int_{\frac{\mu}{-\lambda_1(R,D)}t}^t \rho_{\phi_0}(s)e^{-\lambda_1(R,D)s}ds - \rho_{\phi_0}(t)\int_{\frac{\mu}{-\lambda_1(R,D)}t}^t \rho_{\widetilde{n}}(s)e^{-\lambda_1(R,D)s}ds \\ &+ \rho_{\widetilde{n}}(t)\int_0^{\frac{\mu}{-\lambda_1(R,D)}t} \rho_{\phi_0}(s)e^{-\lambda_1(R,D)s}ds - \rho_{\phi_0}(t)\int_0^{\frac{\mu}{-\lambda_1(R,D)}t} \rho_{\widetilde{n}}(s)e^{-\lambda_1(R,D)s}ds\end{aligned}$$

Note that

$$\int_0^{\frac{\mu}{-\lambda_1(R,D)}t} \rho_{\phi_0}(s)e^{-\lambda_1(R,D)s}ds \leq \max(\rho_{\phi_0})\frac{e^{\mu t} - 1}{-\lambda_1(R,D)} = o(e^{-\lambda_1(R,D)t}).$$

Furthermore

$$\rho_{\widetilde{n}}(t)\int_{\frac{\mu}{-\lambda_1(R,D)}t}^{t}\rho_{\phi_0}(s)e^{-\lambda_1(R,D)s}ds-\rho_{\phi_0}(t)\int_{\frac{\mu}{-\lambda_1(R,D)}t}^{t}\rho_{\widetilde{n}}(s)e^{-\lambda_1(R,D)s}ds$$
$$=\rho_{\widetilde{n}}(t)\int_{\frac{\mu}{-\lambda_1(R,D)}t}^{t}(\rho_{\phi_0}(s)-\rho_{\widetilde{n}}(s))e^{-\lambda_1(R,D)s}ds-(\rho_{\phi_0}(t)-\rho_{\widetilde{n}}(t))\int_{\frac{\mu}{-\lambda_1(R,D)}t}^{t}\rho_{\widetilde{n}}(s)e^{-\lambda_1(R,D)s}ds.$$

Noting that

$$\int_{\frac{\mu}{-\lambda_1(R,D)}t}^{t}|\rho_{\phi_0}(s)-\rho_{\widetilde{n}}(s)|e^{-\lambda_1(R,D)s}ds\leq\max_{\frac{\mu}{-\lambda_1(R,D)}t\leq s\leq t}|\rho_{\phi_0}(s)-\rho_{\widetilde{n}}(s)|\frac{e^{-\lambda_1(R,D)t}-e^{\mu t}}{-\lambda_1(R,D)}=o(e^{-\lambda_1(R,D)t}),$$

we conclude that all terms of $A$ are in fact $o(e^{-\lambda_1(R,D)t})$, and thus $\rho_n(t)-\rho_N(t)=O(e^{\lambda_1(R,D)t})$ as $t\to+\infty$. Thus, $\rho_n(t)-\rho_N(t)\longrightarrow 0$ as $t\to+\infty$.

From this, it is easy to check that $\rho_{\widetilde{n}}(t)-\rho_{\widetilde{N}}(t)\longrightarrow 0$ when $t\to+\infty$. Thus, $\phi_0=\widetilde{N}$, and we conclude that $n(t,x)-N(t,x)\longrightarrow 0$ as $t\to+\infty$.

**The case** $\lambda_1(R,D)\geq 0$**.** First note that $n$ is a subsolution of the parabolic equation satisfied by $C\phi(t,x)e^{-\lambda_1(R,D)t}$, where $C$ is large enough so that $C\phi\geq n_0$. Hence, in the case where $\lambda_1(R,D)>0$, as $\phi$ is periodic in $t$, one gets $n(t,x)\to 0$ as $t\to+\infty$ uniformly with respect to $x\in\Omega$.

If $\lambda_1(R,D)=0$, consider again $\widetilde{n}(t,x):=n(t,x)e^{\int_0^t\rho_n(s)ds}$. This function satisfies

$$\begin{cases}\partial_t\widetilde{n}(t,x) &= D\Delta\widetilde{n}(t,x)+\widetilde{n}(t,x)R(t,x) &\text{in } (0,\infty)\times\Omega,\\ \partial_\nu\widetilde{n}(t,x) &= 0 &\text{for all } (t,x)\in\mathbb{R}\times\partial\Omega,\\ \widetilde{n}(0,x) &= n_0(x) &\text{for all } x\in\Omega.\end{cases}\tag{2.11}$$

The same arguments as in the proof of the attractiveness in Theorem 1.2 yield that $\widetilde{n}(t,x)-C'\phi(t,x)\to 0$ as $t\to+\infty$ uniformly in $x\in\Omega$ (see for example chap.6 of [30]), for some $C'>0$. Next, one has

$$\rho_n'(t)=\rho_n(t)\Big(\frac{\rho_{\widetilde{n}}'(t)}{\rho_{\widetilde{n}}(t)}-\rho_n(t)\Big),$$

and we know that $\rho_{\widetilde{n}}'(t)/\rho_{\widetilde{n}}(t)-\rho_\phi'(t)/\rho_\phi(t)\to 0$ as $t\to+\infty$. It easily follows that, up to extraction, one can assume that $\rho_n$ converges as $t\to+\infty$ to a non-negative bounded solution $\rho$ of

$$\rho'(t)=\rho(t)\Big(\frac{\rho_\phi'(t)}{\rho_\phi(t)}-\rho(t)\Big).$$

Dividing by $\rho$ and integrating over $(0,kT)$ with $k$ large, one finds that the only such solution is $\rho\equiv 0$. Hence, $\lim_{t\to+\infty}\rho_n(t)=0$. It follows that $n(t,\cdot)\to 0$ as $t\to+\infty$ in $L^1(\Omega)$ and the convergence in $L^\infty(\Omega)$ follows by parabolic regularity.

