Stochastic dynamics for adaptation and evolution of microorganisms

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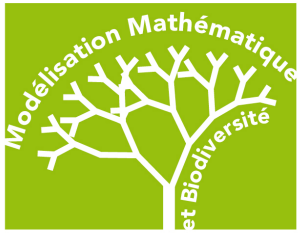


"After years, I have deeply regretted that I did not proceed far enough at least to understand something of the great leading principles of mathematics: for men thus endowed seem to have an extra-sense".

Charles Darwin, Autobiography.

Natural selection and evolution

"As many more individuals of each species are born than can possibly survive; and as, consequently, there is a frequently recurring struggle for existence, it follows that any being, if it vary however slightly in any manner profitable to itself, under the complex and sometimes varying conditions of life, will have a better chance of surviving, and thus be **naturally selected**. From the strong principle of inheritance, any selected variety will tend to propagate its new and modified form".

Charles Darwin, On the origin of species, 1859.

Adaptive Biology

The population has the propensity to generate as well to select individual diversity.

The ability of an individual (bacteria cell) to survive and reproduce depends on phenotypic (or genetic) parameters called traits.

The evolution of the trait distribution results from the following mechanisms:

- Heredity. (Vertical) transmission of the ancestral trait to the offsprings.
- Mutation. Generates variability in the trait values.
- Selection. Individuals with traits increasing their survival probability or their reproduction ability will spread through the population over time. The selection can also result from competition between individuals.
- Horizontal Gene Transfer (HGT): the bacteria exchange genetic information.

Horizontal Transfer

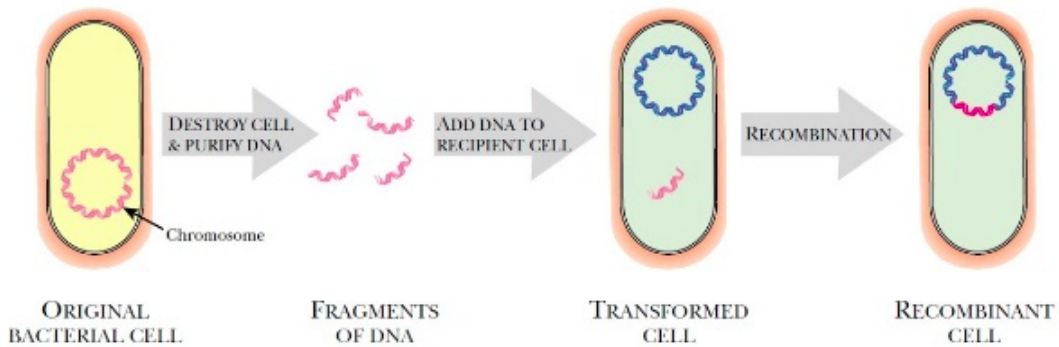
- In a large range of species across the tree of life, horizontal transfer (HT) of information, such as genetic mobile elements, plasmids, endosymbionts or cultural traits, affects the adaptation of populations and the evolution of species.
- HGT is recognized as a major process in the evolution and adaptation of micro-organisms.
- Behaviors or cultural traits can also be socially transmitted between non-kin individuals in animals and have effect on fitness.
- Nevertheless, most of the evolutive models do not take horizontal transfer into account.

Horizontal Gene Transfer

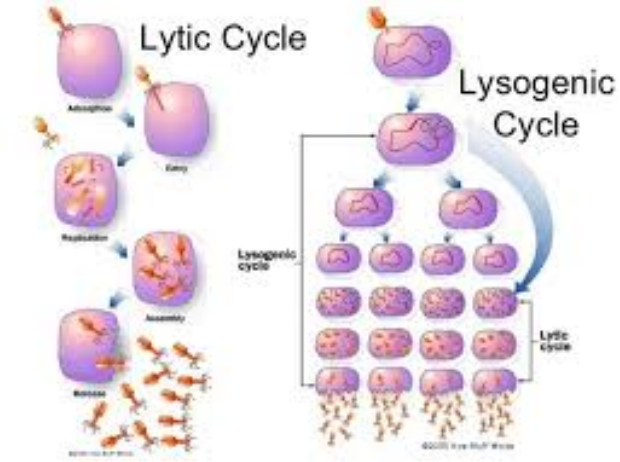
There are several mechanisms for horizontal gene transfer.

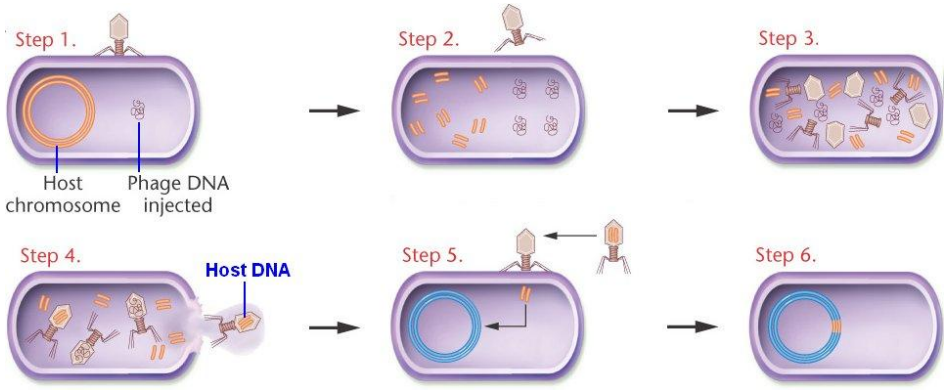
- Transformation

  Some DNA filaments directly enter the cell: direct uptake and incorporation of the exogenous genetic material from its surroundings through the cell membrane.

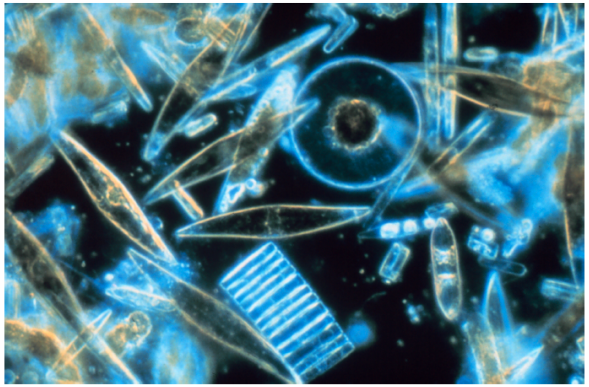


- Transduction: bacterial DNA is moved from a bacterium to another one by viruses (phages) which affect the cell. No physical contact between cells.





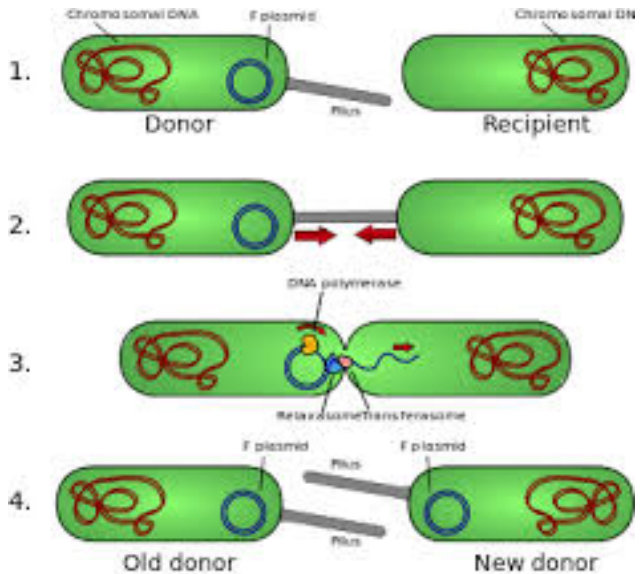
Transduction could explain the large diversity of phytoplanctons (The paradox of the plancton).



