

CEMRACS 2018: HORIZONTAL GENE TRANSFER

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Abstract. Horizontal Gene Transfer (HGT) consists in the moving of genetic material between unicellular/multicellular organisms, which is not through a vertical transmission (DNA transfer from parents to its offspring). It is proved that this motion plays an important role in the evolution of organisms, and it is the principal reason which allows to propagate the resistance to antibiotics (and drugs in general) in bacteria. Here we consider both a stochastic individual-based pure jump process and a non-linear integro-differential equation obtained in the limit of large population size of such stochastic process.

Résumé. in french plz, someone :((((

Keywords: Horizontal gene transfer, stochastic individual-based models, integro-differential equations, Hamilton-Jacobi equation, evolution dynamics, resistance to antibiotics.

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INTRODUCTION

Accurate mathematical description of the evolutionary mechanism is an open question in biology, medicine and industry. In particular, transmission of pathogens, or antibiotic resistance of bacteria is directly linked to the ability of the bacteria population to mutate and exchange genetic material either vertically (from parents to offspring), or horizontally (from interaction between non-parental individuals).

Several mathematical models for describing a population dynamics were proposed. The most intuitive model (see, for reference, [5,11]) is a stochastic birth and death process, which describes the mechanics of reproduction, competition and exchange of genetic material between individuals on a macroscopic level. Genome of each individual is described by a numerical parameter, called trait. Numerical experiments show that the effect of a

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unilateral horizontal gene transfer (HT) may lead to a periodic behaviour of the population. Roughly speaking, while HT drives individuals towards a non fit phenotype — and, consequently, to extinction, very few not affected by transfer fit individuals may eventually repopulate the environment, before being driven again to deleterious phenotypes. This phenomena is called an *evolutionary rescue of a small population*.

However, within a framework of stochastic jump processes, it is hard to accurately define and study the observed periodicity. Second drawback of the stochastic system is that it is costly to compute, especially for a large time scale and population size. Thus, in a case of large population it is more practical to work with a deterministic PDE model, obtained as a limit of *of large population* for a stochastic system [3, 4], or a Hamilton-Jacobi type equation, obtained as a limit of the PDE model for small mutations and a time rescaling [9].

The main goal of our work is to conduct a numerical analysis of the population dynamics on a macroscopic individual based model and to compare it with the deterministic system which is obtained as a limit for a large population. We are especially interested in determining to which extent the limiting Hamilton-Jacobi equation is able to grasp qualitative properties of the stochastic model. This framework has already been successfully used to understand the concentration phenomena, and the location of the dominant trait (see for instance [15, 16]). Our aim is to understand if the Hamilton-Jacobi approach is also well suited to describe the evolutionary rescue phenomena which crucially rely on an accurate description of the small populations.

On this step the choice of an approximation scheme for simulating solutions of the PDE model is of tremendous importance. As it is further explained in Section 2, classical explicit schemes do not preserve the asymptotic behaviour of the solution if the time rescaling step goes to 0. From numerical point of view, it involves operations with exponentially big values, which leads to non-negligible errors for explicit numerical schemes. We address this question by proposing an asymptotic preserving scheme for a Hamilton-Jacobi equation, adapting an approach proposed in [7]. More generally, the numerical approximation problem for solutions of Hamilton-Jacobi equations is treated in [1].

This paper is structured as follows: first, we introduce the model both in stochastic and deterministic setting, and formally derive the limiting Hamilton-Jacobi equation. (To be checked again) Then, we simulate a jump process, describing the bacteria population, and study its properties for different values of parameters. Our aim is to numerically determine the critical HT rate, which leads to an almost sure extinction of the whole population. On the next step, we conduct the same analysis for a Hamilton-Jacobi equation with the help of an asymptotic preserving scheme and compare it with stochastic model on appropriate time scale, and explain why the classical scheme fail to work. We end our study with conclusions and discussion of yet unsolved numerical and theoretical questions.

Check the references to the literature throughout the introduction, there may be inaccuracies

1. MODEL

1.1. Stochastic model

We consider a stochastic model describing the evolution of a population structured by phenotype, which is described at each time t by the point measure

$$\nu_t^K(dx) = \frac{1}{K} \sum_{i=0}^{N_t^K} \delta_{X_i(t)}(dx). \quad (1)$$

Parameter K is a scale parameter, referred to as the *carrying capacity*, which stands for the maximal number of individuals that the underlying environment is able to host (K can represent, for example, the amount of available resources), $N_t^K = K \int \nu_t^K(dx)$ is the size of the population at time t , and $X_i(t) \in \mathbb{R}^d$ is the trait of i -th individual living at t , which summarizes all the informations on phenotype.

The demography of the population is regulated, first of all, by birth and death. An individual with trait x gives birth to a new individual with rate $b(x)$. The trait y of the offspring is chosen from a probability distribution $m(x - y)dy$ DO WE HAVE TO RESCALE IT WITH K TO DERIVE THE PDE ?, referred to as

:model

eq:point_measure

the mutation kernel. An individual with trait x dies according to an intrinsic death rate $d(x)$ plus an additional death rate $C \frac{N_t^K}{K}$ (independent of x) which stands for the competition between individuals.

Finally, an individual with trait x can induce a unilateral Horizontal Transfer to an individual with trait y at rate $h_K(x, y, \nu)$, such that the pair (x, y) becomes (x, x) . For simplicity, we assume $h_K(x, y, \nu)$ to be in the particular form

$$h_K(x, y, \nu) = \tau_0 \frac{\alpha(x - y)}{N}, \quad (2) \quad \text{FormOfh}$$

where $N = K \int_{\mathbb{R}^d} \nu(dx)$ is the number of individuals, $\tau_0 > 0$ is a constant and α a smooth bounded function.