□

*Proof of Proposition 1.5.* Consider the periodic principal eigenfunction $\phi$ associated with $\lambda_1(R,D)$, that is, the unique positive and $T-$periodic solution, up to multiplication, of

$$\begin{cases} \partial_t \phi - D\partial_{xx}\phi - R(t,x)\phi = \lambda_1(R,D)\phi & \text{in } (0,T)\times(0,1), \\ \partial_x\phi(t,0) = \partial_x\phi(t,1) = 0 \text{ for all } t \in (0,T). \end{cases}$$

Let first show that this function is decreasing with respect to $x$. Let $\psi := \partial_x\phi$. As $\partial_x R \leq 0$ and $\psi > 0$ by hypothesis, one has

$$\begin{cases} \partial_t \psi - D\partial_{xx}\psi - R(t,x)\psi - \lambda_1(R,D)\psi \leq 0 & \text{in } (0,T)\times(0,1), \\ \psi(t,0) = \psi(t,1) = 0 \text{ for all } t \in (0,T). \end{cases}$$

Consider now $z := \psi/\phi$. One has

$$\begin{cases} \partial_t z - D\partial_{xx} z - 2D\frac{\partial_x\phi}{\phi}\partial_x z \leq 0 & \text{in } (0,T)\times(0,1), \\ z(t,0) = z(t,1) = 0 \text{ for all } t \in (0,T), \end{cases}$$

and $z$ is $T-$periodic. If $z$ admits a positive maximum over $\mathbb{R}\times[0,1]$, then this maximum is reached at an interior point, and the parabolic maximum principle, together with the $T-$periodicity, would imply that $z$ is constant, meaning that $\psi = \partial_x\phi$ would be proportional to $\phi$. But as $\partial_x\phi(t,0) = \partial_x\phi(t,1) = 0$ for all $t \in (0,T)$, one would then necessarily have $\partial_x\phi \equiv 0$, which is impossible since $R(t,\cdot)$ is not constant with respect to $x$ for a non-negligible set of $t \in (0,T)$. We have thus reached a contradiction, which proves that $z \leq 0$. Moreover, if $z(t,x) = 0$ for some $(t,x) \in \mathbb{R}\times(0,1)$, then this point is an interior maximum point and the parabolic maximum principle would again give $z \equiv 0$ and a contradiction. Hence, $z(t,x) < 0$ in $\mathbb{R}\times(0,1)$, that is, $\partial_x\phi(t,x) < 0$ for all $(t,x) \in (0,T)\times(0,1)$.

Now, we know from Lemma 2.3 of [20] that

$$\frac{d}{dD}\lambda_1(R,D) = \frac{D}{T}\int_{(0,T)\times\Omega} \partial_x\phi(t,x)\partial_x\widetilde{\phi}(t,x)dtdx,$$

where $\widetilde{\phi}$ is the adjoint principal eigenfunction, that is, the positive $T-$periodic solution of

$$\begin{cases} -\partial_t\widetilde{\phi} - D\partial_{xx}\widetilde{\phi} - R(t,x)\widetilde{\phi} = \lambda_1(R,D)\widetilde{\phi} & \text{in } (0,T)\times(0,1), \\ \partial_x\widetilde{\phi}(t,0) = \partial_x\widetilde{\phi}(t,1) = 0 \text{ for all } t \in (0,T) \end{cases}$$

normalized by $\frac{1}{T}\int_{(0,T)\times\Omega}\phi\widetilde{\phi} = 1$. Indeed, one could prove as above that, as $\partial_x R \leq 0$, one has $\partial_x\widetilde{\phi}(t,x) < 0$ for all $(t,x) \in (0,T)\times(0,1)$. It immediately follows that

$$\frac{d}{dD}\lambda_1(R,D) > 0,$$

which yields the result since $\overline{\rho}_N = -\lambda_1(R,D)$.

□

# 3 Advantage of a large mutation rate

This section is devoted to the proof of Theorem 1.4 and Proposition 1.6. The proof of Theorem 1.4 is very similar to the proof of Theorem 2.2 in [20]: for sake of clarity, we state it here, but we would like to refer to it for other corollaries, and to [17] for the crucial part of the proof. We also present an interpretation of the theorem in the case where $R$ is as described in (1.2).

*Proof of Theorem 1.4.* Let $\overline{r} = \max_{x\in\Omega} \frac{1}{T}\int_0^T R(t,x)dt$ and $r(x) = \frac{1}{T}\int_0^T R(t,x)dt - \overline{r}$, so that we have $R(t,x) = \overline{r} + r(x) + \gamma S(t,x)$ and $r(x) \leq 0$ on $\Omega$. Consider the following periodic eigenvalue problem:

$$\begin{cases} \partial_t\psi - D\Delta\psi - (r(x) + \gamma S(t,x))\psi = \mu_1(r,\gamma S, D)\psi \quad \text{in } (0,\infty)\times\Omega, \\ \partial_\nu\psi(t,x) = 0 \quad \text{for all } (t,x)\in\mathbb{R}\times\partial\Omega, \\ \psi(t+T,x) = \psi(t,x) \quad \text{for all } (t,x)\in\mathbb{R}\times\Omega, \end{cases} \tag{3.12}$$

Here $\mu_1(r,\gamma S, D)$ denotes the principal eigenvalue of the problem. Note that $\int_0^T S(t,x)dt = 0$ for all $x\in\Omega$, and that $\int_0^T \max_{x\in\Omega} S(t,x)dt > 0$ since $S$ is not uniform in $x$. Then, Lemma 15.4 in [17] states that:

$$\forall D > 0, \ \lim_{\gamma\to+\infty} \mu_1(r,\gamma S, D) = -\infty. \tag{3.13}$$

Since $\lim_{D\to 0}\mu_1(r,\gamma S,D) = -\max_{x\in\Omega} r(x)$ does not depend on $\gamma$, there exists $\gamma_0 > 0$ such that $\mu_1(r,\gamma_0 S,1) < \lim_{D\to 0}\mu_1(r,\gamma_0 S,D)$. Then there exists $D_0$ in $(0,1)$ such that:

$$\mu_1(r,\gamma_0 S,D_0) < 0 \text{ and } \partial_D\mu_1(r,\gamma_0 S,D_0) < 0.$$

Since for any $D \geq 0$ we have:

$$-\lambda_1(R,D) = -\mu_1(r,\gamma S,D) + \overline{r},$$

this concludes the proof of Theorem 1.4.

□

Parameter $\gamma$ in the proof of 1.4 is a measure of the amplitude of changes in the environment during one period of time. Let us now consider the particular case where $R$ is defined as (1.2). The quantities $\overline{r}$, $r$ and $\gamma S$ can be expressed by:

$$\begin{aligned} \overline{r} &= \max_{x\in\Omega}(p(x) - \alpha(x)\frac{1}{T}\int_0^T C(s)ds), \\ r(x) &= p(x) - \alpha(x)\frac{1}{T}\int_0^T C(s)ds - \overline{r}, \\ \gamma S(t,x) &= \alpha(x)(\int_0^T C(\tau)d\tau - C(t)). \end{aligned}$$

Parameter $\gamma$ can not be isolated simply in this situation. However, we can conclude from Theorem 1.4 that there exist $p$, $\alpha$ such that for certain treatment schedules $C$ that are not

constant in time, the final population $\bar{\rho}_N$ is around some $D_0$ increasing in $D$. In other words, under non constant treatments, more plastic populations might realise a larger final mean population.