Observation of the plancton diversity under microscope.

- Conjugation : transfer of genetic material between bacteria cells by direct cell-to-cell contact. We will focus on plasmid conjugation.

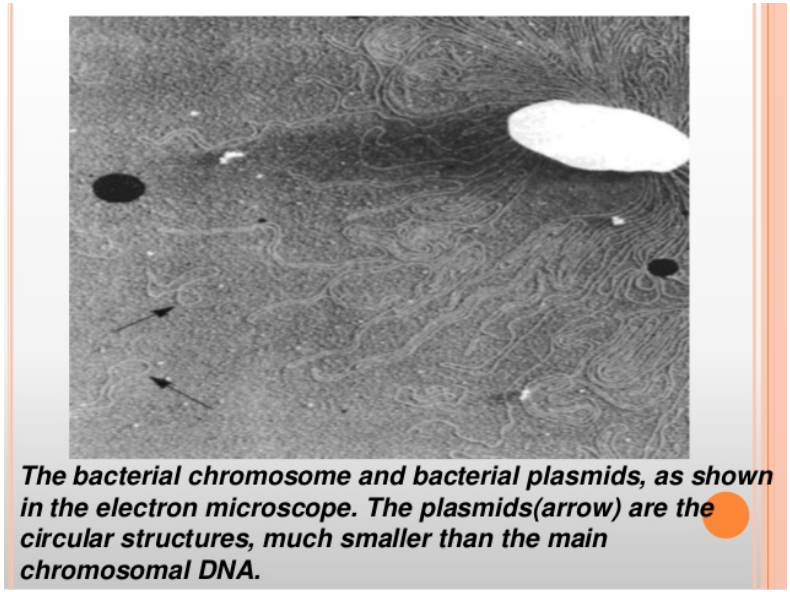
  Plasmids: small circular double-stranded DNA, physically separated from the chromosonal DNA. They replicate from a cell to another one, independently of the chromosome.



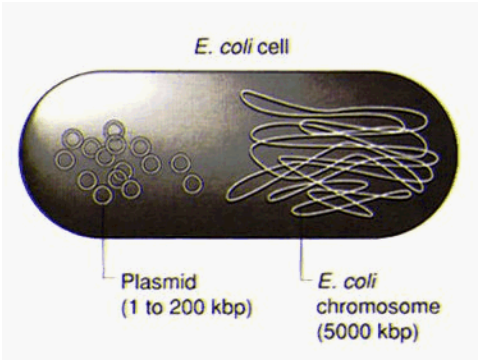
Plasmids in E-Coli

Number of identical plasmids in a cell: from 1 to thousands.

A larger proportion of the genome of plasmids codes for antibiotic resistances than that of the chromosome.



The bacterial chromosome and bacterial plasmids, as shown in the electron microscope. The plasmids(arrow) are the circular structures, much smaller than the main chromosomal DNA.



- Plasmid transfer plays a main role in the evolution, maintenance, and transmission of virulence.
  Indeed, plasmids are known to carry factors that can affect their host's fitness dramatically (as pathogens or genes for antibiotic resistance).
- Plasmid transfer is the primary reason for bacterial antibiotic resistance.
- Artificial plasmids are widely used as vectors in molecular cloning (CRISPR/Cas 9)
- Important role in the degradation of novel compounds by bacteria (such as human-created pesticides).

Trade-off between the cost of their mobility and the advantage imparted by their accelerated spread.

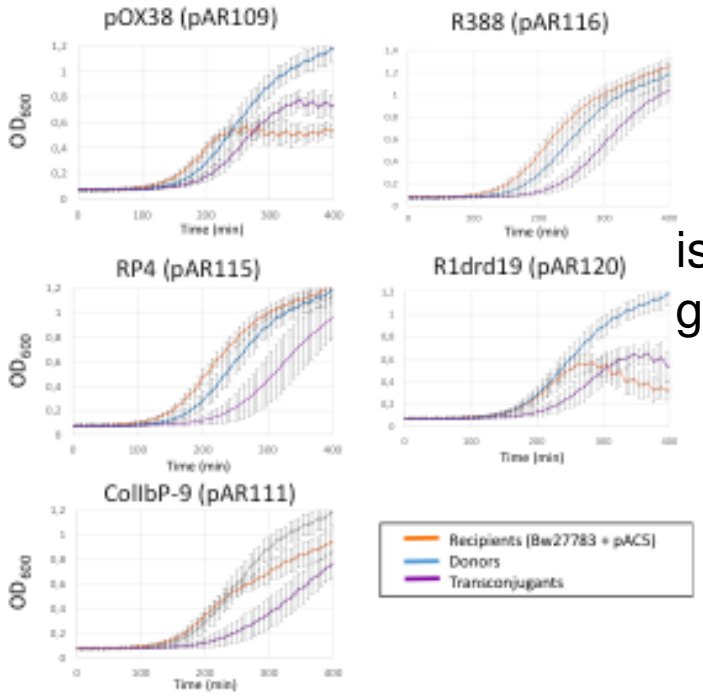
How the demographic parameters and the environment do interplay in the evolution mechanism?

Experiments and data

• Pilus synthesis and conjugation are very costly. In some cases, if a bacterium is in contact with a bacterium carrying the plasmid, it receives a signal impeding the transfer mechanism.

• Population of recipients *a*: they don't get the plasmid. The cells divide every 20 mn.

• Population of donors *A*: they carry a plasmid coding for resistance to antibiotic AB1. The plasmid is costly and the division of a cell happens every 22 mn.



Data: R. Fernandez-Lopez et al.

The populations *a* and *A* are isolated and one can measure their growth rates by spectrophotometry.

Logistic growth

Gene transfer modeling

A few literature on the subject.

Previous models are

- either deterministic:

epidemiological ODE's - No evolution (Levin et al. 1979, Anderson, May 1979, . . .)

Some PDE's models: Hinow et al. 2009, Magal, Raoul 2015.

- or stochastic:

population genetics models with constant population size - No ecology (Novozhilov et al. 2005, Tazzyman, Bonhoeffer 2013).

Our aim

- To propose a general stochastic eco-evolutionary model of population dynamics with horizontal and vertical transmissions.
- To focus on the interplay between ecology, transfer and evolution.
- To study the maintenance of polymorphism and the invasion or elimination of traits
- To show how HGT can drastically affect the evolutionary outcomes.