For a population $\nu = \frac{1}{K} \sum_{i=1}^N \delta_{x_i}$ and a generic measurable bounded function F , the generator of the process is then given by:

$$\begin{aligned} L^K F(\nu) = & \sum_{i=1}^N b(x_i) \int_{\mathbb{R}^d} \left(F\left(\nu + \frac{1}{K} \delta_y\right) - F(\nu) \right) m(x_i, dy) \\ & + \sum_{i=1}^N \left(d(x_i) + C \frac{N}{K} \right) \left(F\left(\nu - \frac{1}{K} \delta_{x_i}\right) - F(\nu) \right) \\ & + \sum_{i,j=1}^N h_K(x_i, x_j, \nu) \left(F\left(\nu + \frac{1}{K} \delta_{x_i} - \frac{1}{K} \delta_{x_j}\right) - F(\nu) \right). \end{aligned}$$

It is standard to construct the measure valued process ν^K as the solution of a stochastic differential equation driven by Poisson point measures and to derive some moment and martingale properties (see for instance [11]).

1.2. The PDE model

[ref. for introduction](#): [4, 10] It is proven (see, in particular [4, 6]) that for $K \rightarrow +\infty$ the stochastic process defined by a sequence of point measures given by (1) converges in probability to a non-linear integro-differential equation, whose solution exists and is unique. This equation is given by:

$$\begin{cases} \partial_t f(t, x) = -(d(x) + C \rho_f(t)) f(t, x) + \int_{\mathbb{R}^d} m(x - y) b(y) f(t, y) dy + f(t, x) \int_{\mathbb{R}^d} \tau(x - y) \frac{f(t, y)}{\rho_f(t)} dy, \\ \rho_f(t) = \int_{\mathbb{R}^d} f(t, x) dx, \\ f(0, x) = f^0(x) > 0, \end{cases} \quad (3) \quad \text{equation:PDE}$$

where $f(t, x)$ is the macroscopic density of the population with trait x at time t and, accordingly to the previous section, $b(x)$, $d(x)$ and C are the birth, death and competition rate respectively, m is the mutation kernel, and

$$\tau(y - x) := \tau_0 [\alpha(x - y) - \alpha(y - x)] \quad (4) \quad \text{eq:tau_def}$$

is the horizontal transfer kernel.

[I'll think about smoother passage here](#) We now perform a rescaling of the equation. On the one hand, we consider the case of small mutations: for a small parameter $\varepsilon > 0$ we define

$$m_\varepsilon(x - y) = \frac{1}{\varepsilon^d} m\left(\frac{x - y}{\varepsilon}\right).$$

With a change of variable $z = \frac{x-y}{\varepsilon}$ we can rewrite the mutation term at (t, x) as

$$\int_{\mathbb{R}^d} m_\varepsilon(x-y)b(y)f(t,y)dy = \int_{\mathbb{R}^d} m(z)b(x+\varepsilon z)f(t,x+\varepsilon z)dz. \quad (5)$$

On the other hand, when ε is small, the effect of mutations can only be observed in a larger time scale. Thus, we rescale time with $t \mapsto \frac{t}{\varepsilon}$.

We end up with the following system, for $\varepsilon > 0$:

$$\begin{cases} \varepsilon \partial_t f_\varepsilon(t, x) = -(d(x) + C\rho_\varepsilon(t))f_\varepsilon(t, x) + \int_{\mathbb{R}^d} m(z)b(x+\varepsilon z)f_\varepsilon(t, x+\varepsilon z)dz + f_\varepsilon(t, x) \int_{\mathbb{R}^d} \tau(x-y) \frac{f_\varepsilon(t, y)}{\rho_\varepsilon(t)} dy, \\ \rho_\varepsilon(t) = \int_{\mathbb{R}^d} f_\varepsilon(t, x)dx, \\ f_\varepsilon(0, x) = f_\varepsilon^0(x) > 0. \end{cases} \quad (6)$$

equation:PDE_eps

1.3. The Hamilton-Jacobi limit

Equations in the form of (6) often give rise to concentration phenomena, i.e the convergence of f_ε towards a Dirac mass when $\varepsilon \rightarrow 0$ (see [8, 16]). The usual way to deal with these asymptotics is to perform a Hopf-Cole transformation (or WKB ansatz), i.e to consider

$$u_\varepsilon(t, x) := \varepsilon \ln(f_\varepsilon(t, x)). \quad (7)$$

eq:u_e_def

This change of variable comes from the intuition that a Dirac mass is no more than a narrow Gaussian, and more precisely that f_ε should behave like a Gaussian of variance ε , when $\varepsilon \rightarrow 0$. Accordingly, we expect u_ε to have a non singular limit when $\varepsilon \rightarrow 0$.