*Proof of Proposition 1.6.* First, as $\min_{x\in\Omega}\big(p(x)-\alpha(x)C_{max}\sigma\big) > 0$, one has $\lambda_1(p-\alpha C_{max}\sigma, D) < 0$. Since $R_{hom}(t,x) := p(x)-\alpha(x)C_{max}\sigma$ does not depend on time, the corresponding limit population $N_{hom}$ is also constant in time, and thus

$$\ell := \liminf_{t\to+\infty} \rho_{n_{hom}}(t) = \bar{\rho}_{N_{hom}} = -\lambda_1(p-\alpha C_{max}\sigma, D) > 0.$$

Notice that $\ell$ does not depend on $T$.

On the other hand, integrating the equation satisfied by $n_{het}$, we find that for any $k\in\mathbb{N}$,

$$\forall t\in(kT+\sigma T,(k+1)T),\quad \rho'_{n_{het}}(t) = \int_\Omega \big(p(x)-C_{max}\alpha(x)\big)n_{het}(t,x)dx - \rho^2_{het}(t) \le -m\rho_{het}(t),$$

where $m := -\max_{x\in\Omega}\big(p(x)-C_{max}\alpha(x)\big) > 0$. Hence, it follows that

$$\rho_{n_{het}}((k+1)T) \le e^{-m(1-\sigma)T}\rho_{n_{het}}(kT+\sigma T).$$

On the other hand, we know that $\rho_{n_{het}} \le \max\big\{\rho_{n_0}, \max_{(0,T)\times\Omega} R\big\}$. Hence,

$$\min_{t\in[kT,(k+1)T]} \rho_{n_{het}}(t) \le e^{-m(1-\sigma)T}\max\big\{\rho_{n_0}, \max_{(0,T)\times\Omega} R\big\} \to 0 \quad \text{as } T\to+\infty.$$

This shows that, for $T$ large enough, one will get

$$\liminf_{t\to+\infty} \rho_{n_{het}}(t) < \liminf_{t\to+\infty} \rho_{n_{hom}}(t).$$

□

# 4 Competition

This section is devoted to the demonstration of Theorem 1.8. We begin with a preliminary lemma.

**Lemma 4.1.** *The solution $(n,m)$ of (1.4) does not converge to $(N,0)$, where $N$ is the $T$-periodic solution of (1.1) with mutation coefficient $D = D_1$.*

*Proof.* Suppose that $(n,m) \longrightarrow (N,0)$ as $t\to+\infty$. Set $\epsilon > 0$ such that $-(\lambda_1(R,D_1)-\lambda_1(R,D_2)) > 2\epsilon$. Then there exists $t_0 > 0$ such that:

$$\forall t\ge t_0,\ \int_\Omega |N(t,x)-n(t,x)|dx \le \epsilon \text{ and } \int_\Omega m(t,x)dx \le \epsilon. \tag{4.14}$$

Let $\phi$ be the $T$-periodic eigenfunction satisfying:

$$\begin{cases} \partial_t \phi(t,x) - D_1 \Delta \phi(t,x) - R(t,x)\phi(t,x) = \lambda_1(R,D_1)\phi(t,x), \\ \partial_\nu \phi(t,x) = 0 \text{ for } t \geq 0,\ x \in \partial\Omega, \\ \int_\Omega \phi(t_0,x)dx = 1. \end{cases} \tag{4.15}$$

Since $m(t_0,x) > 0$ for any $x \in \Omega$, there exists $\eta > 0$ such that:

$$\forall x \in \Omega,\ m(t_0,x) \geq \eta\phi(t_0,x).$$

Now define the following function:

$$\widetilde{m}(t,x) = m(t,x)\exp\left(\int_{t_0}^{t} (\rho_n(s) + \rho_m(s))ds + t\lambda_1(R,D_1)\right).$$

Then $\widetilde{m}$ is a solution of (4.15), and for all $x \in \Omega$ we have $\widetilde{m}(t_0,x) \geq \eta\phi(t_0,x)$. By comparison principle, for any $t \geq t_0$ and $x \in \Omega$, we have $\widetilde{m}(t,x) \geq \eta\phi(t,x)$. Going back to $m$, this implies for any $l \in \mathbb{N}$:

$$\begin{aligned} m(lT+t_0,x) &= \widetilde{m}(lT+t_0,x)\exp\left(-lT\lambda_1(R,D_1) - \int_{t_0}^{lT+t_0} (\rho_n(t) + \rho_m(t))dt\right) \\ &\geq \eta\phi(t_0,x)\exp\left(-lT\lambda_1(R,D_1) - \int_{t_0}^{lT+t_0} \rho_N(t)dt - \int_{t_0}^{lT+t_0} (\rho_n(t) - \rho_N(t) + \rho_m(t))dt\right) \\ &\geq \eta\phi(t_0,x)\exp\left(-lT\lambda_1(R,D_1) + lT\lambda_1(R,D_2) - 2lT\epsilon\right), \end{aligned}$$

so that

$$\rho_m(lT+t_0) \geq \eta\exp\left(-lT\lambda(R,D_1) + lT\lambda_1(R,D_2) - 2lT\epsilon\right).$$

Thus $\rho_m(lT+t_0) \underset{l\to+\infty}{\longrightarrow} +\infty$, which contradicts (4.14).

□

**Lemma 4.2.** *The solution $(n,m)$ of (1.4) satisfies*

$$\liminf_{t\to+\infty} \inf_{x\in\Omega} \big(m(t,x) + n(t,x)\big) > 0.$$

*Proof.* First, the Harnack inequality yields that there exists a constant $C > 0$ such that

$$\forall t > 1, \quad \sup_{x\in\Omega} m(t-1,x) \leq C \inf_{x\in\Omega} m(t,x), \qquad \sup_{x\in\Omega} n(t-1,x) \leq C \inf_{x\in\Omega} n(t,x).$$

Take $\varepsilon < \min\{-\lambda_1(R,D_1), -\lambda_1(R,D_2)\}$ and assume that there exists $t_0 \geq 0$ such that $\inf_{x\in\Omega}\big(n(t_0+1,x) + m(t_0+1,x)\big) \leq \varepsilon/(C|\Omega|)$. Then the above inequalities yield $\sup_{x\in\Omega}\big(n(t_0,x) + m(t_0,x)\big) \leq \varepsilon/(C|\Omega|)$. Let $\tau$ to be the largest time such that $\sup_{x\in\Omega}\big(n(t_0+\tau,x) + m(t_0+\tau,x)\big) \leq \varepsilon/(C|\Omega|)$, even if it means $\tau = +\infty$, and assume that $\tau > 1$.