An individual-based model with two traits

- K scales the size of the population (large K means large population).
- We consider a population structured by a gene x with two alleles A and a: $x \in \{A, a\}$.
- The population at time t is modeled by the vector

$$(Z_t^{A,K}, Z_t^{a,K}) = \frac{1}{K}(N_t^{A,K}, N_t^{a,K}),$$

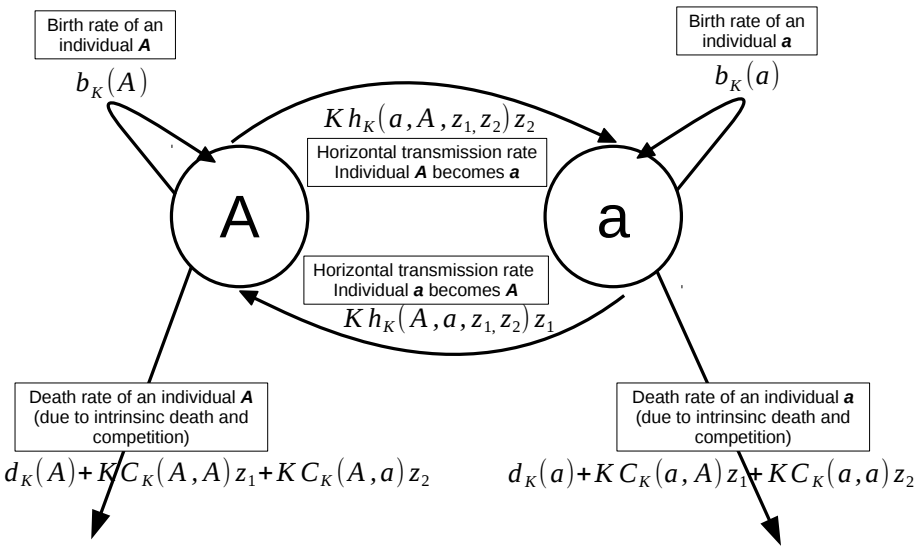
  where $N_t^{A,K}$ and $N_t^{a,K}$ the numbers of individuals with alleles respectively A and a.
- Birth rate of an individual with trait $x \in \{A, a\}$: $b_K(x)$.
- Death rate of an individual with trait x at time t:

$$d_K(x) + \frac{C(x,x)}{K} N_t^{x,K} + \frac{C(x,y)}{K} N_t^{y,K}.$$

HGT: bacteria conjugation

- Transfer rate: In a population (z_1, z_2), a donor transfers its trait x to a recipient with trait y at rate $h_K(x, y, z_1, z_2)$.
- The recipient becomes x.

The Markovian dynamics



The Stochastic process

Let us consider test functions $F \in \mathcal{C}_b(\mathbb{R}^2,\ \mathbb{R})$. The generator of the process $(Z_t^{A,K}, Z_t^{a,K})_{t\geq 0}$ is:

$$
\begin{aligned}
LF(z_1,z_2) &= K\, z_1\, b_K(A)\left(F(z_1+\frac{1}{K},z_2)-F(z_1,z_2)\right)\\
&+ K\, z_2\, b_K(a)\left(F(z_1,z_2+\frac{1}{K})-F(z_1,z_2)\right)\\
&+ K\, z_1\left(d_K(A)+C(A,A)\,z_1+C(A,a)\,z_2\right)\left(F(z^1-\frac{1}{K},z_2)-F(z^1,z_2)\right)\\
&+ K\, z_2\left(d_K(a)+C(a,A)\,z_1+C(a,a)\,z_2\right)\left(F(z^1,z_2-\frac{1}{K})-F(z^1,z_2)\right) \qquad (1)\\
&+ K^2\, z_1\, z_2\, h_K(A,a,z_1,z_2)\left(F(z_1+\frac{1}{K},z_2-\frac{1}{K})-F(z^1,z_2)\right)\\
&+ K^2\, z_1\, z_2\, h_K(a,A,z_1,z_2)\left(F(z_1-\frac{1}{K},z_2+\frac{1}{K})-F(z^1,z_2)\right).
\end{aligned}
$$

Playing with the forms of the demographic parameters and time scales will lead to various asymptotic behaviors.

Large population limit

Consider now the following assumptions:

• We assume that for any $x, y \in \{a, A\}$, we have $b_K(x) \to b(x)$, $d_K(x) \to d(x)$, $KC_K(x, y) \to C(x, y)$ and we set

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

• We also assume that for any $x, y \in \{a, A\}$,

$$h(x, y, z_1, z_2) = \lim_{K\to\infty} K\, h_K(x, y, z_1, z_2) = \frac{\tau(x, y)}{\beta + \mu\,(z_1 + z_2)} \quad .$$

Experimental remark: *HGT rate is density-dependent when the population size is low* and *frequency-dependent when the population is close to its carrying capacity*.

• For $\beta = 1, \mu = 0$ or $\beta = 0, \mu = 1$ or $\beta, \mu \neq 0$, one gets the three cases of density-dependent horizontal transfer rate (DD), frequency-dependent transfer rate (FD) or Beddington-DeAngelis like transfer rate (BDA).

• Denote by $\alpha(x, y) = \tau(x, y) - \tau(y, x)$ the transfer flux, which can be positive or negative.

Theorem

When $K \to \infty$ *, the stochastic process* $(Z_t^{A,K}, Z_t^{a,K})_{t\geq 0}$ *converges in probability to the solution* $(z_t^A, z_t^a)_{t\geq 0}$ *of the ODEs system:*

$$\frac{dz^A}{dt} = \left(r(A) - C(A,A)z^A - C(A,a)z^a + \frac{\alpha(A,a)}{\beta + \mu\left(z^A + z^a\right)} z^a\right) z^A$$

$$\frac{dz^a}{dt} = \left(r(a) - C(a,A)z^A - C(a,a)z^a - \frac{\alpha(A,a)}{\beta + \mu\left(z^A + z^a\right)} z^A\right) z^a.$$

Sketch of Proof (cf. Ethier-Kurz).

Uniform estimates on moments ; Tightness
Identification of the limit.
Uniqueness of the solution of the dynamical system.

Remark: if there is only one type A, the equation becomes

$$\frac{dz^a}{dt} = \left(r(a) - C(a,a)z^a\right) z^a.$$

There is only one stable equilibrium

$$\bar{z}^a = \frac{r(a)}{C(a,a)}.$$

Stability Analysis

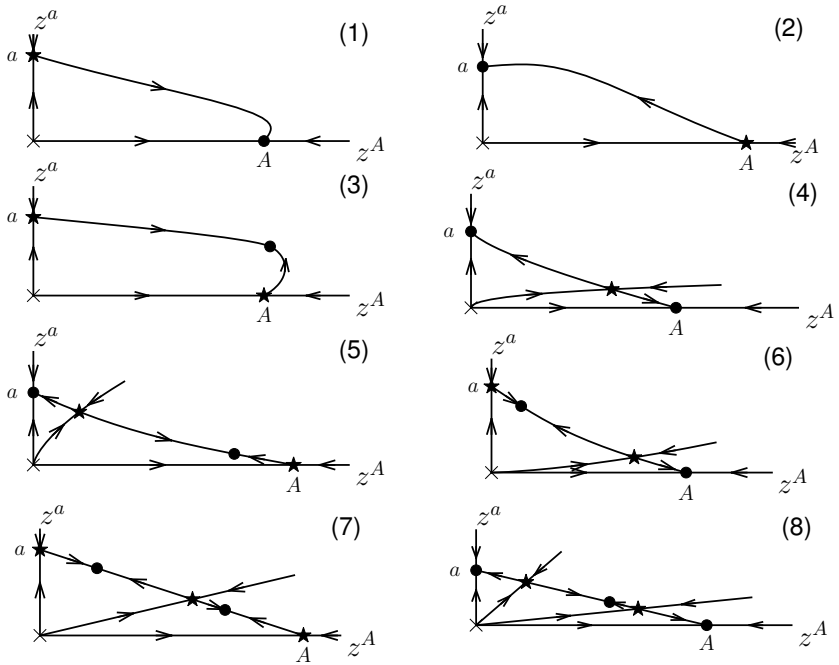
When $\alpha(x, y) \equiv 0$: classical Lotka-Volterra system. The stability is governed by the sign of the invasion fitness function

