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Stochastic dynamics for adaptation and evolution of microorganisms

Sylvain Billiard[*], Pierrre Collet[†], Régis Ferrière[‡], Sylvie Méléard[§], Viet Chi Tran[¶]

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Abstract

We present a modeling framework for the dynamics of a population of individuals with a continuum of traits, who compete for resources and exchange horizontally (transfer) an otherwise vertically inherited trait. Competition influences individual demographics, affecting population size, which feeds back on the dynamics of transfer. This feedback is captured with a stochastic individual-based model, from which a deterministic approximation for large populations is derived. The limiting process is the solution of a non linear integro-differential equation. When there are only two different traits, the equation reduces to a non-standard two-dimensional dynamical system. We show how crucial the forms of the transfer rates are for the long-term behavior of its solutions. For density-dependent transfer rates, the equilibria are those of Lotka-Volterra systems, but horizontal transfer may revert the change of evolution. Frequency-dependence or more general transfert rates reveal new phase diagrams. The interaction between horizontal transfer and competition makes for example possible the stable (or bi-stable) polymorphic maintenance of deleterious traits (including costly plasmids). For an initially rare trait, we describe the dynamics of invasion and fixation and compute the invasion probabilities. Horizontal transfer can have a major impact on the distribution of the mutational effects that are fixed. This allows us to consider then the impact of horizontal transfer on evolution. Our model provides a basis for a general theory of the influence of horizontal transfer on eco-evolutionary dynamics and adaptation.

Keywords: horizontal gene transfer, bacterial conjugation, stochastic individual-based models, long time behavior, large population approximation, interactions, fixation probability, trait substitution sequence, adaptive dynamics, canonical equation.

MSC 2000 subject classification: 92D25, 92D15, 92D30, 60J80, 60K35, 60F99.

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1 Introduction and biological context

A distinctive signature of living systems is Darwinian evolution, that is, a propensity to generate as well as self-select individual diversity. To capture this essential feature of life while describing the dynamics of populations, mathematical models must be rooted in the microscopic, stochastic description of discrete individuals characterized by one or several adaptive traits and interacting with each other. In this paper, we focus on the mathematical modeling of bacteria evolution, whose understanding is fundamental in biology, medicine and industry. The ability of a bacteria to survive and reproduce depends on its genes and evolution mainly results from the following basic mechanisms: heredity, i.e. transmission of the ancestral trait to offspring (also called vertical transmission); mutation which occurs during vertical transmission and generates variability of the traits; selection which results from the interaction between individuals and their environment; exchange of genetic information between non-parental individuals during their lifetimes (also called horizontal gene transfer, HGT). In many biological situations, competition between individuals and vertical and horizontal transfers are involved. The combined effects of these different mechanisms may have a key role in the transmission of an epidemic, the development of antibiotic resistances, epigenetics, or the bacterial degradation of novel compounds such as human-created pesticides. There are several mechanisms for horizontal gene transfer: transformation, where some DNA filaments directly enter the cell from the surrounding environment; transduction, where DNA is carried and introduced into the cell by viruses (phages); and conjugation, when circular DNA (plasmids) replicate into cells and are transmitted from a cell to another one, independently of the chromosome. Conjugation plays a main role for infection diseases since the genes responsible for virulence or antibiotic resistance are usually carried by plasmids. In this paper, we focus on conjugation modeling in order to understand pathogens transmission and the evolution of antibiotic resistances.

We propose a general stochastic eco-evolutionary model of population dynamics with horizontal and vertical genetic transmissions. The stochastic process describes a finite population of discrete interacting individuals characterized by one or several adaptive phenotypic traits, in the vein of the models developed in [14]. Other models for HGT have been proposed in the literature, based on the seminal contribution of Anderson and May on host-pathogen deterministic population dynamics [1] (see also [18, 24]) or on a population genetics framework with strong simplifying assumptions on the ecology (see [3, 22, 25]). Additionally, previous models assume unilateral transfer, to our knowledge, dividing the population into two classes: donors and recipients. In the present paper, we relax most of the previous limitations. The full probabilistic dynamics, over continuous time, of births, mutations, horizontal transfers and deaths, as influenced by the trait values of individuals and ecological interactions among them is described in the next section. Our model covers both cases of frequency- and density-dependent horizontal transfer rates; these dependencies appear as special cases of a more general form of transfer rate, that we call Beddington-DeAngelis by analogy with a similar model used to describe predator-prey contacts ([4, 9]).

The process that we consider presents different evolutionary behaviors depending on the order of magnitude of population size, mutation probability and mutation step size. These phenomena are investigated in the next sections, by systematically deriving macroscopic approximations from the individual-based process. In a large population limit, using ideas

developed in Fournier and Méléard [14], the stochastic process is shown to converge to the solution of a nonlinear integro-differential equation whose existence and uniqueness are proved. In the case where the trait support is composed of two values, the equation reduces to a non-standard two-dimensional dynamical system whose long time behavior is studied (see also Billiard et al. [5]). This study highlights the impact of HGT on the maintenance of polymorphism and the invasion or elimination of pathogens strains. When one trait is initially rare in the population (e.g. a mutation of the common trait), we analyze how HGT influences its probability of invasion and time to fixation. To do so, we combine the stochastic behavior of the mutant population size with the deterministic approximation of the resident population size. We assume that mutations are rare enough to imply a separation between the competition and mutation time scales, following ideas of Champagnat et al. [6] in a case without HGT. Here, under an Invasion-Implies-Fixation assumption, a pure jump process is derived from the population size process at the mutation time scale, for which the jump measure is strongly affected by the horizontal transfer. In the last section we present simulations in a case of unilateral transfer, which highlight the effect of HGT on evolution. In particular, we show how HGT can completely affect the evolutionary outcomes. Depending on the transfer rate, we may obtain drastically different behaviors, from expected evolution scenario to evolutionary suicide.

2 A general stochastic individual-based model for vertical and horizontal trait transmission

2.1 The model

Our model's construction starts with the microscopic description of a population in which the adaptive traits of individuals affect their birth rate, the mutation process, their horizontal transfer rate, their death rate, and how they interact with each other and with their environment. Mathematically, the population can be viewed as a stochastic system of interacting individuals (Cf. Fournier-Méléard [14], Champagnat-Ferrière-Méléard [7, 8]). The individuals are characterized by a quantitative parameter x, called trait, which belongs to a compact set $\mathcal{X}$ of $\mathbb{R}^d$ and summarizes the phenotype or genotype of each individual. The trait is inherited from parent to offspring (except when a mutation occurs, in which case the trait of the offspring takes a new value), it can be transmitted by horizontal transfer between individuals and it determines the demographic rates. The demographic and ecological rates are scaled by K which is taken as a measure of the "system size" (resource limitation, living area, carrying capacity, initial number of individuals). We will derive macroscopic models from the individual process by letting the system size become very large ($K \to \infty$) with the appropriate renormalization $\frac{1}{K}$ for individuals' weight.

At each time t, the population is described by the point measure

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

N_t^K is the size of the population at time t and $X_i(t)$ the trait of the i-th individual living at t, individuals being ranked by lexicographical trait values.

Let us now describe the transitions of the measure-valued Markov process $(\nu_t^K, t \geq 0)$.

An individual with trait x gives birth to a new individual with rate $b_K(x)$. With probability $1-p_K$, the new individual carries the trait x and with probability p_K, there is a mutation on the trait. The trait of the new individual is then z, where z is chosen in the probability distribution $m(x, dz)$.

An individual with trait x dies with intrinsic death rate $d_K(x)$ or from the competition with any other individual alive at the same time. If the competitor has the trait y, the additional death rate is $C_K(x, y)$. Then in the population $\nu = \frac{1}{K}\sum_{i=1}^n \delta_{x_i}$, the individual death rate due to competition is $KC_K * \nu(x) = \sum_{i=1}^n C_K(x, x_i)$.

In addition, individuals can exchange genetic information. Horizontal transfers can occur in both directions: from individuals x to y or the reverse, possibly at different rates. In a population ν, an individual with trait x chooses a partner with trait y at rate $h_K(x, y, \nu)$. The couple (x, y) then becomes $(T_1(x, y), T_2(x, y))$. In the specific case of bacterial conjugation, the recipient y acquires the trait x of the donor (i.e. $(T_1(x, y), T_2(x, y)) = (x, x)$). This occurs for instance when the donor transmits a copy of its plasmid to individuals devoid of plasmid (in that case, transfer is unilateral). We refer to the paper of Hinow et al. [17] for other examples.