We now present how to identify and derive some properties about the asymptotics of u_ε when $\varepsilon \rightarrow 0$, which will be used for discussions in the sequel. The following computations are only formal, since rigorous proofs are often intricate in this context. **Nevertheless, see the following sections for rigorous proofs.**

By substituting (7) into (6) we deduce that u_ε satisfies:

$$\partial_t u_\varepsilon = -(d(x) + \rho_\varepsilon(t)) + \int_{\mathbb{R}^d} m(z)b(x+\varepsilon z) \exp\left\{\frac{u_\varepsilon(t, x+\varepsilon z) - u_\varepsilon(t, x)}{\varepsilon}\right\} dz + \int_{\mathbb{R}} \tau(x-y) \frac{f_\varepsilon(t, y)}{\rho_\varepsilon(t)} dy. \quad (8)$$

equation:hamilton

Formally, at the limit $\varepsilon \rightarrow 0$, u_ε converges to a continuous function u which satisfies the following Hamilton-Jacobi equation in the "viscosity" sense:

$$\partial_t u = -(d(x) + \rho(t)) + b(x) \int_{\mathbb{R}} M(z) e^{z \cdot \nabla_x u} dz + \tau(x - \bar{x}(t)), \quad (9)$$

HJ_limit

where $\rho(t) \geq 0$ is the weak limit of $\rho_\varepsilon(t)$ and $\bar{x}(t) = \operatorname{argmax} u(t, \cdot)$. Note that the limiting function u is not expected to be C^1 for all time. We thus need to deal with a generalized notion of solutions, namely *viscosity solution* (see [2]). Note also that in the previous formal derivation, it was implicitly assumed that $\bar{x}(t)$ was unambiguous, i.e that u reached its maximum on a single point.

Assuming that $\bar{x}(t)$ is uniquely defined, that it is a smooth function of t , that it is a nondegenerate maximum (i.e that u is strictly concave at this point), and that m is centered in 0, i.e $\int_{\mathbb{R}^d} m(z)zdz = 0$, we can derive the dynamics of $\bar{x}(t)$, referred to as the *canonical equation* in the literature: starting from

$$\nabla_x u(t, \bar{x}(t)) = 0, \quad (10)$$

a differentiation with respect to t gives

$$\frac{d}{dt}\bar{x}(t) = [-\nabla_x^2 u(t, \bar{x}(t))]^{-1} \cdot (\nabla_x r(\bar{x}(t)) + \nabla_x \tau(0)), \quad (11)$$

CanonicalEquation

where

$$r(x) := b(x) - d(x), \quad (12)$$

Definition_r

and $\nabla_x^2 u$ denotes the Hessian of u with respect to the x variable. Note that this dynamic is not expected to be always satisfied, since a new maximum of u can arise in finite time, which would cause a "jump" in the dynamics of $\bar{x}(t)$. Especially in our case, which features an oscillating phenomena, we expect $\bar{x}(t)$ to jump periodically, and to follow (11) between two jumps.

Besides, from an integration of (6) with respect to x and classical computations, we deduce that our model satisfies a saturation property, i.e

$$\rho_\varepsilon(t) \text{ is bounded from above, uniformly in } t \geq 0 \text{ and } \varepsilon > 0. \quad (13)$$

SaturationProperty

From this, and $\rho_\varepsilon(t) = \int_{\mathbb{R}^d} e^{\frac{u_\varepsilon(t,x)}{\varepsilon}} dx$, we deduce that for all $t > 0$, $\sup_{x \in \mathbb{R}^d} u(t, x) \leq 0$ and the constraint

$$\sup_{x \in \mathbb{R}^d} u(t, x) = 0 \quad \text{when} \quad \rho(t) > 0. \quad (14)$$

constraint_HJ

Note that our model allows the population to get extinct, thus we cannot expect ρ to be positive at all times. As a byproduct, we derive the concentration property, i.e the formal weak convergence of measures

$$f_\varepsilon(t, x) \rightharpoonup \rho(t) \delta_{\bar{x}(t)}(dx), \quad \text{when } \varepsilon \rightarrow 0. \quad (15)$$

From (14), it is possible to formally derive a formula for ρ . Indeed, either $\rho(t) = 0$ or $\rho(t) > 0$ and

$$\partial_t u(t, \bar{x}(t)) = 0, \quad (16)$$

which implies

$$\rho(t) = r(\bar{x}(t)) + \tau(0) = r(\bar{x}(t)), \quad (17)$$

formula_rho

for τ defined in (4) and r in (12).

1.4. Formal analysis

I would propose to move this part closer to discussions? It would be an important argument when justifying why Hamilton-Jacobi is a good approach for studying the system

Choice of parameters.

In this section, we perform a formal analysis on the Hamilton-Jacobi equation, and put in evidence different regime for certain range of parameter. To fix ideas, we will fix all parameters but the constant τ_0 in (4). For simplicity, we will consider the case $d = 1$ and will neglect the effect of mutation, i.e we take m as a Dirac mass centered at 0. We also make the following choice of parameters

$$b(x) = b > 0, \quad (18)$$

$$d(x) = dx^2, \quad d > 0, \quad (19)$$

$$\alpha \text{ smooth and bounded, s.t for a small } \delta > 0 : \quad \alpha(z) = \begin{cases} 0 & \text{if } z < -\delta \\ 1 & \text{if } z > +\delta \end{cases}, \quad \alpha'(0) = \frac{1}{2\delta}. \quad (20)$$

$$(21)$$

We also assume that the initial condition is "well prepared":

$$f_\varepsilon^0 = \frac{1}{\sqrt{\varepsilon}} e^{-\frac{x^2}{2\varepsilon}}. \quad (22)$$

Smooth dynamics of $\bar{x}(t)$.

As $\bar{x}(0) = 0$ is well defined, at least for short time, $\bar{x}(t)$ satisfies (11), which has a unique singular point x_\star . It satisfies $r'(x_\star) + \tau'(0) = 0$. We find

$$x_\star = \frac{\tau_0}{2d\delta}. \quad (23)$$

Definition_x_sta

The function $t \mapsto \bar{x}(t)$ is increasing when $\bar{x}(t) < x_\star$ and decreasing when $\bar{x}(t) > x_\star$.