Let $\psi$ be the $T$-periodic eigenfunction satisfying:

$$\begin{cases} \partial_t \psi(t,x) - D_2 \Delta \psi(t,x) - R(t,x)\psi(t,x) = \lambda_1(R,D_2)\psi(t,x), \\ \partial_\nu \psi(t,x) = 0 \text{ on } [0,+\infty)\times\partial\Omega, \\ \int_\Omega \psi(0,x)dx = 1, \end{cases} \tag{4.16}$$

and $\phi$ the similar eigenfunction associated with $\lambda_1(R,D_1)$. Then one can easily prove, with the same arguments as in the proof of Lemma 4.1, that

$$\forall t \in (t_0+1, t_0+\tau), \forall x \in \Omega,\ m(t,x) \geq M_0 \psi(t,x) e^{-\lambda_1(R,D_2)(t-t_0)}, \text{ where } M_0 = \frac{\min_{\overline{\Omega}} m(t_0+1,\cdot)}{\max_{\overline{\Omega}} \psi(t_0+1,\cdot)} > 0.$$

Similarly, one gets

$$\forall t \in (t_0+1, t_0+\tau), \forall x \in \Omega,\ n(t,x) \geq N_0 \phi(t,x) e^{-\lambda_1(R,D_1)(t-t_0)}, \text{ where } N_0 = \frac{\min_{\overline{\Omega}} n(t_0+1,\cdot)}{\max_{\overline{\Omega}} \phi(t_0+1,\cdot)} > 0.$$

Adding these two inequalities, using the Harnack inequality and the fact that $\phi$ and $\psi$ are both uniformly positive and bounded, one gets the existence of a positive constant, that we still denote $C > 0$, such that

$$\forall t \in (t_0+1, t_0+\tau), \forall x \in \Omega, \quad m(t,x) + n(t,x) \geq C \sup_{x\in\Omega} \big(m(t_0,x) + n(t_0,x)\big) e^{\varepsilon(t-t_0)}.$$

Thus $\tau < +\infty$ and

$$\varepsilon/|\Omega| = \sup_{x\in\Omega} \big(m(t_0+\tau,x) + n(t_0+\tau,x)\big) \geq C \sup_{x\in\Omega} \big(m(t_0,x) + n(t_0,x)\big) e^{\varepsilon\tau}.$$

If $t_0 = 0$, this provides a bound on $\tau$. Otherwise, one can assume that $t_0$ is such that $\sup_{x\in\Omega} \big(m(t_0,x) + n(t_0,x)\big) = \varepsilon/|\Omega|$, and thus $\tau \leq -\ln C/\varepsilon$. This bound being independent of $t_0$, we thus eventually obtain, by using the parabolic regularity and the Harnack inequality,

$$\inf_{t\in(t_0,t_0+\tau)} \inf_{x\in\Omega} \big(m(t,x) + n(t,x)\big) > C\varepsilon \quad \text{ for some positive constant } C.$$

In other words, we have proved that there exist $\varepsilon > 0$ and $C > 0$ such that for all $t > 1$ such that $\inf_{x\in\Omega} \big(n(t+1,x) + m(t+1,x)\big) \leq \varepsilon/|\Omega|$, one has $\inf_{x\in\Omega} \big(m(t,x) + n(t,x)\big) > C\varepsilon$. It easily follows that $\liminf_{t\to+\infty} \inf_{x\in\Omega} \big(m(t,x) + n(t,x)\big) > 0$. □

*Proof of Theorem 1.8.* Consider the sequences $n_k(t,x) := n(t+kT,x)$ and $m_k(t,x) := m(t+kT,x)$. Parabolic regularity yields that one can assume, up to extraction, that these two sequences converge to some limits $n_\infty$ and $m_\infty$ in $W^{1,p/2;2,p}_{loc}(\mathbb{R},\Omega)$, which are time-global solutions of:

$$\begin{cases} \partial_t n_\infty(t,x) - D_1 \Delta n_\infty(t,x) = n_\infty(t,x)(R(t,x) - \rho_{n_\infty}(t) - \rho_{m_\infty}(t)), \\ \partial_t m_\infty(t,x) - D_2 \Delta m_\infty(t,x) = m_\infty(t,x)(R(t,x) - \rho_{n_\infty}(t) - \rho_{m_\infty}(t)), \\ \rho_{n_\infty}(t) = \int_\Omega n_\infty(t,x)dx,\ \rho_{m_\infty}(t) = \int_\Omega m_\infty(t,x)dx, \\ \partial_\nu n_\infty(t,x) = 0 \text{ on } [0,+\infty)\times\partial\Omega, \\ \partial_\nu m_\infty(t,x) = 0 \text{ on } [0,+\infty)\times\partial\Omega. \end{cases} \tag{4.17}$$

We know from Lemma 4.2 that $\inf_{t\in\mathbb{R},x\in\Omega}\big(n_\infty(t)+m_\infty(t)\big)>0$.

Assume first that $m_\infty\equiv 0$. Then we know from Lemma 4.1 that $n_\infty$ cannot be identically equal to 0 nor $N$. We now use Proposition 2.7 of [19], which yields that the equation

$$\partial_t u - D_1\Delta u = R(t,x)u,$$

admits a unique time-global positive solution $u$ up to multiplication. Using the change of variables

$$u(t,x) := n_\infty(t,x)\exp\left(\int_0^t \rho_{n_\infty}(s)ds\right)$$

we obtain that

$$n_\infty(t,x)e^{\int_0^t \rho_{n_\infty}(s)ds} \equiv CN(t,x)e^{\int_0^t \rho_N(s)ds} \qquad \text{for some constant } C>0.$$

Integrating in $x$, taking the log and derivating in $t$, we obtain, as above, that

$$\rho'_{n_\infty}(t) = \rho_{n_\infty}(t)\Big(\frac{\rho'_N(t)}{\rho_N(t)} + \rho_N(t) - \rho_{n_\infty}(t)\Big).$$

We know (see for instance [27]) that this equation admits a unique time-global solution which is uniformly positive and bounded. As $\rho_N$ is also a solution, we get $\rho_{n_\infty}\equiv\rho_N$ and thus $C=1$ and $n_\infty\equiv N$. This is a contradiction with Lemma 4.1. Hence, $m_\infty\not\equiv 0$. As this is true for any extraction of the sequence $(m_k)$, we have thus even proved that $\inf_{\mathbb{R}\times\Omega} m_\infty>0$.