2.2 Generator

We denote by $\mathcal{M}_K$ the set of point measures on $\mathcal{X}$ weighted by $1/K$ and by M_F the set of finite measures on $\mathcal{X}$. The generator of the process $(\nu_t^K)_{t\geq 0}$ is given for measurable bounded functions F on $\mathcal{M}_K$ and $\nu = \frac{1}{K}\sum_{i=1}^n \delta_{x_i}$ by

$$\begin{aligned} L^K F(\nu) = &\sum_{i=1}^n b_K(x_i)(1-p_K)\big(F(\nu + \frac{1}{K}\delta_{x_i}) - F(\nu)\big) \\ &+ \sum_{i=1}^n b_K(x_i)\, p_K \int_{\mathcal{X}} \big(F(\nu + \frac{1}{K}\delta_z) - F(\nu)\big) m(x_i, dz) \\ &+ \sum_{i=1}^n \big(d_K(x_i) + KC_K * \nu(x_i)\big)\big(F(\nu - \frac{1}{K}\delta_{x_i}) - F(\nu)\big) \\ &+ \sum_{i,j=1}^n h_K(x_i, x_j, \nu)\big(F(\nu + \frac{1}{K}\delta_{T_1(x_i,x_j)} + \frac{1}{K}\delta_{T_2(x_i,x_j)} - \frac{1}{K}\delta_{x_i} - \frac{1}{K}\delta_{x_j}) - F(\nu)\big). \end{aligned} \tag{2.1}$$

In particular, if we consider the function $F_f(\nu) = \langle \nu, f\rangle$ for $f \in \mathcal{C}(\mathcal{X}, \mathbb{R})$, with the notation $\langle \nu, f\rangle = \int f(x)\nu(dx)$, then we get

$$\begin{aligned} L^K F_f(\nu) = \int_{\mathcal{X}} \nu(dx)\Big[&b_K(x)\Big((1-p_K)f(x) + p_K \int_{\mathcal{X}} f(z) m(x, dz)\Big) \\ &- \big(d_K(x) + KC_K * \nu(x)\big) f(x) \\ &+ \int_{\mathcal{X}} Kh_K(x, y, \nu)\Big(f(T_1(x, y)) + f(T_2(x, y)) - f(x) - f(y)\Big)\nu(dy)\Big]. \end{aligned} \tag{2.2}$$

Assuming that for any K, the functions b_K, d_K, KC_K and Kh_K are bounded, it is standard to construct the measure valued process ν^K as the solution of a stochastic differential equation driven by point Poisson measures and to derive the following moment and martingale properties (see for example [7] or Bansaye-Méléard [2]).

Theorem 2.1 *Under the previous assumptions and assuming that for some $p \geq 2$, $\mathbb{E}\left(\langle \nu_0^K, 1\rangle^p\right) < \infty$, we have the following properties.*

(i) *For all measurable functions ϕ from $\mathcal{M}$ into $\mathbb{R}$ such that for some constant C, for all $\nu \in \mathcal{M}$, $|\phi(\nu)| + |L^K\phi(\nu)| \leq C(1 + \langle \nu, 1\rangle^p)$, the process*

$$\phi(\nu_t^K) - \phi(\nu_0^K) - \int_0^t L^K\phi(\nu_s^K)ds \tag{2.3}$$

is a càdlàg $(\mathcal{F}_t)_{t\geq 0}$-martingale starting from 0.

(ii) *Point (i) applies to any function $\phi(\nu) = \langle \nu, f\rangle^q$, with $0 \leq q \leq p-1$ and with f bounded and measurable on $\mathcal{X}$.*

(iii) *For such a function f, the process*

$$\begin{aligned}
&\int f(x)\nu_t^K(dx) = \int f(x)\nu_0^K(dx) + M_t^{K,f} \\
&+ \int_0^t \int_{\mathcal{X}} \Big\{ \Big((1-p_K)b_K(x) - d_K(x) - KC_K * \nu_s^K(x)\Big) f(x) + p_K b_K(x) \int_{\mathcal{X}} f(z)\, m(x,dz) \\
&+ \int_{\mathcal{X}} Kh_K(x,y,\nu^K)\Big(f(T_1(x,y)) + f(T_2(x,y)) - f(x) - f(y)\Big)\nu_s^K(dy)\Big\}\nu_s^K(dx)ds,
\end{aligned} \tag{2.4}$$

where $M^{K,f}$ is a càdlàg square integrable martingale starting from 0 with quadratic variation

$$\begin{aligned}
\langle M^{K,f}\rangle_t = \frac{1}{K}\int_0^t \int_{\mathcal{X}} &\Big\{ \Big((1-p_K)b_K(x) + d_K(x) + KC_K * \nu_s^K(x)\Big) f^2(x) \\
&+ p_K b_K(x) \int_{\mathcal{X}} f^2(z)\, m(x,dz) \\
&+ \int_{\mathcal{X}} Kh_K(x,y,\nu^K)\Big(f(T_1(x,y)) + f(T_2(x,y)) - f(x) - f(y)\Big)^2 \nu_s^K(dy)\Big\}\nu_s^K(dx)ds.
\end{aligned} \tag{2.5}$$

3 Large population limit and rare mutation in the ecological time-scale

3.1 A deterministic approximation

We derive some macroscopic approximation by letting the scaling parameter K tend to infinity with the additional assumption of rare mutation, i.e.

$$\lim_{K\to\infty} p_K = 0. \tag{3.1}$$

The timescale is unchanged. It is called 'ecological' timescale of births, interactions (competition and transfer), and deaths.

The next hypotheses describe the scalings considered in the paper.

Assumptions (H)

(i) The initial population sizes are such that $\nu_0^K \longrightarrow_{K\to\infty} \xi_0 \in M_F(\mathcal{X})$ *in probability and*

$$\sup_K \mathbb{E}(\langle \nu_0^K, 1\rangle^3) < \infty.$$

(ii) When $K \to \infty$, $b_K(.) \to b(.)$, $d_K(.) \to d(.)$ *and* $KC_K(.,.) \to C(.,.)$, *where* b, d *and* C *are continuous functions on* $\mathcal{X}$.

(iii) We assume that for any $x, y \in \mathcal{X}$,

$$b(x) - d(x) > 0\,,\; C(x,y) > 0.$$

In absence of competition, the subpopulation with trait x *is super-critical and the regulation of the population size comes from the competition. We denote by*

$$r(x) = b(x) - d(x)$$

the intrinsic growth rate of the subpopulation of trait x.

(iv) We let the transfer rate Kh_K *go to a finite limit* h. *This limit depends on alternate assumptions about the mechanism of transfer. For the sake of simplicity, we take*

$$Kh_K(x,y,\nu) \to h(x,y,\nu) = \frac{\tau(x,y)}{\beta + \mu\,\langle \nu, 1\rangle}, \tag{3.2}$$

where τ *is continuous on* $\mathcal{X} \times \mathcal{X}$.

The form (3.2) is derived from the so-called "Beddington-DeAngelis" functional response in the ecological literature ([4, 9]). This function covers different interesting cases regarding HGT. For an individual with trait x in the population ν, the total HGT rate is $\int h(x,y,\nu)\nu(dy)$. Assuming $\mu = 0$ or $\langle \nu, 1\rangle$ very small gives a density-dependent HGT rate (denoted DD): the individual HGT rate is proportional to the density of the donors in the population. Assuming $\beta = 0$ or $\langle \nu, 1\rangle$ very large gives a frequency-dependent HGT rate (denoted FD): the individual HGT rate is proportional to the frequency of the donor. Finally, assuming $\beta \neq 0$ and $\mu \neq 0$ gives a mixed HGT rate between frequency and density-dependent HGT rates (denoted BDA). This general case can describe some experimental observations for plasmids, for which a correlation between the form (density- versus frequency-dependent) of the transfer rate and the size of the population (low size versus close to carrying capacity) was suggested (Raul Fernandez-Lopez, pers. com.). We will show that the choice of $h(x,y,\nu)$ has important consequences on the dynamics.