Possible Jump.

When it is well defined (i.e when $\bar{x}(t)$ unambiguous), we consider the fitness function of x in an population concentrated in \bar{x} :

$$F_{\bar{x}}(x) = r(x) + \tau(x - \bar{x}). \quad (24)$$

Let assume that at time t , u reaches its maximum on $\bar{x}(t)$ and on an other value \tilde{x} . This situation implies that we have $F_{\bar{x}(t)}(\tilde{x}) \geq F_{\bar{x}(t)}(\bar{x}(t))$. We claim that if the inequality is strict, then $\bar{x}(t)$ jumps towards \tilde{x} . Indeed, using that τ is an odd function, we have $F_{\bar{x}}(\tilde{x}) > F_{\bar{x}}(\bar{x}(t))$.

Besides, (ASSUMING THAT u IS CONCAVE IN $[\bar{x}(t) \pm \eta]$, with $\eta > \delta$) we must have $\bar{x} \notin [\bar{x}(t), \bar{x}(t) + \delta]$. Assuming furthermore that $F(\bar{x}(t)) > F(\bar{x}(t) + \eta)$ i.e $2\bar{x}(t)\eta + \eta^2 > \frac{\tau_0}{d}$, we have $\tilde{x} < \bar{x}(t) - \delta$.

1.4.1. Threshold for oscillations.

A necessary condition for oscillations to happen is to have $F_{x_\star}(0) \geq F_{x_\star}(x_\star)$, i.e

$$\tau_0 \geq \tau_{osc} := (2\delta)^2 d. \quad (25)$$

On the contrary, if $\tau_0 < \tau_{osc}$, we don't have any oscillations.

Threshold for extinction

According to (17), we define x_{ext} as to solve $r(x_{ext}) = 0$, i.e

$$x_{ext} := \sqrt{\frac{b}{d}}. \quad (26)$$

We never have extinction if $x_\star < x_{ext}$ i.e

$$\tau < \tau_{ext} := 2\sqrt{bd} \quad (27)$$

We always have extinction in the case

$$\tau > \tau_{ext} \quad \text{and} \quad \tau < \tau_{osc}. \quad (28)$$

The case

$$\tau > \tau_{ext} \quad \text{and} \quad \tau > \tau_{osc}. \quad (29)$$

is more intricate, as it contains cases of no extinction, extinction, or even periodical extinction and reborn of the population.

2. NUMERICAL TESTS

2.1. Stochastic model

Basing on the rates we then compute the expected occurrence of each event withing a small time interval Δ . We assume that it is possible that 1, 2 or 3 events happen within the time step. Then we observe the behaviour of the system over the fixed time interval $[0, T]$.

As a first step, we simulate an initial population of size N_0 . We assume that the population is normally distributed around a mean trait X_{mean} with a standard deviation X_σ , so that the resulting vector $X_0 \in \mathbb{R}^{N_0}$. Note that the choice of the mean trait and the deviation is crucial for survival, since choosing an initially "unfit" individuals they risk to go extinct before they mutate enough.

Algorithm 1: Population dynamics on time interval $[0, T]$

Random initialization of a population $X_0 := \mathcal{N}(X_0^{mean}, \sigma_0) \times N_0$;

while $i\Delta \leq T$ **do**

for $\forall x \in X_i$ **do**

$X_i = X_{i-1}$;

$R_b := b(x), R_d := d(x), R_{HT} := h(x)$;

$T_b := \lambda(R_b), T_d := \lambda(R_d), T_{HT} := \lambda(R_{HT})$, where λ denotes an exponential random law;

if $T_b \leq \Delta$ **then**

 pick up a new trait z from $\mathcal{N}(x, \sigma)$;

 add a new individual with trait z to X_i ;

end

if $T_{HT} \leq \Delta$ **then**

 change a trait of a random living individual y to x

end

if $T_d \leq \Delta$ **then**

 remove the individual from X_i

end

end

return X_i

end

For this simulation we consider the transfer rate function defined by (2). Depending on the initial parameters we may observe three types of behavior, (see Figure 1). First possibility is that after some time the population "converges" to a certain optimal value of trait and then stabilizes with occasional oscillations. Second option is that the population drives itself to extinction. It is the case if the horizontal transfer rate is high, so that the individuals with less fit traits occur more often, while the birth and mutation rate prevent the system to reach the balance before the extinction occurs.

The last possibility is the cycling behavior: if the transfer rate τ is high enough with respect to the birth, death and mutation rates, then the population is "pushed" toward the higher trait over time. The side effect of this phenomena is that the individuals become less fit and die with higher rate, until the whole population boils down to its initial state with less individuals, which launches the cycle again.

We simulate the population up to time $T = 1000$ with $\Delta = 0.01$, and then plot the density of the population at each time: brighter colors on plot mean that there is a big amount of individuals with very similar traits. Each experiment is conducted with the same constant birth, death and competition rates ($b_r \equiv 1$, $d_r \equiv 1$, $C \equiv 0.5$ respectively). Initial population is simulated with $N_0 = 10000$, $X_0^{mean} = 1$, $\sigma_0 = 0.01$. Carrying capacity K is equal to N_0 . Then, we vary the parameter τ , regulating the horizontal transfer, and observe how the dynamics change.