Next, using the change of variables

$$\widetilde{m}_\infty(t,x) := m_\infty(t,x)\exp\left(\int_0^t \big(\rho_{n_\infty}(s)+\rho_{m_\infty}(s)\big)ds\right)$$

and, again, by Proposition 2.7 of [19], we get

$$\widetilde{m}_\infty(t,x) \equiv C_1\psi(t,x)e^{-\lambda_1(R,D_2)t}$$

where $C_1>0$ and $\psi$ is the $T$-periodic eigenfunction satisfying:

$$\begin{cases} \partial_t\psi(t,x) - D_2\Delta\psi(t,x) - R(t,x)\psi(t,x) = \lambda_1(R,D_2)\psi(t,x), \\ \partial_\nu\psi(t,x) = 0 \text{ on } [0,+\infty)\times\partial\Omega, \\ \int_\Omega \psi(0,x)dx = 1. \end{cases} \tag{4.18}$$

Assume now by contradiction that $n_\infty\not\equiv 0$. The parabolic strong maximum principle gives $n_\infty>0$. Then we could prove similarly as above that

$$\widetilde{n}_\infty(t,x) \equiv C_2\phi(t,x)e^{-\lambda_1(R,D_1)t}$$

with obvious notations. Hence,

$$\frac{n_\infty}{m_\infty} \equiv \frac{\widetilde{n}_\infty}{\widetilde{m}_\infty} \equiv \frac{C_2\phi}{C_1\psi}e^{\big(\lambda_1(R,D_2)-\lambda_1(R,D_1)\big)t}.$$

The right-hand side goes to $+\infty$ as $t\to+\infty$ since $\phi$ and $\psi$ are both positive and periodic, and $\lambda_1(R,D_2)>\lambda_1(R,D_1)$. But the left-hand side is bounded since $n_\infty$ is bounded and $\inf_{\mathbb{R}\times\Omega} m_\infty>0$. We have thus reached a contradiction. Hence, $n_\infty\equiv 0$.

We then easily deduce from the above identities that $m_\infty\equiv M$, which concludes the proof.

□

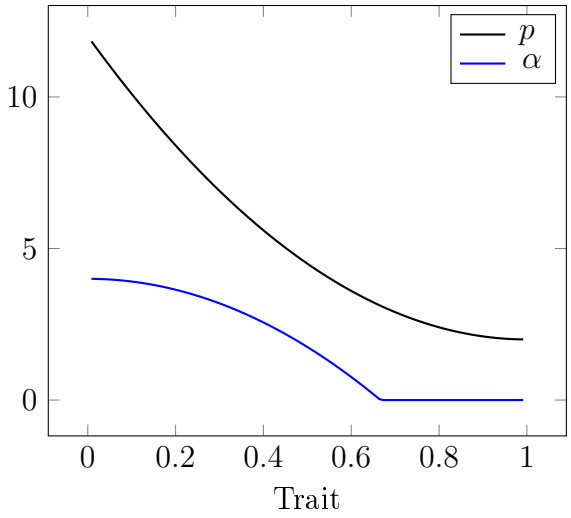



Figure 1: Proliferation and sensitivity functions chosen for the simulations

# 5 Numerical simulations

We present in this section some numerical illustrations of the properties exposed in the previous sections. The simulations were done with $R$ of the form (1.2). We considered functions $p$ and $\alpha$ of the following form:

$$p(x) = 10(x-1)^2 + 2,$$
$$\alpha(x) = 9\max(-x^2 + \frac{4}{9}, 0).$$

These functions were chosen arbitrarily to illustrate our results. They are represented in figure 1. In this case, phenotypes around $x = 0$ represent more proliferative but more sensitive cells, while phenotypes around $x = 1$ represent resistant cells, which have a deficit in proliferation.

## 5.1 Influence of the mutation rate

In figure 2, we represent the final mean population $\bar{\rho}_N$ as a function of the mutation rate $D$ for different treatment schedules. All schedules deliver the same mean quantity of drug $M = \frac{1}{T}\int_0^T C(t)dt = 2$ over each period of time, but the length of the administration time varies. We recall that in this situation, the quantities $\lim_{D\to 0}\bar{\rho}_N$ and $\lim_{D\to+\infty}\bar{\rho}_N$ will not depend on $\tau$: for our particular choice of $p$, $\alpha$ and $M$ they are equal to:

$$\lim_{D\to 0}\bar{\rho}_N = \max_{x\in[0,1]}(p(x) - \alpha(x)\frac{M}{T}) = 3.8,\ \lim_{D\to+\infty}\bar{\rho}_N = \int_0^1 (p(x) - \alpha(x)\frac{M}{T})dx = 1.7.$$

We observe, as stated in Propositions 1.3 and 1.5, that if $R$ is constant in time (case $\tau = T$), then $\bar{\rho}_N$ is a decreasing function of $D$. However, if $\tau$ is shorter, $\bar{\rho}_N$ is in some range of $D$

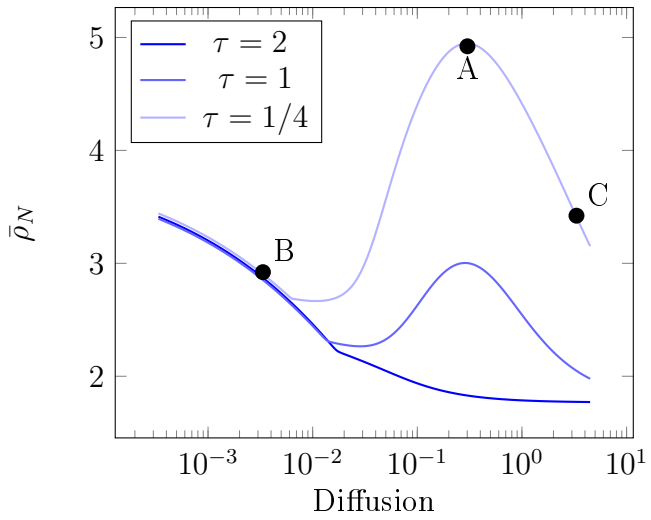



Figure 2: Final mean populations $\bar{\rho}_N$ represented as functions of the mutation rate $D$ for various treatment schedules. The treatments are of the form $C(t) = \mathbf{1}_{0 \leq t \leq \tau} M/\tau$, with $M = 2$ and $\tau$ varying between $1/4$ and $T = 2$. Populations $A$, $B$ and $C$ are detailed in figure 3.

an increasing function of $D$. Moreover, for $\tau = 1/4$, the maximum of $\bar{\rho}_N$ is reached for $D = 0.3 > 0$. In this case, a population with a positive mutation rate will be favoured.

On figure 3, we represent the phenotype repartition for three particular populations $A$, $B$ and $C$, corresponding to $D = 0.3$, $D = 4 * 10^{-3}$, and $D = 2$ respectively, all illustrated for $\tau = 1/4$. As we compare $A$ and $B$, we can argue that $\bar{\rho}_N(D = 0.3) > \bar{\rho}_N(D = 4 * 10^{-3})$ because the high mutation rate is so that, at the beginning of the treatment, a larger population is already present around $x = 1$. Thus during treatment, the resistant part of the population will reach higher levels. However, if $D$ is too large as in population $C$, then it does not profit enough of the high growth rate at $x = 0$ before treatment starts.