Proposition 3.1 *Assume* (H) *and* (3.1). *Let* $T > 0$. *When* $K \to \infty$, *the sequence* $(\nu^K)_{K\geq 1}$ *converges in probability in* $\mathbb{D}([0,T], M_F(\mathcal{X}))$ *to the unique solution* $\xi \in \mathcal{C}([0,T], \mathcal{M}_F(\mathcal{X}))$ *of*

$$\begin{aligned}\langle \xi_t, f\rangle =& \langle \xi_0, f\rangle + \int_0^t \int_{\mathcal{X}} \big(r(x) - C * \xi(x)\big) f(x)\xi_s(dx)\ ds \\ &+ \int_0^t \int_{\mathcal{X}\times\mathcal{X}} \Big(f(T_1(x,y)) + f(T_2(x,y)) - f(x) - f(y)\Big) \frac{\tau(x,y)}{\beta + \mu\,\langle \xi_s, 1\rangle} \xi_s(dy)\xi_s(dx)\ ds.\end{aligned} \tag{3.3}$$

Let us notice (by choosing $f \equiv 1$) that the total size of the population $\langle \xi, 1\rangle$ satisfies the same equation as the one without transfer:

$$\langle \xi_t, 1\rangle = \langle \xi_0, 1\rangle + \int_0^t \int_{\mathcal{X}} \big(r(x) - X * \xi(x)\big)\xi_s(dx)\ ds. \tag{3.4}$$

Because Assumption (H) implies that the functions $r(.)$ and $C(.,.)$ are bounded above and below by positive constants on $\mathcal{X}$, the process $\langle \xi_t, 1\rangle$ is bounded above and below by the solutions of two logistic equations that converge to strictly positive limits when $t \to \infty$. For example, $\forall t \in \mathbb{R}_+,\ \langle \xi_t, 1\rangle \geq \underline{n}_t$ where

$$\frac{d\underline{n}_t}{dt} = \underline{r}\ \underline{n}_t - \bar{C}\underline{n}_t^2,$$

with the notation $\underline{r} = \min_{x\in\mathcal{X}} r(x)$ and $\bar{C} = \max_{x,y\in\mathcal{X}} C(x,y)$.

Proof The proof is standard and consists in a tightness and uniqueness argument. The reader will follow the steps detailed in [14] or in [2]: uniform moment estimates on finite time interval, tightness of the sequence of laws, continuity of the limiting values, identification of the limiting values as solutions of (3.3), uniqueness of the solution of (3.3). The last point deserves attention. Let us consider $(\xi_t^1)_{t\in[0,T]}$ and $(\xi_t^2)_{t\in[0,T]}$ two continuous solutions of (3.3) with the same initial condition ξ_0. From the comment after (3.4), we can assume that $\bar{A}_T = \sup_{t\in[0,T]}\langle \xi_t^1 + \xi_t^2, 1\rangle < \infty$ and $\underline{A}_T = \min\big(\inf_{t\in[0,T]}\langle \xi_t^1, 1\rangle, \inf_{t\in[0,T]}\langle \xi_t^1, 1\rangle\big) > 0$. Let f be a real bounded measurable function on $\mathcal{X}$ such that $\|f\|_\infty \leq 1$. We obtain

$$\begin{aligned}\langle \xi_t^1 - \xi_t^2, f\rangle =& \int_0^t \int_{\mathcal{X}} \Big(\big(r(x) - C * \xi_s^1(x)\big) f(x)(\xi_s^1 - \xi_s^2)(dx) - C * (\xi_s^1 - \xi_s^2)(x)\, f(x)\, \xi_s^2(dx)\Big)\, ds \\ +& \int_0^t \int_{\mathcal{X}\times\mathcal{X}} \Big(f(T_1(x,y)) + f(T_2(x,y)) - f(x) - f(y)\Big)\, \tau(x,y) \Bigg(\frac{1}{\beta + \mu\,\langle \xi_s^1, 1\rangle}(\xi_s^1 - \xi_s^2)(dy)\xi_s^1(dx) \\ &+ \frac{1}{\beta + \mu\,\langle \xi_s^2, 1\rangle}\xi_s^2(dy)(\xi_s^1 - \xi_s^2)(dx) + \Big(\frac{1}{\beta + \mu\langle \xi_s^2, 1\rangle} - \frac{1}{\beta + \mu\langle \xi_s^1, 1\rangle}\Big)\xi_s^2(dy)\xi_s^1(dx)\Bigg)\, ds.\end{aligned}$$

By an elementary computation using Assumptions (H), we obtain that for any $t \in [0,T]$,

$$|\langle \xi_t^1 - \xi_t^2, f\rangle| = C(T) \int_0^t \|\xi_s^1 - \xi_s^2\|_{TV}\, ds, \tag{3.5}$$

where $C(T)$ is a positive constant. So taking the supremum over all functions f such that $\|f\|_\infty \leq 1$ and applying Gronwall's Lemma we conclude that for all $t \in [0,T]$

$$\|\xi_t^1 - \xi_t^2\|_{TV} = 0. \tag{3.6}$$

Therefore uniqueness holds for (3.3). □

3.2 Trait replacement and the bacteria conjugation subcase

We now emphasize on the case where horizontal transmission results in the replacement of the recepient's trait by the donor's trait, i.e. $T_1(x,y) = x$ and $T_2(x,y) = x$.

In this case, (3.3) becomes:

$$\begin{aligned}\langle \xi_t, f\rangle =& \langle \xi_0, f\rangle + \int_0^t \int_{\mathcal{X}} \big(r(x) - C * \xi(x)\big) f(x) \xi_s(dx)\, ds \\ &+ \int_0^t \int_{\mathcal{X}\times\mathcal{X}} f(x) \frac{\tau(x,y) - \tau(y,x)}{\beta + \mu \langle \xi_s, 1\rangle} \xi_s(dy)\xi_s(dx)\, ds. \end{aligned} \tag{3.7}$$

We note that the behavior of the deterministic dynamical system is influenced by HGT only through the 'horizontal flux' rate

$$\alpha(x,y) = \tau(x,y) - \tau(y,x).$$

The horizontal flux rate quantifies the asymmetry between transfers in either directions and can be positive as well as negative (or zero in the case of perfectly symmetrical transfer). In Section 5.1, we will show that in contrast, the fully stochastic population process depends not only on the flux α but also on τ itself. Note that bacteria conjugation is a subcase: a plasmid is transferred from the plasmid bearer x to the empty individual y, while the reverse is not possible (emptiness can not be transferred). This corresponds to the case where $T_1(x,y) = x$ and $T_2(x,y) = x$ and $\tau(y,x) = 0$.

Proposition 3.2 *Assume that the initial measure ξ_0 is absolutely continuous with respect to the Lebesgue measure, then this property propagates in time and for any $t > 0$, $\xi_t(dx) = u(t,x)dx$, with u weak solution of the integro-differential equation*

$$\partial_t u(t,x) = \big(r(x) - C * u(t,x)\big)u(t,x) + \frac{u(t,x)}{\beta + \mu \|u(t,.)\|_1} \int_{\mathcal{X}} \alpha(x,y) u(t,y) dy,$$

with $C * u(t,x) = \int C(x,y)u(t,y)dy$.

Let us mention that in the case without transfer, the long time behavior of this equation has been studied by Desvillettes et al. [10]. Some close equations with transfer have been considered and studied in the long time by Hinow et al. [17] and by Magal-Raoul [19].

4 The two traits case

4.1 The dynamical system

Let us now assume that the population is dimorphic and composed of only two subpopulations characterized by the traits x and y. We set $\mathcal{X} = \{x, y\}$ and define $N_t^{x,K} = \nu_t^K(\{x\})$; $N_t^{y,K} = \nu_t^K(\{y\})$. Let us assume that $(N_0^{x,K}, N_0^{y,K})$ converges in probability to the deterministic vector (n_0^x, n_0^y). Then Proposition 3.1 is stated as follows.

Proposition 4.1 *When $K \to \infty$, the stochastic process $(N_t^{x,K}, N_t^{y,K})_{t\geq 0}$ converges in probability to the solution $(n_t^x, n_t^y)_{t\geq 0}$ of the following system of ordinary differential equations (ODEs):*

$$\begin{aligned}\frac{dn^x}{dt} =& \Big(r(x) - C(x,x)n^x - C(x,y)n^y + \frac{\alpha(x,y)}{\beta + \mu\,(n^x + n^y)}\,n^y\Big)n^x = P(n^x, n^y)\,;\\ \frac{dn^y}{dt} =& \Big(r(y) - C(y,x)n^x - C(y,y)n^y - \frac{\alpha(x,y)}{\beta + \mu\,(n^x + n^y)}\,n^x\Big)n^y = Q(n^x, n^y). \end{aligned} \tag{4.1}$$

When $\alpha(x,y) \equiv 0$, we get the classical competitive Lotka-Volterra system. Point $(0,0)$ is an unstable equilibrium and there are 3 stable equilibria: a co-existence equilibrium and two monomorphic equilibria $(\bar{n}^x, 0)$ and $(0, \bar{n}^y)$, where $\overline{n^x} = \frac{r(x)}{C(x,x)}$ is the unique stable equilibrium of the standard logistic equation

$$\frac{dn}{dt} = \big(r(x) - C(x,x)n\big)n. \tag{4.2}$$

It is well known that the sign of the invasion fitness function, defined as

$$f(y;x) = r(y) - C(y,x)\,\bar{n}^x = r(y) - C(y,x)\,\frac{r(x)}{C(x,x)},$$

governs the stability. If $f(y;x) < 0$ and $f(x;y) > 0$, the system converges to $(\bar{n}^x, 0)$ while if $f(y;x) > 0$ and $f(x;y) < 0$, the system converges to $(0, \bar{n}^y)$ and if $f(y;x) > 0$ and $f(x;y) > 0$, the system converges to a non trivial co-existence equilibrium. In the case where the competition kernel C is constant and r is a monotonous function, the fitness function is equal to $f(y;x) = r(y) - r(x) = -f(x;y)$, which prevents co-existence in the limit.