As we see on the first plot on Figure 1, the population goes very fast to the optimal trait, which is in this case close to 0.4, and keeps reproducing within reached limits with a relatively small variance. On the second plot, population shows periodic behaviour. "Strains" are visible when the majority of individuals acquires higher, thus non-fit, traits, and eventually goes extinct. At the same time, a very small number of individuals which remains fit, manages to repopulate the system (since the competition, and hence the death term is almost zero). On the last plot high transfer rate pushes the whole population to extinction leaving no survivors.

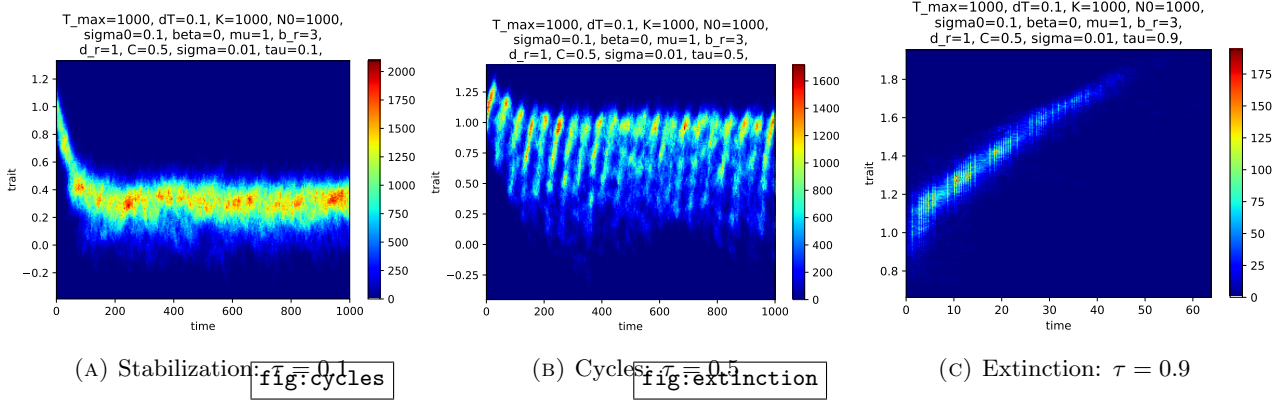


FIGURE 1. Behavior of the population dynamics as the mutation rate τ is changing, ($b_r = d_r = 1$, $\sigma = 0.01$). I'll change those pictures to show bigger population and make it consistent in style to the other experiments

Then the question arises — which value of τ is critical for extinction, given the birth and the death rates? Concerning this point we compute the dependency of the critical τ from the birth and death terms separately (see Figure 2). On this step, we run several experiments, varying both parameters b_r and τ for the first procedure, and parameters d_r and τ for the second. Then, we fix on the plot the first pairs of parameters, where we reach extinction within the considered time horizon. It is expected that the dependency on the birth term is rather linear — since more "fertile" population has more survival chances than less fertile even for high transfer rate. At the same time, results for the death rate are rather surprising. It seems almost natural that in more hostile environment it is easier to push the population to extinction. However, for a very high death rate, effect of horizontal transfer gets weaker, since the non-fit individual die faster than they manage to transmit their genetic information.

2.2. Numerical scheme for the PDE model

In this section, a numerical scheme for (6) is presented, and its properties are numerically investigated. For the discretization of (6), we consider a bounded space of traits $[X_{\min}, X_{\max}]$, discretized with N_x points. Denoting N_x the number of discretization points of the interval $[X_{\min}, X_{\max}]$, we define

$$\Delta x = \frac{X_{\min} - X_{\max}}{N_x - 1},$$

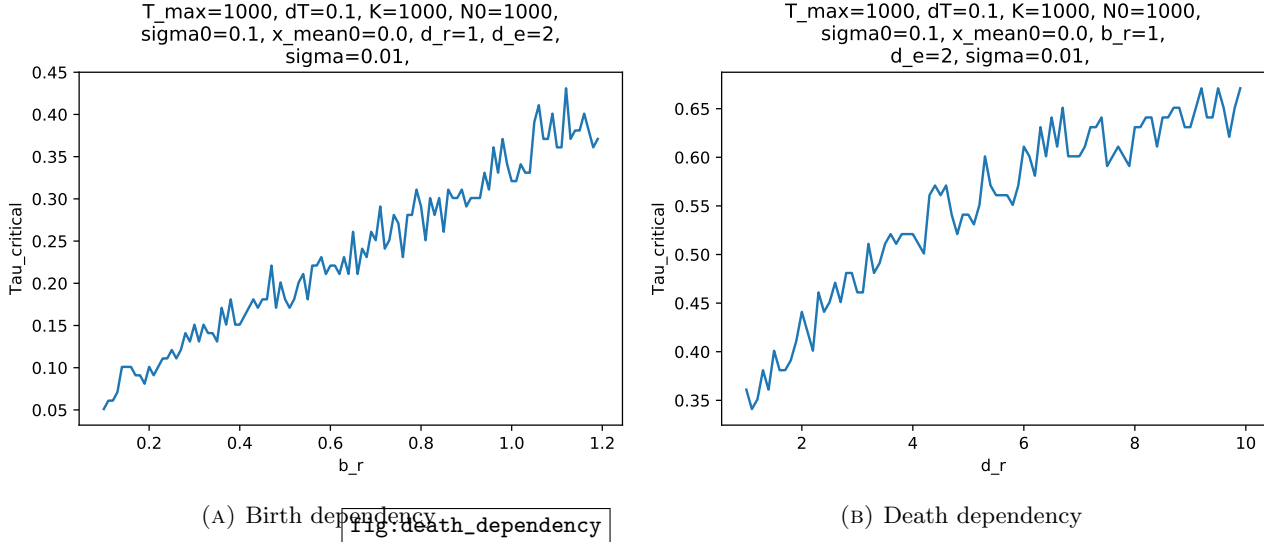
and

$$x_i = X_{\min} + i\Delta x, \quad 0 \leq i \leq N_x - 1.$$

We consider the time interval $[0, T_{\max}]$, discretized with N_t points $t_n = n\Delta t$, with $0 \leq n \leq N_t - 1$, and where Δt is defined as

$$\Delta t = \frac{T_{\max}}{N_t - 1}.$$

The approximations of the solution f of (6) at (t_n, x_i) , and of its density ρ at t_n are denoted f_i^n and ρ^n .