## 5.2 Influence of the time of administration

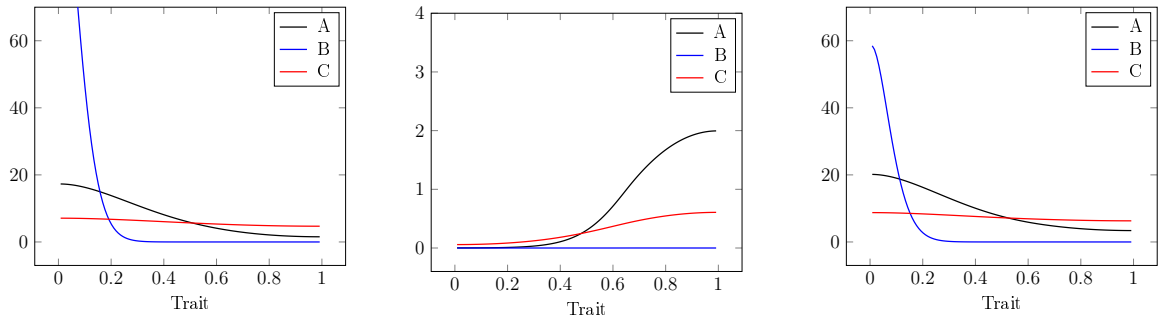
We stated in the introduction that for any $\kappa \in \mathbb{N}$, a convexity argument proves that if $0 < \kappa\tau < T$ and

$$C_1(t) = \begin{cases} \frac{M}{\tau} \text{ if } 0 < t \leq \tau, \\ 0 \text{ if } \tau < t \leq T \end{cases}, \quad C_2(t) = \begin{cases} \frac{M}{\kappa\tau} \text{ if } 0 < t \leq \kappa\tau, \\ 0 \text{ if } \kappa\tau < t \leq T \end{cases},$$

then $\lambda_1(p - \alpha C_1, D) < \lambda_1(p - \alpha C_2, D)$. We conjectured that this is true for any $\kappa \in [1, T/\tau]$, in other words, that if $C_\tau$ is defined by

$$C_\tau(t) = \begin{cases} \frac{M}{\tau} \text{ if } 0 < t \leq \tau, \\ 0 \text{ if } \tau < t \leq T \end{cases},$$

then the final mean population $(\bar{\rho}_N)$ associated to $R_\tau = p - \alpha C_\tau$ is a non-increasing function of $\tau$. This is illustrated in figure 4.

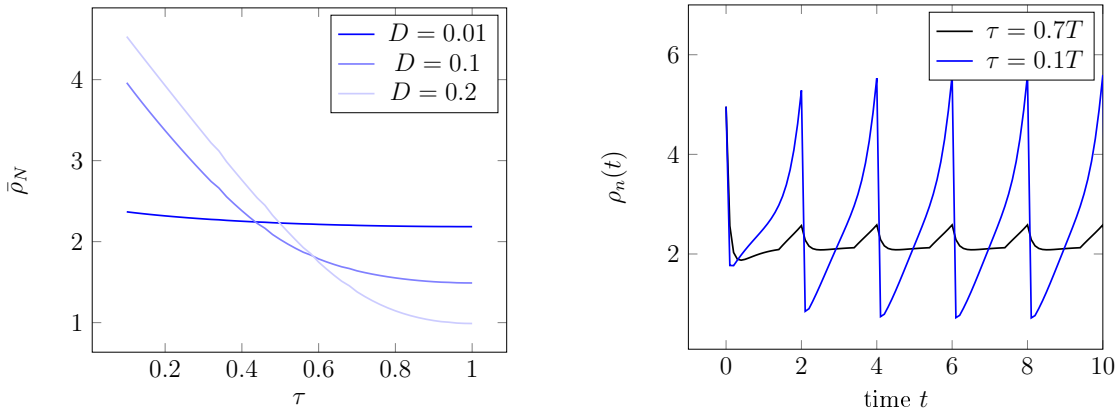



(a) Populations before treatment

(b) Populations after treatment

(c) Populations, mean over time

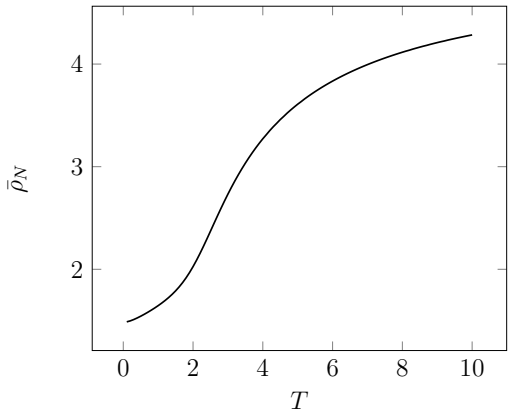
Figure 3: Populations $A$, $B$ and $C$ of figure 2 are detailed for $\tau = 1/4$. We represent the population repartition in phenotypes just before treatment, just after treatment and the mean population.



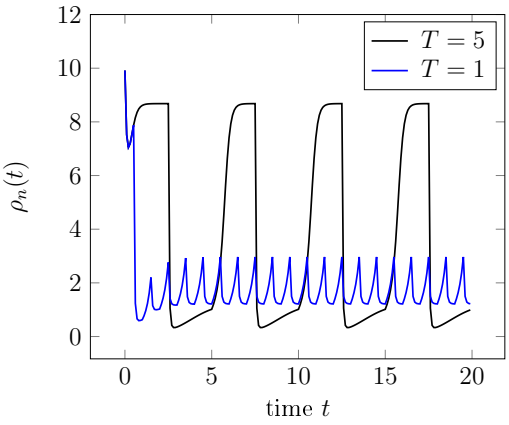

(a) Final mean population $\bar{\rho}_N$ as a function of the time of administration $\tau$.

(b) Total populations over time for different times of administration $\tau$, with $D = 0.1$.

Figure 4: Illustration of the conjecture that $\bar{\rho}_N$ is a decreasing function of the time of drug administration $\tau$. These numerical simulations were performed for $T = 2$.




(a) Final mean population $\bar{\rho}_N$ as a function of the period length $T$.




(b) Total populations over time for different period length $T$.

Figure 5: Illustration of Proposition 1.7 on the influence of $T$ on the population size. These numerical simulations were performed for $\tau = T/2$ and a fixed diffusion coefficient $D = 0.1$.

On figure 4a, we observe that for different values of the diffusion $D$, the final mean population $\bar{\rho}_N$ is a decreasing function of $\tau$. On figure 4b, we observe the population over time under two types of treatments: one with $\tau = 0.7T$, the other with $\tau = 0.1T$. We see there that for a short $\tau$, the population oscillates during each period between two extreme values, while for a larger $\tau$ the population fluctuates less.

On figure 5, we illustrate Proposition 1.7, which concerns the influence of the period length $T$ on the final mean population $\bar{\rho}_N$. As the function $R$ we chose does satisfy the conditions of application of Proposition 1.7, we observe on figure 5a that $\bar{\rho}_N$ is a non-decreasing function of $T$. Furthermore, we depict on figure 5b the time evolution of two particular populations, where we only changed the period length $T$. We observe that when $T$ is large, the population $\rho_n(t)$ approaches, at each period, a maximal plateau during the time without treatment ($C = 0$). On the contrary, if $T$ is smaller, $\rho_n(t)$ does not have time to reach these values before treatment is applied again. However, if $T$ is large, the population $\rho_n(t)$ reaches at each period very low values. As discussed in Proposition 1.6, biologically, there exists at these moments a possibility of extinction of the population.