When $\alpha(x,y) \neq 0$, the behavior of the system is drastically different as it can be seen in the phase diagrams of Figure 4.1.

Figure 4.1 shows eight possible phase diagrams for the dynamical system (4.1), where the circles and stars indicate stable and unstable fixed points, respectively. Figures (1)-(4) are possible for all forms of HGT rates, Figures (5)-(6) can happen in density-dependent or Bedington-deAngelis cases, while Figures (7)-(8) can be observed only in Bedington-deAngelis case. Compared to the classical two-species Lotka-Volterra system, at least 4 new phase diagrams are possible: Figures (5)-(8).

Now, define the invasion fitness of individuals with trait y in the x-resident population by

$$S(y;x) \;=\; r(y) - \frac{C(y,x)r(x)}{C(x,x)} + \frac{\alpha(y,x)r(x)}{\beta C(x,x) + \mu r(x)}. \tag{4.3}$$

4.2 Properties of the dynamical system (4.1)

Let us now analyze the behavior of the system (4.1).

We first exclude the possibility of cycles contained in the positive quadrant.

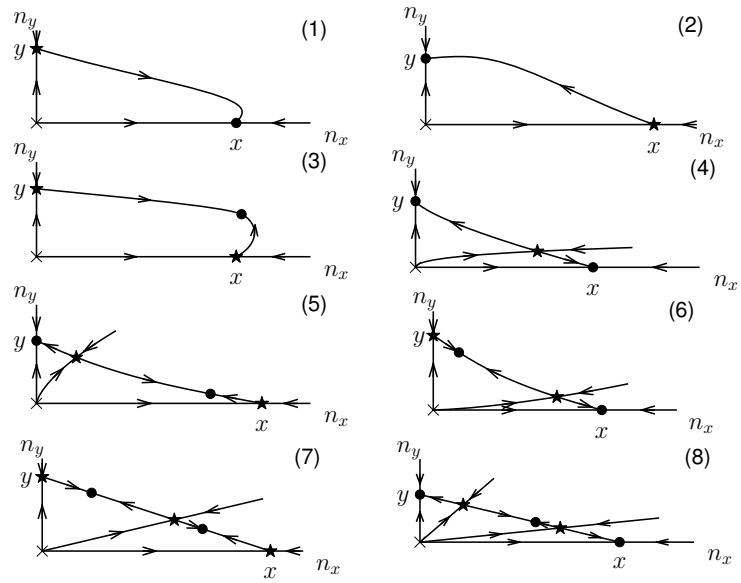

Figure 4.1: *Phase diagrams for the system* (4.1)

Proposition 4.2 *Assume that* $C(x,x) > 0$ *and* $C(y,y) > 0$ *. Then the function* $\varphi(u,v) = \frac{1}{u\,v}$ *is a Dulac function in* $(\mathbb{R}_+^*)^2$*. As a consequence, the system* (4.1) *has no cycle in* $(\mathbb{R}_+^*)^2$*.*

Proof A Dulac function $\varphi(u,v)$ in $(\mathbb{R}_+^*)^2$ is a smooth non vanishing function such that

$$\Big(\partial_u(\varphi P) + \partial_v(\varphi Q)\Big)(u,v)$$

has the same sign in the domain $(\mathbb{R}_+^*)^2$. A simple computation gives

$$\partial_u(\varphi P) + \partial_v(\varphi Q)(u,v) = -\frac{C(x,x)\,u + C(y,y)\,v}{u\,v} < 0,$$

for $(u,v) \in (\mathbb{R}_+^*)^2$. The Bendixson-Dulac Theorem (see e.g. [12, Th.7.12 p.189] or [16, Th.1.8.2, p.44]) allows to conclude that there is no cycle in the domain. □

From this result and the Poincaré-Bendixson theorem ([12, Section 1.7] or [16, Th.1.8.1, p.44]) we conclude that any accumulation point of any trajectory starting inside the positive quadrant is either a fixed point or is on the boundary.

Expressing (4.1) in terms of the size of the population $n_t = n_t^x + n_t^y$ and proportion of trait

x, $p_t = n_t^x/n_t$, we obtain:

$$\begin{aligned}\frac{dn}{dt} =& n\Big(p\,r(x) + (1-p)\,r(y) \\ & - C(x,x)\,p^2 n - (C(x,y)+C(y,x))\,p(1-p)n - C(y,y)\,(1-p)^2 n\Big) \\ \frac{dp}{dt} =& p\,(1-p)\Big(r(x) - r(y) \\ & + np(C(y,x)-C(x,x)) + n(1-p)(C(y,y)-C(x,y)) + \alpha(x,y)\frac{n}{\beta+\mu n}\Big).\end{aligned} \tag{4.4}$$

These equations are generalizations of the classical equations of population genetics with two alleles under selection [23], in which we have made the influence of demography explicit. Eq. (4.4) is useful to investigate the dynamics on the boundary of the positive quadrant which is an invariant set.

Proposition 4.3 *Let us recall that*

$$\bar{n}^x = \frac{r(x)}{C(x,x)}\,;\ \bar{n}^y = \frac{r(y)}{C(y,y)}.$$

The points $(0,0)$, $(0,\bar{n}^y)$ *and* $(\bar{n}^x,0)$ *are the only stationary points on the boundary. The origin is unstable and the two other points are stable for the dynamics on the boundary. Their transverse stability/instability is given by the sign of the fitness function* $S(x;y)$ *given in* (4.3).

The proof is left to the reader. This implies that any accumulation point of any trajectory starting inside the positive quadrant is a fixed point. We now investigate the fixed points inside the positive quadrant.

Proposition 4.4 *Besides the fixed points in the boundary, there is*

i) in the BDA case, $\beta \neq 0\,;\ \mu \neq 0$*, there are at most* 3 *stationary points,*

ii) in the FD case ($\beta = 0\,;\ \mu = 1$*), there are at most* 2 *stationary points,*

iii) in the DD case ($\beta = 1\,;\ \mu = 0$*), there is at most* 1 *stationary point,*

or a line of fixed points inside $\mathbb{R}_+^2$.

Proof It is easier to consider the system in its form (4.4). The stationary points are denoted by (n,p) for convenience. They satisfy

$$\begin{aligned}0 =& n\Big(p\,r(x) + (1-p)\,r(y) \\ & - C(x,x)\,p^2 n - (C(x,y)+C(y,x))\,p(1-p)n - C(y,y)\,(1-p)^2 n\Big) \\ 0 =& p\,(1-p)\Big(r(x) - r(y) \\ & + np(C(y,x)-C(x,x)) + n(1-p)(C(y,y)-C(x,y)) + \alpha(x,y)\frac{n}{\beta+\mu n}\Big).\end{aligned}$$

If $n \neq 0$ and $p \notin \{0,1\}$, we deduce from the first equation that

$$n = \frac{pr(x) + (1-p)r(y)}{Q(p)}$$

where

$$Q(p) = C(x,x)p^2 + (C(x,y) + C(y,x))p(1-p) + C(y,y)(1-p)^2 \neq 0$$

for $p \in (0,1)$. Replacing n by this quantity, we write the second equation as

$$\begin{aligned} 0 = \frac{p(1-p)}{Q(p)\big(\beta Q(p) + \mu(pr(x) + (1-p)r(y))\big)} \times \\ \Big((r(x) - r(y))Q(p)\big(\beta Q(p) + \mu(pr(x) + (1-p)r(y)\big) \\ + (pr(x) + (1-p)r(y))\big(\beta Q(p) + \mu(pr(x) + (1-p)r(y))\big) \\ \big(p(C(y,x) - C(x,x)) + (1-p)(C(y,y) - C(x,y)\big) \\ + \alpha(x,y)\big(pr(x) + (1-p)r(y)\big)Q(p)\Big). \end{aligned}$$

When $\beta \neq 0$ and $\mu \neq 0$ (BDA case), the term between the large brackets is a priori a polynomial in p of degree 4. But explicit computation shows that the term of order 4 vanishes. Then this polynomial is of degree 3 and there are at most 3 stationary points inside the domain. In FD cases, the expression simplifies as $\frac{p(1-p)}{Q(p)}$ times a polynomial of degree 2 and there are at most two stationary points. The DD case reduces to a Lotka-Volterra system. □

To obtain more insight on the limiting dynamics, we use the Poincaré index (see [12, Chapter 6] or [16, p.50-51]).