$$f(y; x) = r(y) - C(y, x)\,\overline{z^x} = r(y) - C(y, x)\,\frac{r(x)}{C(x, x)}.$$

For C constant and r bijective, $f(y; x) = r(y) - r(x)$: no co-existence.

When $\alpha(x, y) \neq 0$:

The circles and stars respectively show the stable and unstable fixed points.



- Invasion fitness of individuals with trait A in the a-resident population:

$$\begin{aligned} S(A;a) &= r(A) + \left(\frac{\alpha(A,a)\,\bar{z}^a}{\beta + \mu\,\bar{z}^a} - C(A,a)\right)\bar{z}^a \\ &= r(A) + \frac{\alpha(A,a)r(a)}{\beta C(a,a) + \mu r(a)} - \frac{C(A,a))r(a)}{C(a,a)}. \end{aligned}$$

- Compared to the classical two-species Lotka-Volterra system, 4 new phase diagrams are possible: Figures (5)-(8).
- Figures (1)-(4) are possible for all forms of HGT rates while Figures (5)-(6) are not possible when the HGT rate is DD and Figures (7)-(8) are only possible when the HGT rate is BDA.
- Figures (5)-(8): depending on the initial conditions, the population can be stably polymorphic or can fix one of the two traits.
- Classical two-species LV system without HGT: coexistence of both species $\Longleftrightarrow$ $S_{Aa} > 0$ and $S_{aA} > 0$.

  Our results show that HGT changes dramatically the picture: a stable polymorphic state can exist whatever the sign of the fitness.

Study of the dynamical system

- If $C(A,A) > 0$ and $C(a,a) > 0$, then $\phi(z^1, z^2) = \frac{1}{z^1 z^2}$ is a Dulac function.
- Dulac Theorem : the system has no cycle in $(\mathbb{R}_+^*)^2$.
- Fixed points in the positive quadrant: it's easier to consider the system "population size and frequencies".

$$n(t) = x(t) + y(t) \quad ; \quad q(t) = \frac{x(t)}{x(t) + y(t)}.$$

$$\begin{aligned}\frac{dn}{dt} &= n\Big(q\,r(A) + (1-q)\,r(a) - C_{AA}\,q^2 n - (C_{Aa} + C_{aA})\,q(1-q)n \\ &\qquad - C_{aa}\,(1-q)^2 n\Big) \\ \frac{dq}{dt} &= q\,(1-q)\Big(r(A) - r(a) + nq(C_{aA} - C_{AA}) + n(1-q)(C_{aa} - C_{Aa}) + \\ &\qquad + \alpha(a,A)\frac{n}{\beta + \mu n}\Big).\end{aligned}$$

- Use of the Poincaré index and of Poincaré-Hopf Theorem to get the sources and the sinks.

Invasion, fixation or polymorphism persistence of a costly plasmid

Our results show that HGT can dramatically change the usual picture.

Fate of a deleterious mutant A in a resident population a.

Here the usual fitness $f(A;a) < 0$ and the transfer is unilateral.

The case where C is constant and r bijective.

Without transfer:

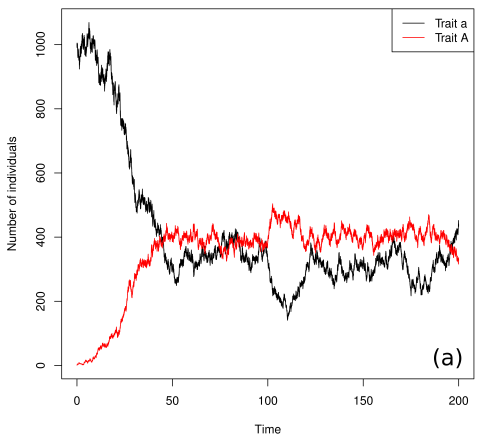
$$f(A;a) = r(A) - r(a).$$

No polymorphism is possible.

With tranfer:

- **Unilateral DD transfer.**

$$S(A;a) = r(A) - r(a) + \tau(A,a)\frac{r(a)}{C} \; ; \; S(a;A) = r(a) - r(A) - \tau(A,a)\frac{r(A)}{C}.$$

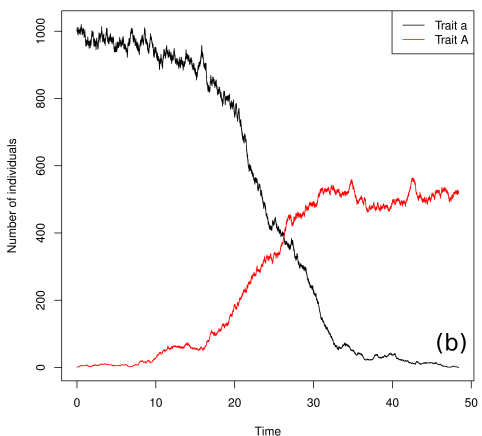


$b(A) = 0.5 \; ; \; b(a) = 1 \; ; \; \tau(A,a) = \alpha(A,a) = 0,7 \; ; \; K = 1000 \; ; \; C = 1 \; ; \; d \equiv 0.$

Polymorphism with C constant.

- **Unilateral FD transfer.**

$$S(A;a) = r(A) - r(a) + \tau(A,a) \; ; \; S(a;A) = -S(A;a).$$

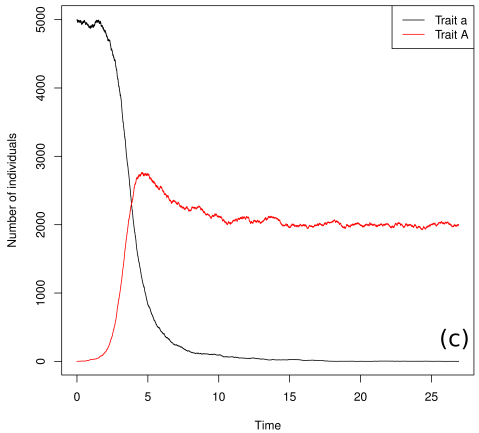


$b(A) = 0.5 \; ; \; b(a) = 1 \; ; \; \tau(A,a) = \alpha(A,a) = 0,7 \; ; \; K = 1000 \; ; \; C = 1 \; ; \; d \equiv 0.$

Fixation of a deleterious mutant.