FIGURE 2. Dependency of the critical τ from the birth and death rate

The initial condition f^0 is a given function of x , and the initial density ρ^0 is computed using a left-point quadrature rule for f

$$\rho^0 = \Delta x \sum_{i=0}^{N_x-1} f^0(x_i).$$

The scheme is written with an explicit Euler scheme, in which the integrals are computed with a left-point quadrature rule. For $n \geq 1$ and $0 \leq i \leq N_x - 1$, it reads

$$\varepsilon \frac{f_i^{n+1} - f_i^n}{\Delta t} = (d(x_i) + C\rho^n) f_i^n + [m * (bf)]_i^n + f_i^n \Delta x \sum_{j=0}^{N_x-1} \tau(x_i - x_j) \frac{f_j^n}{\rho^n}. \quad (30)$$

eq:scheme

In (30), the convolution product $[m * (bf)]_i^n$ is computed with a left-point quadrature rule, as well of the other integrals. To do so, a grid in the z variable is defined as for the x variable. Let Z_{\min} and Z_{\max} , and the number N_z of discretization points be given. The grid in z is defined as

$$\forall 0 \leq k \leq N_z - 1, z_k = Z_{\min} + k\Delta z,$$

where $\Delta z = (Z_{\max} - Z_{\min}) / (N_z - 1)$. When $x_i + \varepsilon z_k \in [X_{\min}, X_{\max}]$, the value of $f(t_n, x_i + \varepsilon z_k)$ is approximated by linear interpolation of the $(f_i^n)_{0 \leq i \leq N_x-1}$. When $x_i + \varepsilon z_k < X_{\min}$, or $x_i + \varepsilon z_k > X_{\max}$, it is computed with a linear extrapolation of the $(f_i^n)_{0 \leq i \leq N_x-1}$, using the slope at the corresponding end of the X domain. Using the notation $f^n(x_i + \varepsilon z_k)$ for the approximation of $f(t_n, x_i + \varepsilon z_k)$, we then define

$$[m * (bf)]_i^n = \Delta z \sum_{k=0}^{N_z-1} m(z_k) b(x_i + \varepsilon z_k) f^n(x_i + \varepsilon z_k).$$

2.2.1. Case $\varepsilon = 1$: comparison with stochastic model

First thing that we are interested in is whether under identical initial condition we may reproduce the same evolutionary behaviour as in the stochastic model. It is of particular interest to track the critical value of the

horizontal transfer rate. Thus, we conduct several experiments, fixing parameter ε to 1 (thus, we do not rescale time, nor mutation rate), leaving all the other parameters fixed to the same values as in stochastic simulation case).

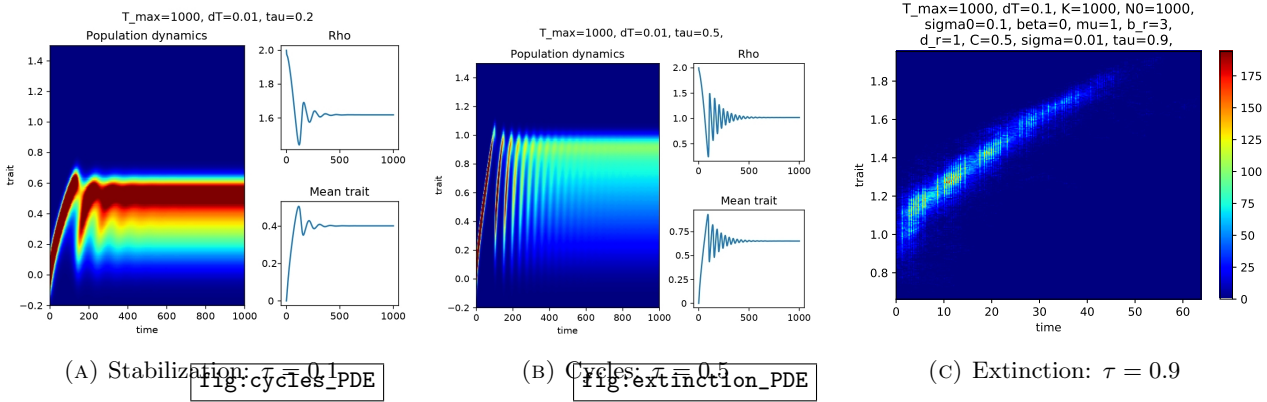


FIGURE 3. Behavior of the population dynamics described by a PDE model as the mutation rate τ is changing, ($b_r = d_r = 1$, $\sigma = 0.01$, $\varepsilon = 1$). **fix last pictures**

As we may see on Figure 3, simulation in overall correspond to those of stochastic model. Nevertheless, there is an important difference in how the cycles are replicated. Let us focus on the results for $\tau = 0.5$, which are the closest to a critical value. In this case, the system shows damping oscillations with a certain period, representing one life cycle. However, starting from some moment in time, those oscillations almost vanish and converge to a mean value. It is especially easy to notice on plots for mean trait and ρ , which in stochastic case correspond to a ratio $\frac{N}{K}$.