Let us first remark that the trace of the Jacobian matrix of any fixed point (u_0, v_0) inside $\mathbb{R}^2_+$, is equal to

$$-C(x,x)\,u_0 - C(y,y)\,v_0 < 0.$$

This implies that any fixed point inside the positive quadrant is either a sink (index 1), a saddle (index -1) or a non-hyperbolic point of index 0 with a negative eigenvalue of the Jacobian matrix (because the vector field is analytic, see [12, Th.6.34]). We use the circuit with anticlockwise orientation drawn in Fig. 4.2. The largest radius is chosen large enough such that there are no fixed points outside the loop. The fixed points $(\bar{n}^x, 0)$ and $(0, \bar{n}^y)$ on the boundaries are denoted by A and a on Fig. 4.2.

The arrows represent the directions of the vector field along the different part of the circuit. Note that the arrow on the largest arc is only for FD or BDA cases. It can be shown in all cases that for a radius large enough, the large arc contributes 1/4 to the index.

Proposition 4.5 *Assume all fixed points are hyperbolic. The only possibilities are as follows:*

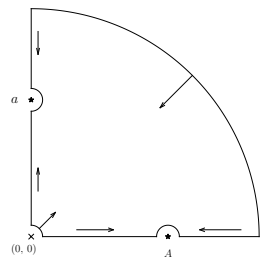

Figure 4.2: *Circuit used to compute the Poincaré index and determine the nature of fixed points inside the positive quadrant.*

- if $(\bar{n}^x, 0)$ *and* $(0, \bar{n}^y)$ *are unstable points, the index of the circuit is* 1 *and there is either one stable point inside the domain or* 3 *fixed points:* 2 *stable nodes and one saddle point.*

- if $(\bar{n}^x, 0)$ *and* $(0, \bar{n}^y)$ *are stable points, the index is -1 and there is either one saddle point inside or* 3 *fixed points:* 2 *saddle points and one stable point.*

- if one of the points $(\bar{n}^x, 0)$ *or* $(0, \bar{n}^y)$ *is an unstable node and the other one a saddle point, then the index is* 0 *and we have either* 0 *fixed point or two fixed points: one saddle point and one stable point.*

This proposition follows from the Poincaré-Hopf theorem: the index of the curve is equal to the sum of the indices of the fixed points inside the domain (see [12, Prop.6.26, p.175] or [16, Prop.1.8.4, p.51]). Combining this result with Proposition 4.3, one can decide between the different possibilities depending on the parameters.

The diagrams in Figure 3.1 realize the different situations described above. However, there may exist other diagrams in accordance with Proposition 4.5 that we have never observed numerically. We are yet unable to prove or disprove the existence of such other diagrams. One can nevertheless show that in the case where x and y are sufficiently similar, the phase diagrams of Figure 4.1 are the only possible ones. In the case of non hyperbolic fixed points inside the positive quadrant (with index 0 as mentioned previously), an analogue of Proposition 4.5 can established. This situation is however exceptional since it implies a nonlinear (polynomial) relation between the coefficients.

4.3 The case of constant competition

Assume that the competition kernel is constant $C(u, v) \equiv C$ for all $u, v \in \mathcal{X}$. Eq. (4.4) gives:

$$\begin{aligned} \frac{dn}{dt} =& n\left(p\, r(y) + (1-p)\, r(x) - Cn\right) \\ \frac{dp}{dt} =& p\,(1-p)\left(r(y) - r(x) + \alpha(y,x)\frac{n}{\beta + \mu n}\right). \end{aligned} \tag{4.5}$$

Let us consider separately the cases of FD transfer rate and DD or BDA transfer rates.

Frequency-dependent horizontal transfer rate. With $\beta = 0$ and $\mu = 1$, (4.5) shows that there are only two equilibria for the second equation: $p = 0$ or $p = 1$ (Figures 4.1 (1)-(2)). Therefore there is no polymorphic fixed point and we get a very simple "Invasion-implies-Fixation" criterion: trait y will invade a resident population of trait x if and only if

$$S(y;x) \quad = \quad f(y;x) + \alpha(y,x) = -S(x;y) > 0. \tag{4.6}$$

Thus, compared to a system without HGT, horizontal transfer can revert the direction of selection (*i.e.* $S(y;x)$ and $f(y;x)$ have opposite signs) provided that

$$|\alpha(y,x)| > |f(y;x)| \quad \text{and} \quad \mathrm{Sgn}(\alpha(y,x)) = -\mathrm{Sgn}(f(y;x)).$$

This implies that HGT can drive a deleterious allele to fixation.

Density-dependent or BDA horizontal transfer rate. When $\beta \neq 0$, there exists a polymorphic fixed point when

$$0 < -\frac{f(y;x)(\beta C + \mu r(x)) + \alpha(y,x) r(x)}{\mu f(y;x)^2 + \alpha(y,x)\, f(y;x)} < 1. \tag{4.7}$$

If $f(y;x)$ and $\alpha(y,x)$ are both positive, the above expression is negative and there is fixation of y. If $f(y;x)$ and $\alpha(y,x)$ are both negative, $\widehat{p} < 1 \iff -f(y;x)\beta C < r(y)(\mu f(y;x) + \alpha(y,x))$ which never happens since the left hand side is positive and the right hand side is negative. So there is fixation of x in this case. When $f(y;x)$ and $\alpha(y,x)$ have opposite signs, there may exist a non-trivial fixed point which is stable if

$$\mu f(y;x) + \alpha(y,x) > 0. \tag{4.8}$$

In contrast to the classical Lotka-Volterra competition model in which constant competition prevents stable coexistence, HGT with DD or BDA transfer rates allows the maintenance of a deleterious trait ($f(y;x) < 0$) in a stable polymorphic state; this requires that the flux rate ($\alpha(y,x)$) be positive and large enough in favor of y to x.

5 Rare mutation probability in the evolutionary time-scale

As seen in Section 3, it is not possible to capture the effect of rare mutations ($p_K \to 0$) at the ecological time scale. We have to consider a much longer time scale to observe this effect. The mutation time scale is of order $\frac{1}{K\, p_K}$ and we will assume in the following that when K is large enough,

$$\forall\, V > 0, \quad \log K \ll \frac{1}{K\, p_K} \ll e^{VK}. \tag{5.1}$$

A separation of time scales, between competition phases and mutation arrivals, results from this assumption. Indeed, mutations being rare enough, the selection will have time to eliminate deleterious traits or to fix advantageous traits before the arrival of a new mutant.

Let us now give a rigorous approach of the mechanisms governing the successive invasions of successful mutants.

5.1 Probability and time of invasion and fixation under competition with horizontal transfer

As an intermediate step, we investigate the fate of a newly mutated individual with trait y in a resident population in which trait x is common. We assume that the invasion fitness of trait y defined in (4.3) is positive, $S(y;x) > 0$. According to Table 1, this includes both cases of an advantageous trait ($f(y;x) > 0$), or a deleterious trait ($f(y;x) < 0$) provided that the HGT rate from y to x is high enough. Figure 5.1 gives illustration of the different stochastic dynamics one can obtain under frequency or density-dependent HGT, in the simple case of unilateral transfer. Figure 5.1 shows that a deleterious trait can invade a resident population and go to fixation (Fig.5.1(b) and (c)) or traits can stably coexist (Fig.5.1(a) and (d)). Fig.5.1(a) especially shows that both traits stably coexist even though competition is constant, which is made possible by density-dependent HGT (we have recalled in Subsection 4.1 that it cannot occur for a usual Lotka-Volterra system).