The case of a very consuming mutant

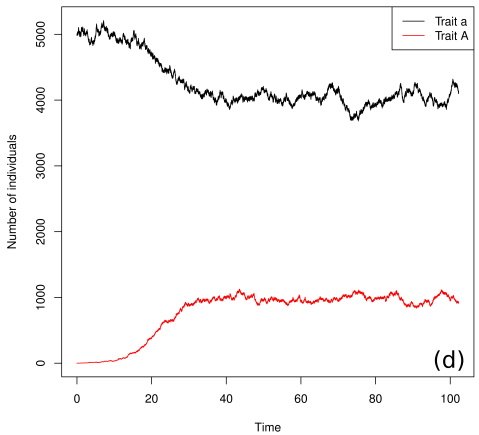
- **Unilateral DD transfer.**



$b(A) = 0.8$; $b(a) = 1$; $\tau(A, a) = \alpha(A, a) = 0.5$; $K = 5000$, $C_{Aa} = C_{aa} = 2$; $C_{AA} = 4$; $C_{aA} = 1$; $d \equiv 0$.

Fixation of a deleterious and very consuming mutant.

- **Unilateral FD transfer.**



$b(A) = 0.8$; $b(a) = 1$; $\tau(A, a) = \alpha(A, a) = 0.5$; $K = 5000$; $C_{Aa} = C_{aa} = 2$; $C_{AA} = 4$; $C_{aA} = 1$; $d \equiv 0$.

Polymorphism with a deleterious and very consuming mutant.

- **Invasion probability of A in a resident population of type a:** $S(A;a) > 0$.

$$P_{Aa} = \frac{[S(A;a)]_+}{b(A) + h(A,a,0,\bar{z}^a)\,\bar{z}^a} = \frac{[b(A) - d(A) + \left(h(A,a,0,\bar{z}^a) - C_{Aa}\right)\bar{z}^a]_+}{b(A) + h(A,a,0,\bar{z}^a)\,\bar{z}^a}.$$

  Unilateral HGT increases the probability of invasion of A.

  Time for the population A to be of order K: $\log K / S(A;a)$.

- **Competition (deterministic)**: follows the EDOs system - Duration of order 1.

- **Fixation** (when the deterministic system converges to $(\bar{z}^A, 0)$): birth-death process with negative fitness $S(a;A) < 0$.

  Duration of order $\log K / |S(a;A)|$.

  Fixation times are decreased by HGT.

Evolution: mutations of traits

- The trait values belong to a continuum.
- Phenotypic trait under selection x in a compact subset $\mathcal{X}$ of $\mathbb{R}^d$ (rate of nutrient intake, body size at maturity, age at maturity ...).
- K scales the size of the population (large K means large population).
- Population of $N^K(t)$ individuals weighted by $\frac{1}{K}$ with trait vector

$$(X_t^1, \cdots, X_t^{N^K(t)}) \in \mathcal{X}^{N^K(t)}.$$

- The population is described by the Markovian random measure-valued process $(\nu_t^K, t \geq 0)$ defined by

$$\nu_t^K = \frac{1}{K} \sum_{i=1}^{N^K(t)} \delta_{X_t^i}$$

Transitions

BIRTHS:

Each individual with characteristics x gives birth to a single individual at rate $b(x)$.

The function b is continuous on $\mathcal{X}$.

p_K scales the mutation probability (small p_K means rare mutation).

At each birth time:

- with probability $1 - p_K$, the offsprings inherits of x. (Clonal reproduction)
- Otherwise mutations on trait occur independently with probability p_K.
- Trait mutation: the new trait is z chosen according to $m(x, z)dz$.
  The mutation measure $m(., z)dz$ is continuous.

HORIZONTAL GENE TRANSFER (HGT)

Individuals exchange information by conjugation. In the population ν, an individual with trait x chooses a partner with trait y at rate $h_K(x, y, \nu)$.The new traits are (x, x).

Unilateral plasmid transfer: the donor transmits a copy of its plasmid to individuals devoid of plasmid: $h_K(x, y, \nu) = 0$ for $x < y$.

DEATHS:

- Each individual with characteristics x dies at rate

$$d(x) + \frac{1}{K} \sum_{i=1}^{N^K(t)} C(x, x_i) = d(x) + C * \nu_t^K(x).$$

- The term $\frac{C(x, x_i)}{K}$: competition pressure between two individuals.

  The functions d and C are bounded continuous.

For some $p \geq 2$,

$$\mathbb{E}\left(\langle \nu_0^K, 1 \rangle^p\right) < +\infty.$$

Moment conditions propagate and imply the existence and uniqueness of the process.

Let us introduce $F_f(\nu) = \int f(x)\nu(dx)$, for $f \in \mathcal{C}_b$ and $\nu = \frac{1}{K}\sum_{i=1}\delta_{x_i}$.

The infinitesimal generator of $(\nu_t^K)_t$ is then given by

$$L^K F_f(\nu) = \int_{\mathcal{X}} \nu(dx)\Big[b(x)\Big((1-p_K)f(x) + p_K \int_{\mathcal{X}} f(z)m(x,z)dz\Big) - \big(d(x) + C * \nu(x)\big)f(x) + \int_{\mathcal{X}} K\, h_K(x,y,\nu)\big(f(x)-f(y)\big)\nu(dy)\Big].$$

Moreover,

$$\int_{\mathcal{X}} f(x)\nu_t^K(dx) = \int_{\mathcal{X}} f(x)\nu_0^K(dx) + \int_0^t L^K F_f(\nu_s^K)ds + M_t^{K,f},$$

where $M^{K,f}$ is a càdlàg square-integrable martingale issued from 0 and

$$\mathbb{E}((M_t^{K,f})^2) = \frac{1}{K}\,\mathbb{E}\Big(\int_0^t \int_{\mathcal{X}} \Big\{\Big((1-p_K)b(x) - d(x) - C * \nu_s^K(x)\Big)\Big)f^2(x) + p_K\, b(x)\int_{\mathcal{X}} f^2(z)\, m(x,z)dz + \int_{\mathcal{X}} K\, h_K(x,y,\nu^K)\big(f(x)-f(y)\big)^2\nu_s^K(dy)\Big\}\nu_s^K(dx)ds\Big).$$

Grande population, échelle de temps $O(1)$

$K \to \infty$, $p_K \to p$ and $b_K \to b$, $d_K \to d$, $KC_K \to C$.

$$\lim_{K\to\infty} K\, h_K(x,y,\nu) = h(x,y,\langle \nu, 1\rangle) = \frac{\tau(x,y)}{\beta + \mu\,\langle \nu, 1\rangle},$$

where τ is a continuous function .