Explain damping oscillation.

2.2.2. Case $\varepsilon \rightarrow 0$

Show, when the algorithm breaks and comment on numerical drawbacks of numerical scheme. Why it is difficult to deal with the small ε . What is the most costly part computationally. Explain which profits we have from the Hamilton-Jacobi equation.

In this part, we present a numerical scheme for (6) which enjoys stability properties in the limit $\varepsilon \rightarrow 0$. Indeed, for small ε , the solution f^ε of (6), is expected to concentrate at a dominant trait. To be able to catch its stiffness numerically, one then has to refine the grid in x , to ensure enough precision in the computation of f . As a consequence, the computational cost of the numerical simulations increases when $\varepsilon \rightarrow 0$, and reaching the asymptotic regime with this scheme is not possible.

Here : add a numerical test which displays the behavior of scheme (30) for small ε . Use this test to comment precisely on the difficulty of using the scheme for f for computations in the small ε regimes.

To avoid the increase of computational cost when reaching the asymptotics, and to ensure the scheme approaches the limit Hamilton-Jacobi equation for small ε , a scheme for the solution u^ε of (8) which enjoys the Asymptotit Preserving (AP) property is proposed here. Such schemes have been introduced in [12–14], their properties are often summarized by the following diagram

$$\begin{array}{ccc}
 P_\varepsilon & \xrightarrow{\varepsilon \rightarrow 0} & P_0 \\
 \uparrow h \rightarrow 0 & & \uparrow h \rightarrow 0 \\
 S_\varepsilon^h & \xrightarrow{\varepsilon \rightarrow 0} & S_0^h
 \end{array}$$

that should be understood as follows: when the parameter $\varepsilon > 0$ is fixed, the scheme S_ε^h is consistent with the ε -dependent problem P_ε . When ε goes to 0, the solution of P_ε converges to the solution of the limit problem P_0 . The AP scheme S_ε^h is stable along the transition to the asymptotic regime. It means that, when ε goes to 0 with fixed discretization parameters h , the scheme becomes a limit scheme S_0^h , which is consistent with the limit problem P_0 .

As an AP scheme is required to enjoy stability properties when ε is going to 0, one has to ensure that all the quantities that have to be computed enjoy this property. In the case we are considering, the main concerns are the computation of the integral containing the birth term, the computation of the integral containing the transfer term and the computation of ρ . If all of them are correctly defined, the scheme we propose reads

$$\frac{u_i^{n+1} - u_i^n}{\Delta t} = -(d(x_i) + \rho^{n+1}) + B_i^n + T_i^n, \quad (31)$$

scheme:AP

where B_i^n stands for an approximation of

$$\int_{\mathbb{R}} m(z) b(x_i + \varepsilon z) e^{(u^\varepsilon(t^n, x_i + \varepsilon z) - u^\varepsilon(t^n, x_i))/\varepsilon} dz, \quad (32)$$

AP:Bni

and T_i^n is for

$$\int_{\mathbb{R}} \tau(x_i - y) \frac{f(t^n, y)}{\rho(t^n)} dy. \quad (33)$$

AP:Tni

Here, we used the notations and discretization grids defined in the beginning of Section 2.2, and the dependence in ε are omitted to simplify the notations. In what follows, we present how T_i^n , B_i^n and ρ^{n+1} can be computed in a way that ensures they are both consistent with their definition for fixed ε , that they can be computed with a constant computational cost with respect to ε , and that their asymptotic behavior when ε goes to 0 is meeting the continuous one (9).

- **Computation of T_i^n .** The direct approximation of (33) with a quadrature rule is consistent for $\varepsilon \sim 1$. However, since f is expected to concentrate when $\varepsilon \rightarrow 0$, it lacks precision in the asymptotic regime. Especially, the convergence of f/ρ to a Dirac is not ensured when the integral is approximated directly. Remarking that

$$\frac{f^\varepsilon(t^n, y)}{\rho^\varepsilon(t^n)} = \frac{e^{u^\varepsilon(t^n, y)/\varepsilon}}{\int_{\mathbb{R}} e^{u^\varepsilon(t^n, z)/\varepsilon} dz} = \frac{e^{(u^\varepsilon(t^n, y) - \max_x u^\varepsilon(t^n, x))/\varepsilon}}{\int_{\mathbb{R}} e^{(u^\varepsilon(t^n, z) - \max_x u^\varepsilon(t^n, x))/\varepsilon} dz},$$

(33) is computed with a left-point quadrature rule in the integrals of the previous expression. It reads

$$T_i^n = \Delta x \sum_{j=1}^{N_x-1} \tau(x_i - y_j) \frac{e^{(u_j^n - \max_l u_l^n)/\varepsilon}}{\Delta x \sum_{k=0}^{N_x-1} e^{(u_k^n - \max_l u_l^n)/\varepsilon}} = \frac{\sum_{j=1}^{N_x-1} \tau(x_i - x_j) e^{(u_j^n - \max_l u_l^n)/\varepsilon}}{\sum_{k=0}^{N_x-1} e^{(u_k^n - \max_l u_l^n)/\varepsilon}}. \quad (34)$$

AP:Tni_formula

For fixed ε , (34) is consistent with (33). Since all the arguments of the exponentials are nonpositive, the limit of (34) for small ε can be read on that expression. Denoting j_O the index such that

$$u_{j_O}^n = \max_l u_l^n,$$

and supposing that there exists an unique such j_O , the limit of (34) for small ε is

$$\tau(x_i - x_{j_O}).$$

This is consistent with the last term in the limit Hamilton-Jacobi equation (9).