## 5.3 Varying the treatment dosage

In this part, we numerically investigate the role of $M = \int_0^T C(t)dt$, the total drug used during each period, on the final mean population $\bar{\rho}_N$.

On Figure 6, we represent $\bar{\rho}_N$ for a treatment of the form $C(t) = \mathbf{1}_{0\leq t\leq \tau} M/\tau$ with $\tau = 1/4$, for different values of the diffusion $D$ and on the drug dosage $M$.

If $M$ is small, $\bar{\rho}_N$ reaches its maximum for $D = 0$. Indeed, if $M$ is too small, $R$ is decreasing in $x$ for all $t \geq 0$, and thus $\bar{\rho}_N$ is a decreasing function of $D$, as stated in Proposition 1.5. But if $M$ increases, around $M = 3$ we see that bet hedging occurs, in the sense that $\bar{\rho}_N$ is in some region increasing in $D$, illustrating the phenomenon described in

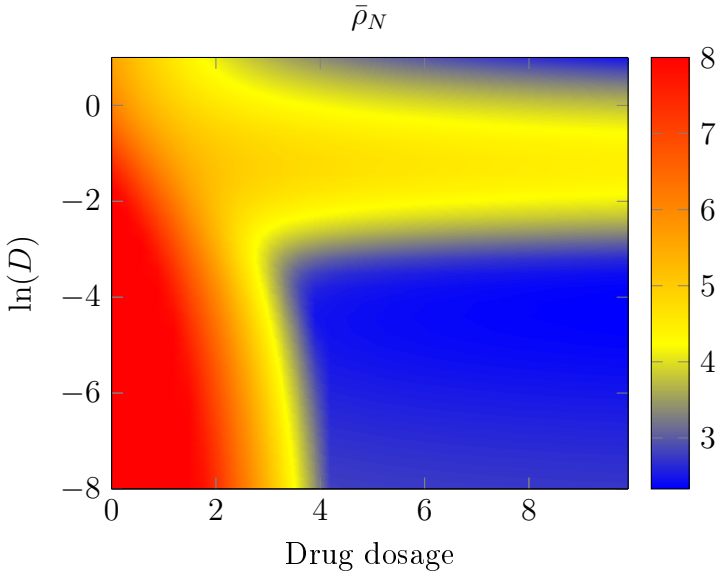



Figure 6: Mean limit population $\bar{\rho}_N$ as a function of both diffusion and drug dosage per period $M$.

Theorem 1.4. Moreover, for $M > 4$, $\bar{\rho}_N$ reaches its maximum for a positive value of $D$. As $M$ increases further, the maximum of $\bar{\rho}_N$ over diffusion $D$ slowly decreases.

## 5.4 Random fluctuations in the environment

The results we presented in this article address periodic changes of the environment, corresponding in the framework of cancer treatment to a regular chemotherapy schedule. But, as we stated in the introduction, chemotherapy is not the only reason why the environment changes: tumour vascularisation, immune system reaction and other phenomena can vary over time, with a less regular timing. We present here a numerical simulation where the environment no longer changes periodically, but randomly. More precisely, still using the same $p$, $\alpha$, $M$ defined in Section 5.1, for each time unit $\Delta t$ we have:

$$R(t,x) = \begin{cases} p(x) \text{ with probability } 1-\gamma, \\ p(x) - \alpha(x)\frac{M}{\gamma} \text{ with probability } \gamma, \end{cases}$$

for a certain $\gamma \in (0,1)$. Notice that the expected value of the growth rate $\mathbb{E}(R)$ does not depend on $\gamma$: this way, we are doing something similar as in 5.1, with $\gamma$ being an analogue of $\frac{\tau}{T}$. We are interested in the mean value of $\rho_n$ over time, namely the following quantity:

$$\hat{\rho}_n = \lim_{t\to\infty} \frac{1}{t} \int_0^t \int_\Omega n(s,x)dxds$$

when it exists. We conjecture it to be independent of the initial condition.

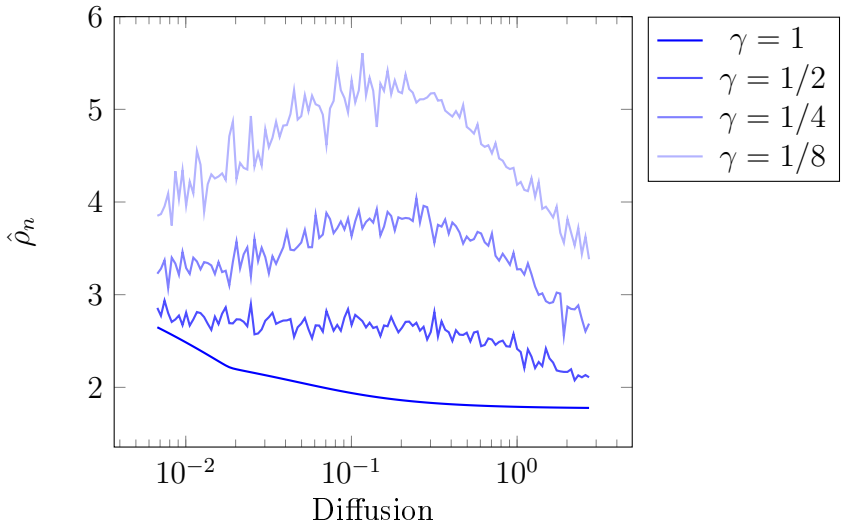



Figure 7: Populations for random changing of environment with same mean value.

Figure 7 presents simulations for different values of $\gamma$, and an initial condition $n_0(x) = 1$ for all $x \in \Omega$. If $\gamma = 1$, we are in fact in a situation of constant environment, and thus retrieve previous results: $\hat{\rho}_n$ is a non-increasing function of $D$, and its limit values for $D \to 0$ and $D \to +\infty$ are known. If $\gamma$ decreases, we observe that for the same $D$ the mean population $\hat{\rho}_n$ increases, and for $\gamma$ small enough, $D \mapsto \hat{\rho}_n$ seems to no longer be a non-increasing function.

As far as the authors know, the influence of stochastic fluctuations of the environment has only been investigated numerically for an ODE in [16]. Simulation suggest that theoretical results on periodic fluctuations might be extended to stochastic ones. It would be of great interest to investigate this, as biological phenomena often present stochastic fluctuations.