Proposition: *Let $T > 0$. If $\nu_0^K \Longrightarrow \xi_0$ when $K \to +\infty$, the sequence $(\nu^K)_{K\geq 1}$ converges in probability in $\mathbb{D}([0,T], \mathcal{M}_F(\mathbb{R}^d))$ to the solution $\xi \in \mathcal{C}([0,T], \mathcal{M}_F(\mathbb{R}^d))$ of*

$$\begin{aligned}\langle \xi_t, f\rangle = \langle \xi_0, f\rangle + \int_0^t \int_{\mathcal{X}} \Big\{ \big(b(x)(1-p) - d(x) - C * \xi(x)\big) f(x) \\ + pb(x) \int_{\mathcal{X}} f(z) m(x,z) dz \\ + \int_{\mathcal{X}} \big(f(x) - f(y)\big) \frac{\tau(x,y)}{\beta + \mu\langle \xi_s, 1\rangle} \xi_s(dy) \Big\} \xi_s(dx) ds.\end{aligned}$$

Preuve: usual argument compactness-identification-uniqueness using moment estimates.

Conjugation - time scale $O(1)$

Let us introduce the transfer flux $\alpha(x,y) = \tau(x,y) - \tau(y,x)$ (positive or negative or 0).

Proposition: *If $\xi_0 \ll$ leb meas., then for any $t > 0$, the measure $\xi_t \ll$ leb meas. and its density is given by $(u(t,x), x \in \mathcal{X})$ positive solution of the equation*

$$\partial_t u(t,x) = \big(b(x)(1-p) - d(x) - C * u(t,x)\big)u(t,x) + p\int_{\mathcal{X}} b(y)m(y,x)u(t,y)dy$$
$$+ \frac{u(t,x)}{\beta + \mu\|u(t,.)\|_1}\int_{\mathcal{X}} \alpha(x,y)u(t,y)dy,$$

with $C * u(t,x) = \int C(x,y)u(t,y)dy$, $\|u(t,.)\|_1 = \int u(t,y)dy$.

Long time behaviour? (Cf. Desvillettes, Jabin, Mischler, Raoul '08 ($\alpha = 0$), Hinow, Le Foll, Magal, Webb '09, Magal, Raoul '15).

Rare mutation $p = 0$: **The mutations disappear at this time scale.**

Large population, Rare mutations, Evolution time scale $\frac{t}{Kp_K}$

Adaptation of Champagnat 2006 - Heuristics Metz et al. 1996.

We stay in this framework with the continuum of traits $x \in \mathcal{X}$.

Invasion implies fixation: For simplicity, we assume that the stable equilibria of the dynamical system with any two traits x and y are only on the boundary of the positive quadrant (no coexistence).

Rare mutations assumption:

$$\log K \ll \frac{1}{Kp_K} \ll e^{KV}, \forall V > 0.$$

It results a separation of time scales, between competition phases and mutation arrivals.

- $\frac{1}{Kp_K} \ll e^{KV}$, for any $V > 0$: before the first mutation, the population size stays close to its deterministic equilibrium.

- When a mutation occurs, the duration for the competition phase is of order $\log K$ (as seen in the previous slides).

- $\log K \ll \frac{1}{Kp_K}$: the selection process has sufficient time to eliminate disadvantaged trait before the next mutation event arrives with high probability.

- **At the mutation time scale**: we will only see a jump from $\bar{z}^x$ bacteria with trait x to $\bar{z}^y$ bacteria with trait y.

- Succession of phases of trait mutant invasion, and phases of competition between traits.

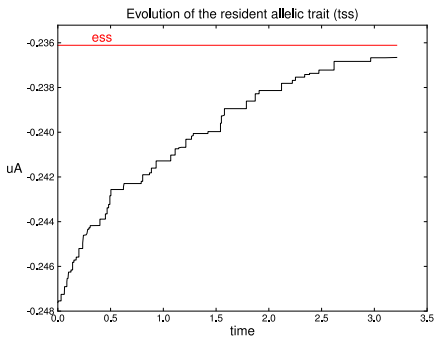
Theorem (TSS Approximation)

Assume: the initial conditions $\nu_0^K = n_0^K \, \delta_{x_0}(dx)$ *converge to* $\bar{z}^{x_0} \delta_{x_0}(dx)$.

As soon as Invasion-implies-fixation, the the population process at time $\frac{t}{Kp_K}$ *is approximated by a process which charges monomorphic equilibrium states.*

The process jumps from $\bar{z}^x$ *individuals with trait* x *to* $\bar{z}^y$ *individuals with trait* y *, where* y *is chosen according to the mutation measure* $m(x, dy)$
with rate

$$b(x)\,\bar{z}^x \, \frac{[S(y;x)]_+}{b(y) + h(y,x,\bar{z}^x)\bar{z}^x} \qquad \text{with} \qquad \bar{z}^x = \frac{r(x)}{C(x,x)}.$$



Each jump corresponds to the successful invasion of a new mutant trait.

Transfer events may drastically change the evolution.

Constant competition pressure C:

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

Example: $x \in [0,4]$. $b(x) = 4 - x$; $d \equiv 1$, $C(x,y) \equiv C$ and $\overline{n^x} = \dfrac{3-x}{C}$.

(i) **Without HGT**: the fitness function equals

$$\begin{aligned} f(y;x) &= x - y\,, \\ f(y;x) > 0 &\iff y < x. \end{aligned}$$

A mutant with trait y will invade the population $\iff y < x$.
The evolution will yield decreasing traits.

(ii) **With frequency-dependence HGT**: We consider the transfer rates

$$\begin{aligned} \tau(x,y) &= e^{x-y}\,,\ \beta = 0\,,\ \mu = 1, \\ S(y;x) &= -(y-x) + e^{y-x} - e^{-(y-x)} \\ S(y;x) > 0 &\iff y > x. \end{aligned}$$

The evolution will lead to larger and larger traits: may lead the population to evolutive suicide.

Canonical equation - Small mutations

The mutation steps are of order σ:
$\int g(z)\, m_\sigma(x,z)dz = \int g(x+\sigma h)\, \overline{m}(x,h)dh$, where $\overline{m}$ independent of σ.

Theorem *When $\sigma \to 0$, the TSS process at time t/σ^2 is approximated by the solution of the ODE*

$$x'(t) = \overline{n^x}\left(r'(x) + \partial_1\tau(x,x) - \partial_2\tau(x,x)\right) \int h^2\, \overline{m}(x,h)dh.$$

In the example:

Without transfer:

$$x'(t) = -\frac{3-x(t)}{C} \int h^2\, \overline{m}(x(t),h)dh$$

leads to the nul optimal trait which maximises the birth rate.

With transfer:

$$x'(t) = \frac{3-x(t)}{C} \int h^2\, \overline{m}(x(t),h)dh.$$

makes the reproduction rate decrease.

Unilateral HGT: transfer of plasmid

(Simulations: Lucie Desfontaines and Stéphane Krystal).

- $x \in [0,4]$; $m(x,z)dz = \mathcal{N}(x,\sigma^2)$.
- Frequency-dependent unilateral HGT model. $\tau(x,y) = \tau \mathbf{1}_{x>y}$.

  The constant $\tau > 0$ will be the varying parameter.
- $b(x) = 4 - x$; $d(x) = 1$; $C = 0,5$; $p = 0,03$; $\sigma = 0,1$; $K = 1000$.
- Initial state: 1000 individuals with trait 1. Equilibrium of population size with trait 1: $1000 \times \frac{b(1)-d(1)}{C} = 4000$ individuals.
- Optimal trait 0 and size at equilibrium: $1000 \times \frac{b(0)-d(0)}{C} = 6000$ individuals.