- **Computation of B_i^n .** Once again, the numerical approximation of (32) is done with a quadrature in the integral. Using the notations of Section 2.2, a grid in z is defined. The functions m and b are respectively evaluated at z_k and $x_i + \varepsilon z_k$, but the interpolation of u^n at $x_i + \varepsilon z_k$ has to be done with special care to make the scheme enjoy the expected asymptotic behavior. Using a left-point quadrature rule, (32) is approximated by

$$\Delta z \sum_{\substack{k=0 \\ \varepsilon|z| \leq dx}}^{N_z-1} m(z_k) b(x_i + \varepsilon z_k) e^{(u^\varepsilon(t^n, x_i + \varepsilon z_k) - u^\varepsilon(t^n, x_i)) / \varepsilon \nabla} \quad (35)$$

AP:Bni_epz_small

$$+ \Delta z \sum_{\substack{k=0 \\ \varepsilon|z| > dx}}^{N_z-1} m(z_k) b(x_i + \varepsilon z_k) e^{\nabla(u^\varepsilon(t^n, x_i + \varepsilon z_k) - u^\varepsilon(t^n, x_i)) / \varepsilon}, \quad (36)$$

AP:Bni_epz_large

- **Computation of ρ^{n+1} .**

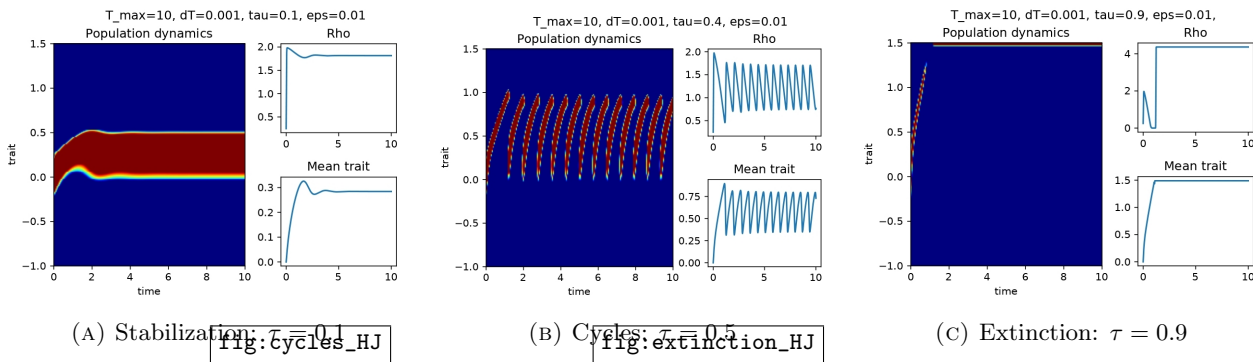
(A) Stabilization: $\tau = 0.1$ (B) Cycles: $\tau = 0.5$ (C) Extinction: $\tau = 0.9$

FIGURE 4. Behavior of the population dynamics described by a PDE model as the mutation rate τ is changing, ($b_r = d_r = 1$, $\sigma = 0.01$, $\varepsilon = 1$). **fix the last picture**

On Figure 4 we simulate the population dynamics for $\varepsilon = 0.01$. Upon rescaling time (for chosen ε time scale $T = 10$ correspond, in fact, to $\frac{T}{\varepsilon} = 1000$ in previous simulations), we see the same patterns, with few differences. First difference in comparison to a stochastic model is that we see absolutely no stochasticity both in the case of stabilized population and in case of cycles. Second important point is that, on the contrary to PDE model, oscillations are not dumping over time.

It is particularly interesting to discuss Figure 4c. On the plot we definitely see as whole population reaches unfit state and goes extinct, which causes scheme to break as ρ becomes too small. In our case it breaks with ρ of order 10^{-11} . This is caused by a physical limitation of computational power, as depending on used programming language, values starting from order 10^{-9} to 10^{-12} are indistinguishable from 0. In experimental setting, it may be advised to use set a threshold after which the computation stops and the population considered to be extinct.

On Figure 4b we may notice that due to the fact that the system is deterministic and we see no stochasticity on curves, describing the mean trait and the density of the population, it is easy to estimate the periods of the system, computing distances between local maximums on each curve. For stochastic system this task is more difficult, especially for a small population, because it includes filtering problem of noisy signal. To get more accurate results in stochastic model we have to increase the time scale and number of individuals, which is costly from computational point of view (see Table ...). However, if our goal is to study numerically the lineages which lead to the evolutionary rescue of the population, it is still more straightforward to use the individual-based model. **We may include picture with lineages here if you want**

	$\Delta = 0.1, T = 10$	$\Delta = 0.01, T = 10$
SM ($N = 1000$)	smth	smth
SM ($N = 10000$)	smth	smth
PDE ($\varepsilon = 1$)	smth	smth
HJ ($\varepsilon = 10^{-2}$)	smth	smth
HJ ($\varepsilon = 10^{-6}$)	smth	smth

TABLE 1. Elapsed time for simulation of population dynamics for different models (other parameters are fixed to values used throughout all the other simulations)

Add a table with a computation time over different number of points

CONCLUSIONS AND DISCUSSION

Stochastic model is the most costly one from computational point of view, but the most straightforward and stable.
 HJ is more fast, but is tricky.
 Hamilton-Jacobi convergence.

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