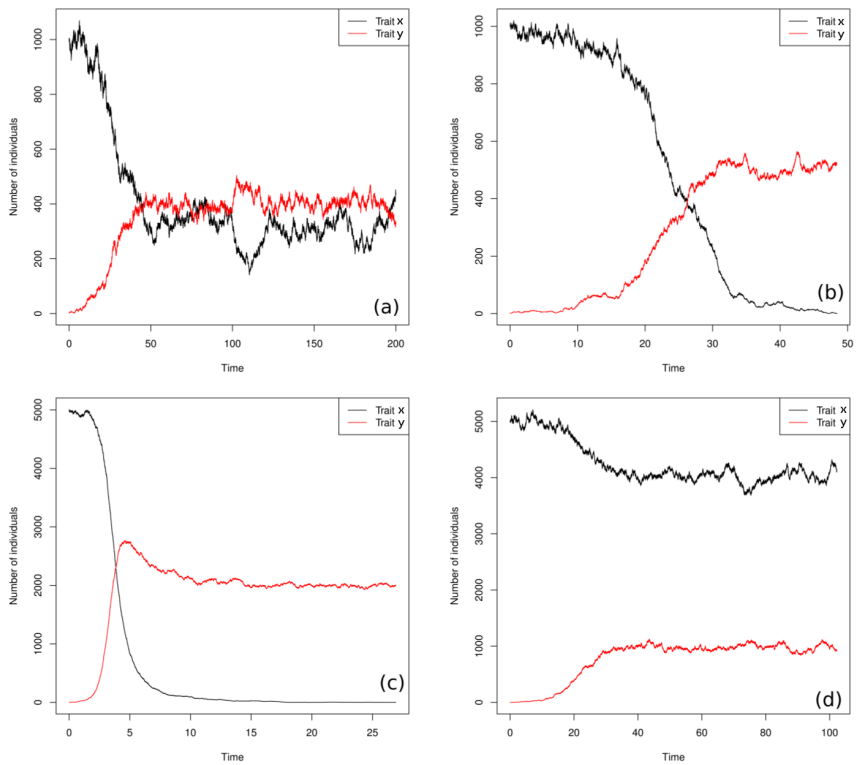

Figure 5.1: *Invasion and fixation or polymorphic persistence of a deleterious mutation with density-dependent (left, (a) and (c), $\mu = 0$, $\beta = 1$) or frequency-dependent (right, (b) and (d), $\mu = 1$, $\beta = 0$,) unilateral HGT rates. The deleterious nature of the mutation means that its invasion fitness without HGT is negative. Other parameters: Top figures (a) and (b): constant competition coefficients $C(y,x) = C(x,y) = C(x,x) = C(y,y) = 1$, $b(y) = 0.5$, $b(x) = 1$, $d(x) = d(y) = 0$ $K = 1000$, $\alpha = 0.7$; Bottom figures (c) and (d): $C(y,x) = C(x,x) = 2$, $C(y,y) = 4$, $C(x,y) = 1$, $b(y) = 0.8$, $b(x) = 1$, $d(x) = d(y) = 0$, $K = 10000$, $\alpha = 5$ under density-dependent rate, $\alpha = 0.5$ under frequency-dependent rate.*

An individual with trait y is introduced in the resident population of individuals with trait x, whose size is at equilibrium. During the first phase, $N^{y,K}$ is very small with respect to $N^{x,K}$. It can be approximated by a linear birth-death branching stochastic process in a population of $K\bar{n}^x$ individuals with trait x, at least until $N^{y,K}$ reaches the threshold $\eta\, K$, for a given $\eta > 0$. In this birth-death process, the transfer $x \to y$ acts as a birth term and the transfer $y \to x$ as a death term. When $K \to \infty$, the probability of the event where $N^{y,K}$ reaches $K\eta$ is approximatively the survival probability for the process (e.g. [6, 8]) and is given by

$$P(y;x) = \frac{S(y;x)}{b(y) + h(y,x,\overline{n}^x\delta_x)\,\overline{n}^x} = \frac{b(y) - d(y) + \left(\frac{\alpha(y,x)}{\beta+\mu\,\overline{n}^x} - C(y,x)\right)\overline{n}^x}{b(y) + \frac{\tau(y,x)\,\overline{n}^x}{\beta+\mu\,\overline{n}^x}}. \tag{5.2}$$

In Table 1, the probability of invasion is expounded for each form of HGT rate.

Transfer rate model	Invasion fitness $S(y;x)$	Invasion probability $P(y;x)$
No transfer	$f(y;x) = r(y) - \frac{r(x)C(y,x)}{C(x,x)}$	$\frac{[f(y;x)]_+}{b(y)}$
DD : $\tau(y,x)$	$f(y;x) + \frac{\alpha(y,x)r(x)}{C(x,x)}$	$\frac{\left[f(y;x)+\frac{\alpha(y,x)r(x)}{C(x,x)}\right]_+}{b(y)+\frac{\tau(y,x)r(x)}{C(x,x)}}$
FD : $\frac{\tau(y,x)}{n^x+n^y}$	$f(y;x) + \alpha(y,x)$	$\frac{\left[f(y;x)+\alpha(y,x)\right]_+}{b(y)+\tau(y,x)}$
BDA : $\frac{\tau(y,x)}{\beta+\mu(n^x+n^y)}$	$f(y;x) + \frac{\alpha(y,x)r(x)}{\beta C(x,x)+\mu r(x)}$	$\frac{\left[f(y;x)+\frac{\alpha(y,x)r(x)}{\beta C(x,x)+\mu r(x)}\right]_+}{b(y)+\frac{\tau(y,x)r(x)}{\beta C(x,x)+\mu r(x)}}$

Table 1: *Invasion fitness and invasion probability for each model of transfer rates and compared to the case of no transfer. DD and FD are special cases of BDA with $\beta = 1$, $\mu = 0$ and $\beta = 0$, $\mu = 1$ respectively.*

5.2 Times of invasion and fixation

We refer here to [6], where the results are rigorously proved. As the selectively advantageous trait y increases from rare, the first phase of the y-population growth has a duration of order $\log K/S(y;x)$. If $N^{y,K}$ reaches the threshold $\eta\, K$, then the second phase begins, where the processes $(N^{x,K}, N^{y,K})$ stay close to the dynamical system (4.1). The deterministic trajectory, which has a duration of order 1, can reach one of two final states: either both types of individuals stably coexist, or individuals with trait y invade the population and the x-population density reaches the threshold η (i.e. $N_t^{x,K} < \eta\, K$). Should the latter happens, the third phase begins and $N^{x,K}$ can be approximated by a subcritical linear birth-death branching process, until y is fixed and x is lost. In this birth-death process, the transfer $y \to x$ acts as a birth term and the transfer $x \to y$ as a death term. The third phase has an expected duration $\mathbb{E}_{\eta\, K}\,[T_0]$ of (see [20, Section 5.5.3, p.190])

$$\mathbb{E}_{\eta\, K}\,[T_0] = \frac{1}{b}\sum_{j\geq 1}\left(\frac{b}{d}\right)^j \sum_{k=1}^{\eta K-1}\frac{1}{k+j}$$

where $b = \; b(x) + \frac{\tau(x,y)r(y)}{\beta C(y,y)+\mu r(y)}$, $d = \; d(x) + \frac{C(x,y)r(y)}{C(y,y)} + \frac{\tau(y,x)r(y)}{\beta C(y,y)+\mu r(y)}$.

When $K \to \infty$, $\mathbb{E}_{\eta\, K}\,[T_0] \simeq \dfrac{\log K}{d-b}$, which means that the third phase is of order $\log K/|S(x;y)|$ in duration. Summing up, the fixation time of an initially rare trait y going to fixation is of order

$$T_{fix} = \log K\Big(\frac{1}{S(y;x)} + \frac{1}{|S(x;y)|}\Big) + O(1), \tag{5.3}$$

where the expressions for $S(y;x)$ and $S(x;y)$ are given in Table 1 and $O(1)$ is a negligible term.

5.3 The Trait Substitution Sequence

The limiting population process at the mutation time scale $\frac{t}{K\,p_K}$ will describe the evolutionary dynamics of invasions of successful mutants.

Let us assume in what follows that the ecological coefficients impede the coexistence of two traits. This is known as the *Invasion Implies fixation* (IIF) assumption.

Assumption (IIF):
Given any $x \in \mathcal{X}$, Lebesgue almost any $y \in \mathcal{X}$ satisfies the Invasion Implies Fixation. Either $(\bar{n}^x, 0)$ is a stable steady state of (4.1), or we have that $(\bar{n}^x, 0)$ and $(0, \bar{n}^y)$ are respectively unstable and stable steady states, and that any solution of (4.1) with initial state in $(\mathbb{R}_+^*)^2$ converges to $(0, \bar{n}^y)$ when $t \to \infty$.

From Section 4 we know that invasion does not necessarily imply fixation, even when the invasion fitnesses of the two types have opposite signs, as shown by Fig. 4.1 (5) and (6). In these cases, fixation depends on initial conditions and is usually not achieved when the invading type starts from a small density. Considering the special case of constant competition, however, invasion does imply fixation (Cf. Section 4.3) if HGT rates are FD or when condition (4.7) is not satisfied if HGT rates are DD or BDA.

Assumption (5.1) together with Assumption (IIF) imply that for a monomorphic ancestral population, the dynamics at the time scale $t/(Kp_K)$ can be approximated by a jump process over the trait space, called Trait Substitution Sequence (TSS). This jump process has been heuristically introduced in [21], and rigorously studied in [6], in the case without transfer.