  The transfer favorizes the large traits: a trade-off between reproduction and transfer.

$\tau = 0$

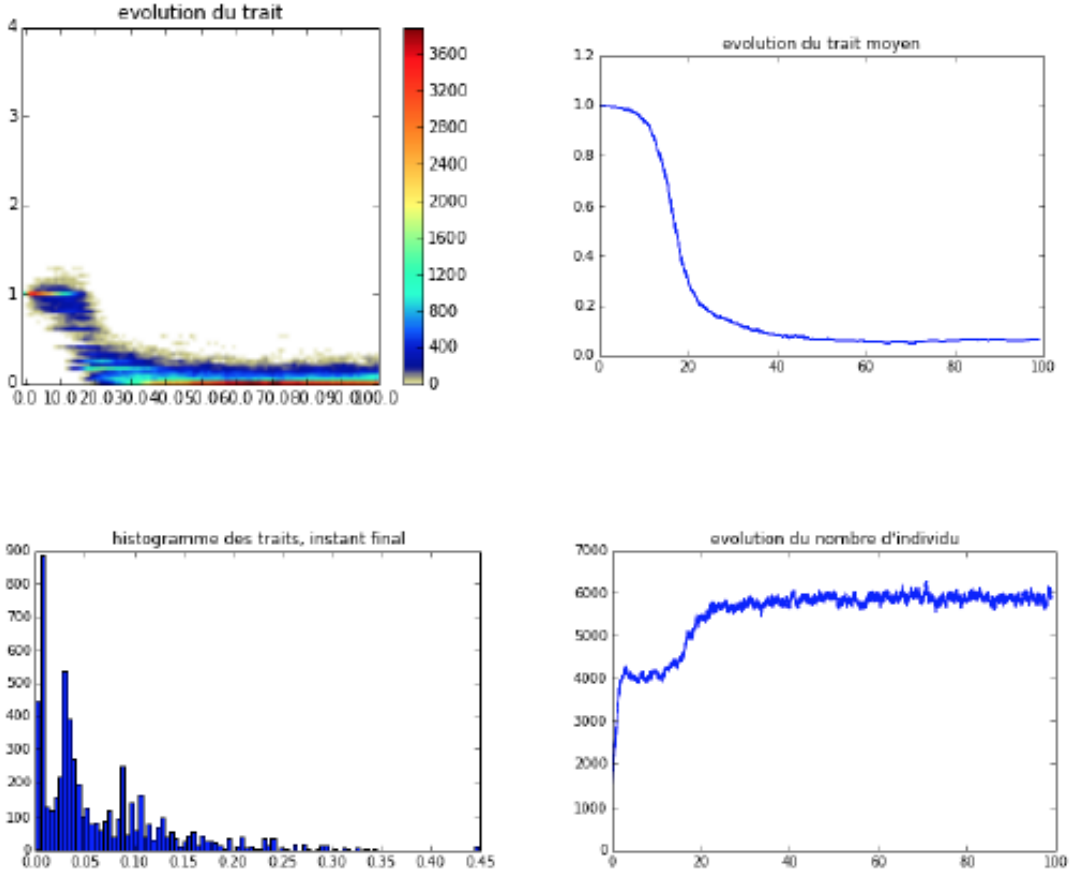


FIGURE 7 – Simulations pour $\tau = 0$.