# Conclusion

We demonstrated in this article some properties of trait-structured populations in time periodic environment. Especially, we showed that in some situations, a population might benefit from a large mutation rate. Moreover, in such an environment, a more plastic population would replace a less plastic one. This motivates the study of this equation in the regime of intermediate mutations, thus of large diffusion rates.

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# References


[1] M. Alfaro and M. Veruete. Evolutionary branching via replicator–mutator equations. *Journal of Dynamics and Differential Equations*, Jul 2018.

[2] A. Ardaševa, R. A. Gatenby, A. R. A. Anderson, H. M. Byrne, P. K. Maini, and T. Lorenzi. Evolutionary dynamics of competing phenotype-structured populations in periodically fluctuating environments. *arXiv:1905.11712 [q-bio]*, May 2019. arXiv: 1905.11712.

[3] D. Basanta, H. Hatzikirou, and A. Deutsch. Studying the emergence of invasiveness in tumours using game theory. *The European Physical Journal B*, 63(3):393–397, Jun 2008.

[4] P.L. Bedard, A.R. Hansen, M.J. Ratain, and L.L. Siu. Tumour heterogeneity in the clinic. *Nature*, 501(7467):355, 2013.

[5] H. Berestycki, F. Hamel, and L. Roques. Analysis of the periodically fragmented environment model: I-species persistence. *Journal of Mathematical Biology*, 51(1):75–113, Jul 2005.

[6] H. Berestycki, F. Hamel, and L. Roques. Analysis of the periodically fragmented environment model: II-biological invasions and pulsating travelling fronts. *Journal de Mathématiques Pures et Appliquées*, 84(8):1101–1146, Aug 2005.

[7] A. Calsina and S. Cuadrado. Small mutation rate and evolutionarily stable strategies in infinite dimensional adaptive dynamics. *Journal of Mathematical Biology*, 48(2):135–159, Feb 2004.

[8] R. S. Cantrell and C. Cosner. Diffusive logistic equations with indefinite weights: Population models in disrupted environments II. *SIAM Journal on Mathematical Analysis*, 22(4):1043–1064, Jul 1991.

[9] N. Champagnat, R. Ferrière, and S. Méléard. Individual-based probabilistic models of adaptive evolution and various scaling approximations. In *Seminar on Stochastic Analysis, Random Fields and Applications V*, pages 75–113. Springer, 2007.

[10] N. Champagnat and A. Lambert. Evolution of discrete populations and the canonical diffusion of adaptive dynamics. *The Annals of Applied Probability*, 17(1):102–155, Feb 2007.

[11] J. Coville. Convergence to equilibrium for positive solutions of some mutation-selection model. *arXiv:1308.6471 [math]*, Aug 2013. arXiv: 1308.6471.

[12] L. Desvillettes, P. E. Jabin, S. Mischler, and G. Raoul. On selection dynamics for continuous structured populations. *Communications in Mathematical Sciences*, 6(3):729–747, 2008.

[13] T. Epstein, R.A. Gatenby, and J.S. Brown. The Warburg effect as an adaptation of cancer cells to rapid fluctuations in energy demand. *PLOS ONE*, 12(9):e0185085, Sep 2017.

[14] S. Figueroa Iglesias and S. Mirrahimi. Long time evolutionary dynamics of phenotypically structured populations in time-periodic environments. page 30, 2018.

[15] S. Geritz. Evolution and the theory of games. *EVOLUTION AND THE THEORY OF GAMES*, page 6, 2011.

[16] C. A. Gravenmier, M. Siddique, and R. A. Gatenby. Adaptation to stochastic temporal variations in intratumoral blood flow: The warburg effect as a bet hedging strategy. *Bulletin of Mathematical Biology*, 80(5):954–970, May 2018.

[17] P. Hess. *Periodic-parabolic boundary value problems and positivity*. Longman Scientific & Technical, 1991.

[18] D. Horvath and B. Brutovsky. Study of selected phenotype switching strategies in time varying environment. *Physics Letters A*, 380(13):1267–1278, Mar 2016.

[19] J. Hùska. Harnack inequality and exponential separation for oblique derivative problems on lipschitz domains. *Journal of Differential Equations*, 226(2):541–557, Jul 2006.

[20] V. Hutson, K. Mischaikow, and P. Poláčik. The evolution of dispersal rates in a heterogeneous time-periodic environment. *Journal of Mathematical Biology*, 43(6):501–533, Dec 2001.

[21] V. Hutson, W. Shen, and G. T. Vickers. Estimates for the principal spectrum point for certain time-dependent parabolic operators. page 11.

[22] E. Kisdi. Dispersal: Risk spreading versus local adaptation. *The American Naturalist*, 159(6):579–596, Jun 2002.

[23] E. Kisdi. Conditional dispersal under kin competition: extension of the hamilton–may model to brood size-dependent dispersal. *Theoretical Population Biology*, 66(4):369–380, Dec 2004.

[24] U. Ledzewicz, H. Schättler, M.R. Gahrooi, and S.M. Dehkordi. On the MTD paradigm and optimal control for multi-drug cancer chemotherapy. *Mathematical Biosciences and Engineering*, 10(3):803–819, Apr 2013.

[25] S. Liu, Y. Lou, R. Peng, and M. Zhou. Monotonicity of the principal eigenvalue for a linear time-periodic parabolic operator. *arXiv:1903.11757 [math]*, Mar 2019. arXiv: 1903.11757.

[26] T. Lorenzi, R. H. Chisholm, L. Desvillettes, and B. D. Hughes. Dissecting the dynamics of epigenetic changes in phenotype-structured populations exposed to fluctuating environments. *Journal of Theoretical Biology*, 386:166–176, Dec 2015.

[27] G. Nadin. The principal eigenvalue of a space–time periodic parabolic operator. *Annali di Matematica Pura ed Applicata*, 188(2):269–295, Apr 2009.

[28] G. Nadin. Some dependence results between the spreading speed and the coefficients of the space–time periodic fisher–kpp equation. *European Journal of Applied Mathematics*, 22(2):169–185, Apr 2011.

[29] R. Peng and X.-Q. Zhao. Effects of diffusion and advection on the principal eigenvalue of a periodic-parabolic problem with applications. *Calculus of Variations and Partial Differential Equations*, 54(2):1611–1642, 2015.

[30] B. Perthame. *Transport equations in biology*. Springer Science & Business Media, 2006.

[31] A.O. Pisco, A. Brock, J. Zhou, A. Moor, M. Mojtahedi, D. Jackson, and S. Huang. Non-Darwinian dynamics in therapy-induced cancer drug resistance. *Nature Communications*, 4(1), Dec 2013.

[32] C. Pouchol, J. Clairambault, A. Lorz, and E. Trélat. Asymptotic analysis and optimal control of an integro-differential system modelling healthy and cancer cells exposed to chemotherapy. *Journal de Mathématiques Pures et Appliquées*, 116:268–308, Aug 2018.