Theorem 5.1 *We work under Assumptions (5.1) and (IIF). The initial conditions are $\nu_0^K(dx) = n_0^K\,\delta_{x_0}(dx)$ with $x_0 \in \mathcal{X}$, $\lim_{K\to\infty} n_0^K = \bar{n}^{x_0}$ and $\sup_{K\in\mathbb{N}^*}\mathbb{E}((n_0^K)^3) < +\infty$.*

Then, the sequence $(\nu^K_{\cdot/(Kp_K)})_{K\geq 1}$ converges in law to the $\mathcal{M}_F(\mathcal{X})$-valued process $(V_t(dx) = \widehat{n}_{Y_t}\,\delta_{Y_t}(dx), t \geq 0)$ where the process $(Y_t)_{t\geq 0}$ is a pure jump process on $\mathcal{X}$, started at x_0, and that jumps from x to y with the jump measure

$$b(x)\,\bar{n}^x\,[P(y;x)]_+\,m(x,dy), \tag{5.4}$$

where $P(y;x)$ has been defined in Table 1.

The convergence holds in the sense of finite dimensional distributions on $\mathcal{M}_F(\mathcal{X})$ and in the sense of occupation measures in $\mathcal{M}_F(\mathcal{X}\times[0,T])$ for every $T > 0$. □

The process $(Y_t, t \geq 0)$ (with $Y_0 = x_0$) describes the support of $(V_t, t \geq 0)$ and is called the Trait Substitution Sequence (TSS).

Main remark Let us remark that the transfer events may change the direction of evolution.

For example, let us consider a size model of trait $x \in [0, 4]$, where

$$b(x) = 4 - x \, , \, d(x) = 0 \, , \, \tau(x, y) = e^{x-y}. \tag{5.5}$$

Then if $h > 0$,

$$S(x + h; x) = r(x + h) - r(x) + \tau(x + h, x) - \tau(x, x + h) = -h + e^h - e^{-h},$$

which is positive if and only if $h > 0$. Thus the evolution with transfer is directed towards larger and larger traits.

On the other hand, without transfer, the invasion fitness $f(x + h; x)$ is negative for $h > 0$ and a mutant of trait $x+h$ with $h > 0$ would not appear in the TSS asymptotics. Therefore, adding the transfer totally changes the situation.

Proof [Proof of Theorem 5.1]The proof is a direct adaptation of the work of [6]. Accounting for the transfer parameters, the birth and death rates, respectively of the resident x and mutant y, become

$$b(x) + \frac{\tau(x, y)N^{y,K}}{\beta + \mu N^K} \quad , \quad d(x) + C(x, x)N^{x,K} + C(x, y)N^{y,K} + \frac{\tau(y, x)N^{y,K}}{\beta + \mu N^K} \, ;$$

$$b(y) + \frac{\tau(y, x)N^{x,K}}{\beta + \mu N^K} \quad , \quad d(y) + C(y, x)N^{x,K} + C(y, y)N^{y,K} + \frac{\tau(x, y)N^{x,K}}{\beta + \mu N^K}.$$

The main idea is as follows. If mutations are rare, the selection has time to eliminate the deleterious traits or to fix advantageous traits before a new mutant arrives. We can then combine the results obtained in Sections 4, 5.1 and 5.2.

Let us describe the steps of the invasion of a mutant and the stabilization of the population which follows, with or without fixation of the mutant trait. Let us fix $\eta > 0$. Assume that at $t = 0$, the population is monomorphic with trait x_0 and satisfies the assumptions of Theorem 5.1. For t and K large enough, the density process $\langle \nu_t^K, \mathbf{1}_x \rangle$ belongs to the η-neighborhood of $\bar{n}^x$ with large probability (cf. Prop. 3.1). We need the process to remain in this neighborhood until the first mutation occurs. We thus use a large deviations result for exit times of neighborhoods of $\bar{n}^x$, stated in Freidlin-Wentzell [15] and Feng-Kurtz [13]: the time taken by the density process to leave the η-neighborhood of $\bar{n}^x$ is larger than $\exp(VK)$, for some $V > 0$, with high probability. Hence, the first mutant will appear with large probability before the population exits the η–neighborhood of $\bar{n}^x$, if Assumption (5.1) is satisfied.

Simulations of the invasion dynamics of the mutant with trait y are given in Fig. 5.1 (a) and (c). At the beginning, the number of individuals with mutant trait y is small and the resident population's size is close to $\bar{n}^x$. Thus the mutant dynamics is close to a linear birth

and death process whose rates depend on $\bar{n}^x$. If $S(y;x) > 0$, the birth and death process is supercritical, and therefore, for large K, the probability that the mutant population's density attains η is close to $P(y;x)$ (given in Table 1 for each form of HGT rate, see Section 5.1).

After this first step, it is the competition step. When K increases, the density process $(\langle \nu_t^K, \mathbf{1}_x \rangle, \langle \nu_t^K, \mathbf{1}_y \rangle)$ tends to the solution of the dynamical system system (4.1). Thus the population process will attain with large probability an η-neighborhood of the unique globally asymptotically stable equilibrium n^* of (4.1) in time t_2, for small η.

The third step has been studied in Section 5.2. It is also shown that if the initial population is of order K, then the time taken for these three steps is given by (5.3). Hence, if $\log K \ll \frac{1}{Kp_K}$, with a large probability these three phases of competition-stabilization will happen before the occurrence of the next mutation and we can reiterate the reasoning after every mutation event.

Thanks to this analysis, we obtain the pure jump process $(V_t, t \geq 0)$ which describes the successive stationary states and only keeps in its support the favorable mutations. Let us assume that at some time t, $V_t = \bar{n}^x \delta_x$. If the process belongs to a η-neighborhood of $\bar{n}^x$, the mutation rate from an individual with trait x is close to $p_K b(x) K \bar{n}^x$. Hence, in the time scale $\frac{t}{Kp_K}$, it is approximatively $b(x)\bar{n}^x$. When a mutation occurs, the mutant trait y is chosen following $m(x, dy)$. Its invasion probability is then approximatively the survival probability of the mutant with trait y in the resident population, given by $[P(y;x)]_+$. In this case, the process will jump to $\bar{n}^y \delta_y$. This explains Formula (5.4). □

6 Canonical equation of the adaptive dynamics

The impact of transfer on evolution can also be captured and highlighted with the canonical equation. The canonical equation, first introduced by Dieckmann Law [11] (see also [8]) is the limit of the TSS when we accelerate further time and consider small mutation steps.

Let us now assume that the mutations are very small in the sense that the mutation distribution m_ε depends on a parameter $\varepsilon > 0$ as follows:

$$\int g(z) m_\varepsilon(x, dz) = \int g(x + \varepsilon h) m(x, dh),$$

where m is a reference symmetric measure. Then the generator of the TSS Y^ε (which now depends on the parameter ε), is given by

$$L^\varepsilon g(x) = \int (g(x + \varepsilon h) - g(x))\, b(x)\, \bar{n}^x \, \frac{[S(x + \varepsilon h; x)]_+}{b(x + \varepsilon h) + \tau(x + \varepsilon h, x)\bar{n}^x} \, m(x, dh).$$

If we assume that $x \mapsto \tau(x, y)$ and $x \mapsto b(x)$ are continuous and since $f(x;x) = \tau(x,x) = 0$, then standard tightness and identification arguments allow us to show the convergence in law of the process $\frac{1}{\varepsilon^2} Y^\varepsilon$ to the deterministic equation

$$x'(t) \quad = \quad \frac{1}{2} \bar{n}^{x(t)} \, \partial_1 S(x(t); x(t)) \int h^2 m(x(t), dh), \tag{6.1}$$

the so-called *canonical equation of adaptive dynamics* introduced in [11].

When the mutation law m is not symmetric, (6.1) involves the whole measure m, instead of its variance.

Let us come back to the example (5.5) introduced previously. In this case, the canonical equation is given by

$$x'(t) = \frac{4 - x(t)}{C} \int h^2 m(x(t), dh),$$

since $r'(x) = -1$ and $\partial_1 \tau(x, x) = -\partial_2 \tau(x, x) = 1$. Then the trait support is an increasing function. That means that the evolution with transfer decreases the reproduction rate until it vanishes, and therefore drives the population to an evolutionary suicide. Let us remark that without transfer, the canonical equation would be

$$x'(t) = -\frac{4 - x(t)}{C} \int h^2 m(x(t), dh),$$

and would drive to the optimal trait which maximizes the birth rate.