$\tau = 0,2$ - Almost no modification

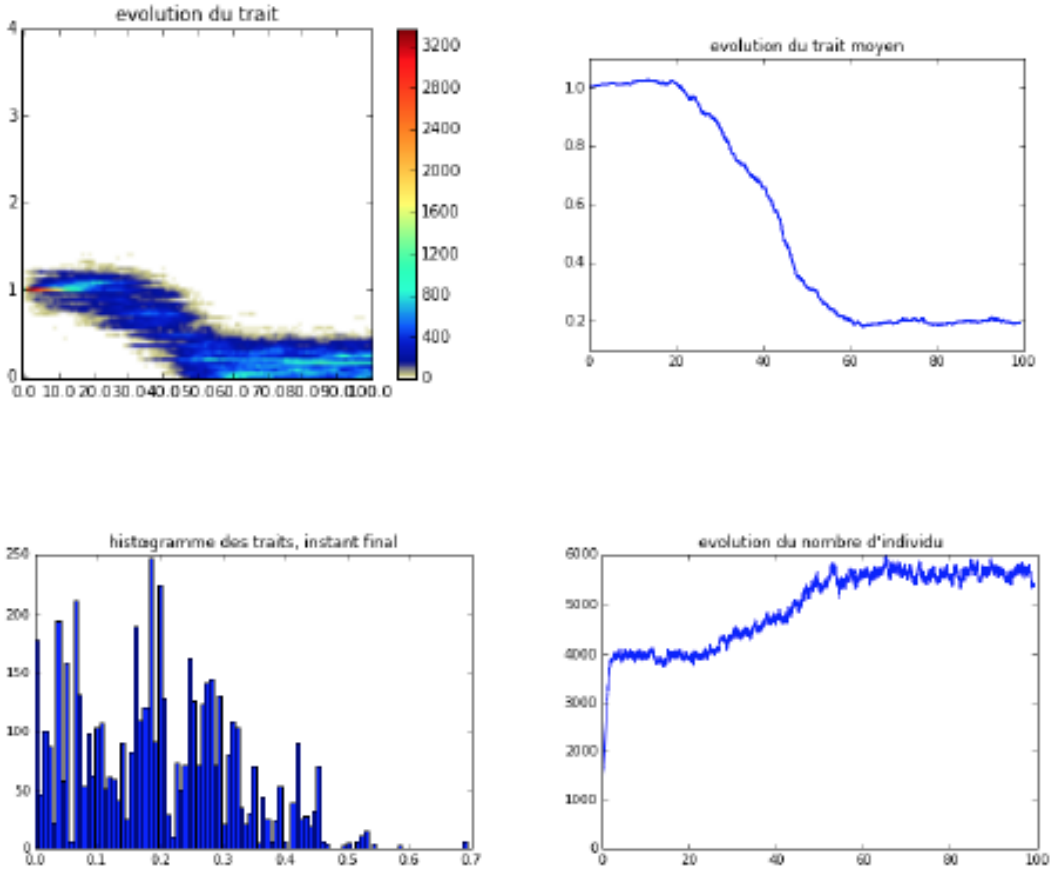


FIGURE 8 – Simulations pour $\tau = 0.2$

$\tau = 0,6$ - Stepwise Evolution

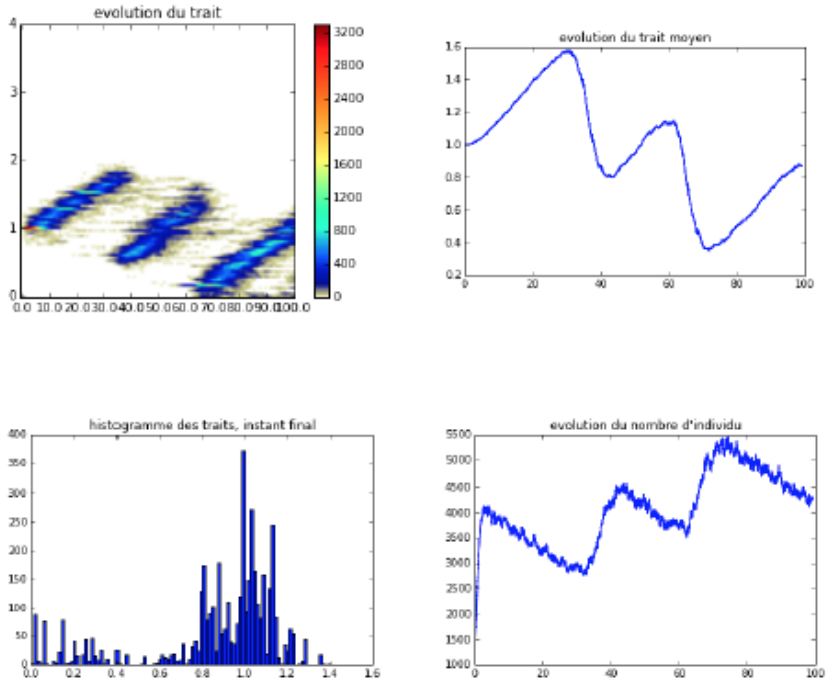


FIGURE 9 – Simulations pour $\tau = 0.6$ sur un temps de 100

- Transfer will convert individuals to larger traits.
- Then, the population decreases. For a given trait x, the equilibrium size $N_{eq} = \frac{b(x)-d}{C} \times 1000 = 2000(3 - x)$.
- Brutal appearance of new strains.

- Mutants with small trait x_{small} appear in the resident population with trait $\overline{x}$. Invasion fitness:
$$S(x_{small}; \overline{x}) = \overline{x} - x_{small} - \tau.$$
- Thus, mutants will survive $\iff$ $\overline{x} - x_{small} > \tau$.
- If such a mutant appears, it reproduces faster and its subpopulation immediately kills the population with trait $\overline{x}$.

Interpretation in terms of appearance of antibiotics resistant strains.

$\tau = 0,7$ - Random Macroscopic Evolution

Four simulations with the same parameters. Big differences due to the aptitude of a mutant to create a new strain.

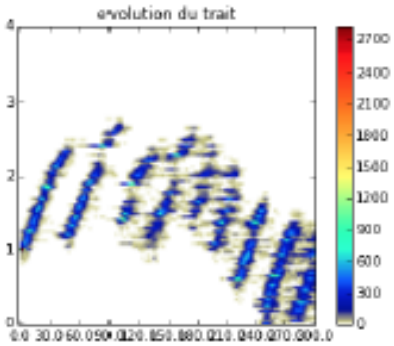


FIGURE 12 – simulation 1

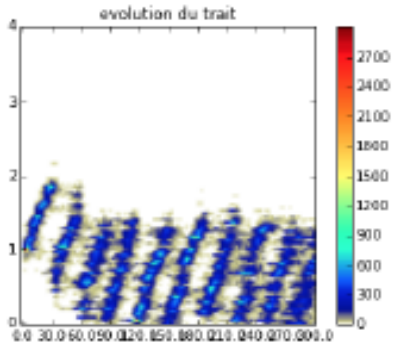
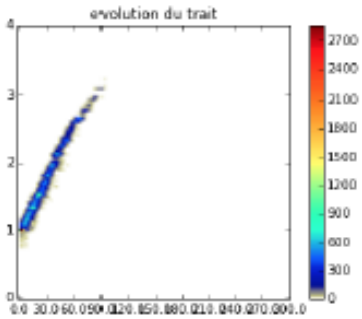
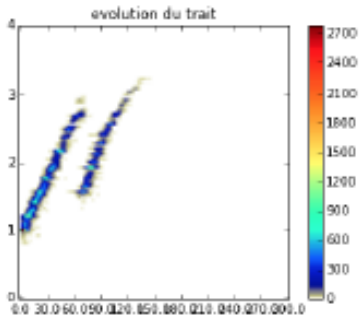


FIGURE 13 – simulation 2





$\tau = 1$ - Evolutive Suicide

HGT impedes the population to keep a small mean trait to survive.

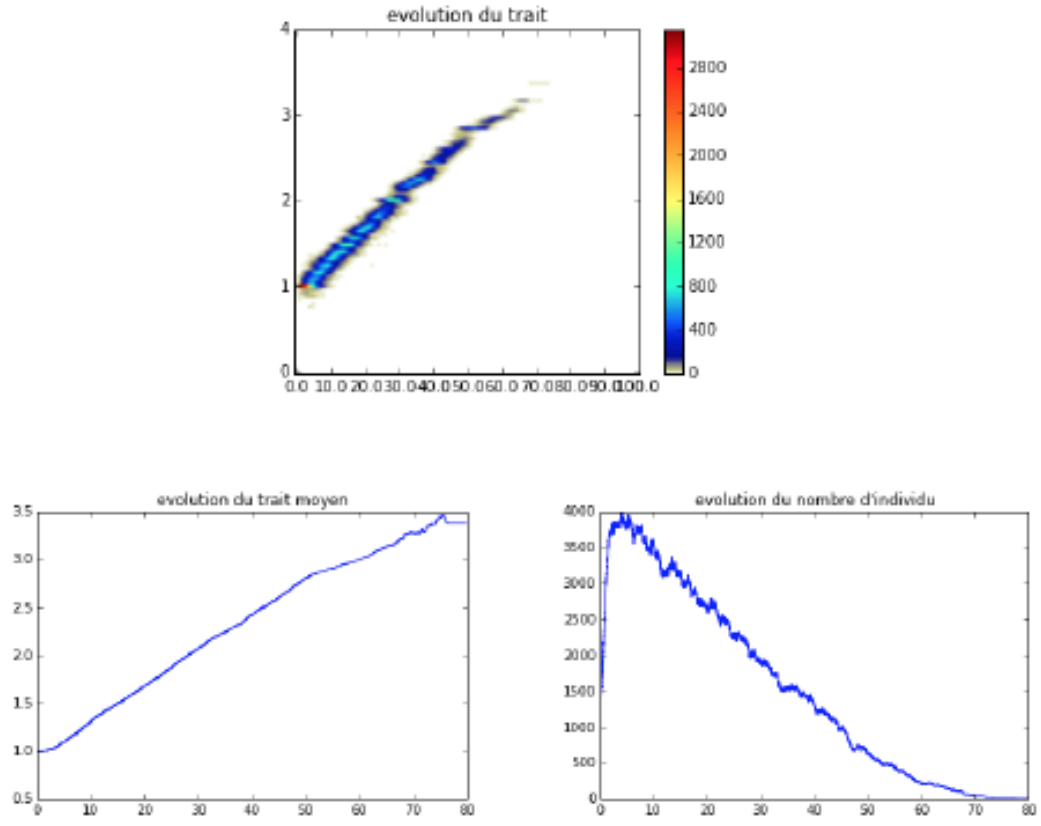


FIGURE 17 – Simulations pour $\tau = 1$

Co-authors and biologists collaborators




Figure: S. Billiard , N. Champagnat , P. Collet , M. El Karoui



Figure: R. Fernandez-Lopez , R. Ferrière , C.V. Tran

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Thank you for your attention!