Then we observe that transfer may drastically change the direction of evolution, leading in the worst cases to an evolutionary suicide. Such situation will be observed on the numerical simulations of the next section.

7 Simulations - Case of Frequency-Dependence

(With the help of the master students Lucie Desfontaines and Stéphane Krystal).

In this section, we focus on the special case of unilateral transfer, which is relevant to address the question of fixation of mobile genetic elements such as plasmids. Plasmid transfer is unilateral: individuals containing a specific plasmid can transmit one copy to another individual which does not carry this plasmid. Let us assume that trait y indicates that the individual carries the plasmid of interest; individuals with trait x are devoid of this plasmid. Unilateral transfer then means $\tau(y, x) > 0$ and $\tau(x, y) = 0$, hence $\alpha(y, x) = \tau(y, x)$.

Unilateral transfer has been modelled in a stochastic two-type population genetics framework by Novozhilov et al. [22] and Tazzyman and Bonhoeffer [25]. These studies focused on FD transfer rates, and assumed constant population size (Novozhilov et al. used a Moran model, and Tazzyman and Bonhoeffer used a Wright-Fisher model with non-overlapping generations). In [5], we compared our results with theirs and showed the influence of demography and ecological competition on the effects of horizontal transfer and vertical transmission.

The next simulations will be concerned with the particular case of frequency-dependent unilateral HGT model with $x \in [0, 4]$, $m(x, h)dh = \mathcal{N}(0, \sigma^2)$, $\tau(x, y, \nu) = \dfrac{\tau \, \mathbf{1}_{x>y}}{\langle \nu, 1 \rangle}$.

$b(x) = 4 - x$; $d(x) = 1$; $C = 0,5$; $p = 0,03$; $\sigma = 0,1$; $K = 1000$.

Initial state: 1000 individuals with trait 1. Equilibrium of population size with trait 1: $1000 \times \frac{b(1)-d(1)}{C} = 4000$ individuals.

The constant τ will be the varying parameter. In the rest of the section we present different simulations highlighting the influence of τ and show how, depending on τ, we may obtain drastically different behaviors, from expected evolution scenario to evolutionary suicide.

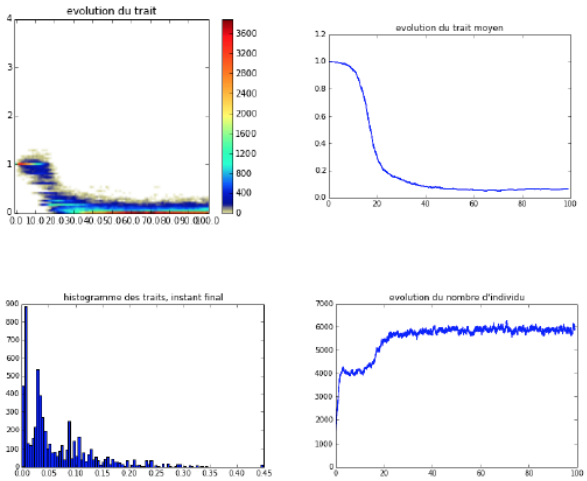

FIGURE 7 – Simulations pour $\tau = 0$.

Figure 7.1: *Case* $\tau = 0$

The case $\tau = 0$ (Fig. 7.1) is the null scenario without transfer. The evolution drives the population to its optimal trait 0 corresponding to a size at equilibrium equal to $1000 \times \frac{b(0)-d(0)}{C} = 6000$ individuals.

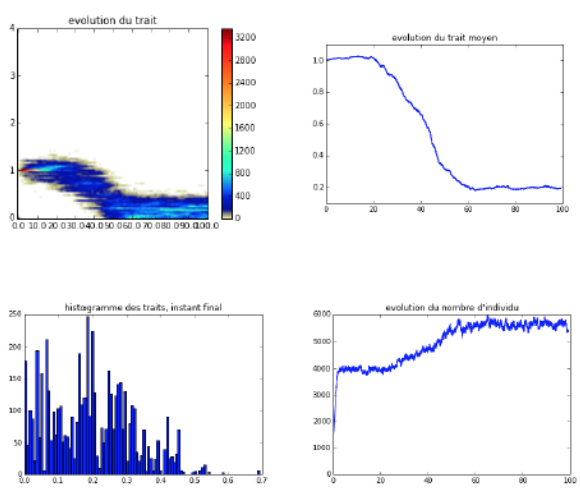

FIGURE 8 – Simulations pour $\tau = 0.2$

Figure 7.2: *Case* $\tau = 0.2$ - *Almost no modification*

The case $\tau = 0.2$ (Fig. 7.2) has characteristics similar to the case $\tau = 0$.

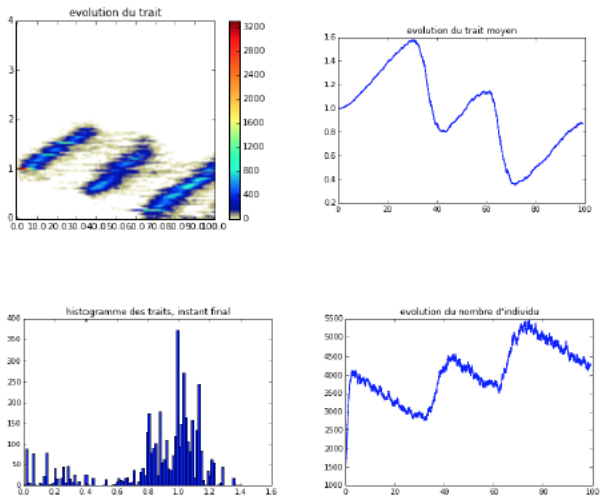

FIGURE 9 – Simulations pour $\tau = 0.6$ sur un temps de 100

Figure 7.3: *Case* $\tau = 0.6$ - *Stepwise Evolution*

The evolution scenario in the case $\tau = 0.6$ (Fig. 7.3) is rather different than the one for small τ. High transfer converts at first individuals to larger traits and in the same time the population decreases since for a given trait x, the equilibrium size $N_{eq} = \frac{b(x)-d(x)}{C} \times 1000 = 2000(3-x)$. At some point, the population size is so small that the transfer doesn't play a role anymore leading to the brutal resurgence of a quasi-invisible strain, issued from a few well adapted individuals with small traits. Computation shows that a small trait x_{small} can invade the resident population with trait $\overline{x}$ if $S(x_{small}; \overline{x}) = \overline{x} - x_{small} - \tau > 0$. If such a mutant appears, it reproduces faster and its subpopulation immediately kills the population with trait $\overline{x}$.

Note that the successive resurgences drive the mean trait towards the optimal trait 0.

Increasing further the transfer rate to $\tau = 0.7$ (Fig. 7.4), we can see either patterns as those above, with resurgences driving the mean trait towards the optimal trait, or extinctions of the population when there is no resurgence. The two simulations in the second line of Fig. 7.4 show evolutionary suicides: because τ is big, no small trait is left in these simulations to allow resurgence and the population reaches a state where the traits are so maladapted that the dies.

When $\tau = 1$ (Fig. 7.5), HGT impedes the population to keep a small mean trait to survive and we get evolutionary suicide in all the simulations that were done wih these parameters. The transfer drives the traits to larger and larger values, corresponding to lower and lower population sizes.

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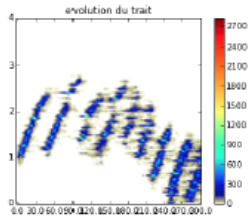


FIGURE 12 – simulation 1

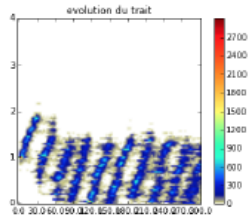
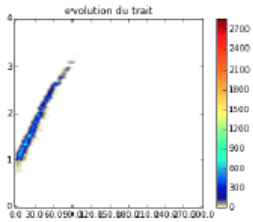


FIGURE 13 – simulation 2



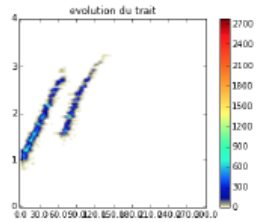
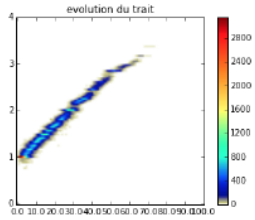


Figure 7.4: *Case* $\tau = 0.7$ - *Random Macroscopic Evolution*



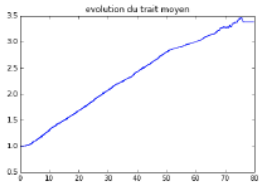


FIGURE 17 – Simulations pour $\tau = 1$

Figure 7.5: *Case* $\tau = 1$ - *Evolutive Suicide*

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