Stochastic dynamics for adaptation and evolution of microorganisms

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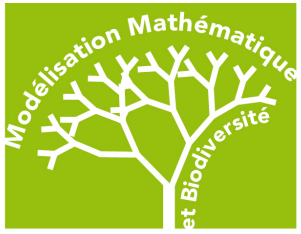


Darwinian or Adaptive Evolution

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

The ability of an individual (bacteria) 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. Results from competition between individuals. Individuals with traits increasing their survival probability or their reproduction ability will spread through the population over time.
- Horizontal Gene Transfer (HGT): the bacteria exchange genetic information.

Adaptation, Evolution and Horizontal Gene Transfer

- Evolution consists in successive invasions of successful mutants.
- Evolution time scale is very long with respect to demographic time scale but can be very fast with respect to human time scale.
  - Bacteria E. Coli antibiotic resistance through an evolutive procedure appears after $\sim$ 5 years.
  - From a virus, its shorter ($\sim$ 6 months).
- Most of the evolutive models do not take horizontal transfer into account.
- Nevertheless, HGT is recognized as a major process in the evolution and adaptation of populations, especially for micro-organisms.
  - A main role in the evolution, maintenance, and transmission of virulence.
  - The primary reason for bacterial antibiotic resistance.
  - Important role in the degradation of novel compounds by bacteria (such as human-created pesticides).

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 pathogens strains
- To show how HGT can drastically affect the evolutionary outcomes.
- Biological assumptions of Adaptive Dynamics (large population, rare mutations, small mutations).

(1) Gene transfer modeling

Previous models are

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

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

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

(2) Adaptive Dynamics: Successive invasions of successful mutants.

- Hofbauer, Sigmund 1990, Marrow, Law, Cannings 1992, Metz, Geritz et al. 1992, 1996, Dieckmann, Law 1996, Diekmann 2004
- PDE's tools (Perthame-Barles-Mirrahimi 07-10, Jabin, Desvillettes, Raoul, Mischler 08-10, . . .)
- **Individual-based model** (birth and death process with mutation and selection): (Bolker, Pacala 97, Kisdi 99, Dieckmann, Law 00, Fournier, M. 04, Ferrière, Champagnat, M. 06, Champagnat 06, Champagnat, M. 10, . . .)

An individual-based model

- 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).
- p_K scales the mutation probability of the traits under selection (small p_K means rare mutation).
- Population of $N^K(t)$ individuals weighted by $\frac{1}{K}$.

  It is represented by the point measure

$$\nu_t^K = \frac{1}{K} \sum_{i=1}^{N^K(t)} \delta_{x_i} \quad ; \quad N^K(t) = K \langle \nu_t^K, 1 \rangle,$$

  where x_i is the type of the individual i.
- $\mathcal{M}_K$ is the set of point measures on $\mathcal{X}$ weighted by $\frac{1}{K}$.

Transitions

BIRTHS:

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

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

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.

- In a population ν, an individual with trait x chooses a partner with trait y at rate $h_K(x, y, \nu)$.The new traits are $(T_1(x, y), T_2(x, y))$, where

$$T_1(x, y) = x + a(y - x) \; ; \; T_2(x, y)) = y + b(x - y),$$

  with $a, b \in [0, 1]$.

- **Main examples**.

  Bacteria conjugation: the donor transfers its trait to the recipient, $a = 0$ and $b = 1$.

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

  Exchange: the bacteria exchange their genes: $a = b = 1$.

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

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 $\dfrac{C(x, x_i)}{K}$ describes the 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.

$$r(x) = b(x) - d(x) > 0 \; ; \;\; C(x, y) \geq \underline{c} > 0.$$

Consider the function $F_f(\nu) = \int f(x)\nu(dx)$, for $f \in \mathcal{C}_b(\mathbb{R}^d, \mathbb{R})$ and $\nu = \frac{1}{K}\sum_{i=1} \delta_{x_i}$. The generator of $(\nu_t^K)_t$ on functions F_f is given by

$$L^K F_f(\nu) = \int_{\mathcal{X}} \nu(dx)\Big[b(x)\Big((1-p_K)f(x) + p_K \int_{\mathcal{X}} f(z)m(x,z)dz\Big) - \big(d(x) + C * \nu(x)\big)f(x) + \int_{\mathcal{X}} K\, h_K(x,y,\nu)\Big(f(T_1(x,y)) + f(T_2(x,y)) - f(x) - f(y)\Big)\nu(dy)\Big].$$

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 starting from 0 with quadratic variation

$$\langle M^{K,f}\rangle_t = \frac{1}{K}\int_0^t \int_{\mathcal{X}} \Big\{\Big((1-p_K)b(x) - d(x) - C * \nu_s^K(x)\Big)f^2(x) + p_K\, b(x)\int_{\mathcal{X}} f^2(z)\, m(x,z)dz + \int_{\mathcal{X}} K\, h_K(x,y,\nu^K)\Big(f(T_1(x,y)) + f(T_2(x,y)) - f(x) - f(y)\Big)^2 \nu_s^K(dy)\Big\}\nu_s^K(dx)$$

Large population, rare mutations, time scale $O(1)$

$K \to \infty$ and $p_K \to 0$ and

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

where τ is a continuous function.

$\beta = 1, \mu = 0$: density dependent transfer rate (DD) ;
$\beta = 0, \mu = 1$: frequency dependent transfer rate (FD) ;
$\beta, \mu \neq 0$: Beddington-deAngelis transfer rate (BDA). (Cf. Geritz, Gyllenberg)

Proposition: *Let $T > 0$. 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*

$$\begin{aligned}\langle \xi_t, f\rangle =& \langle \xi_0, f\rangle + \int_0^t \int_{\mathcal{X}} \big(r(x) - C * \xi(x)\big) f(x) \xi_s(dx)\, ds \\ &+ \int_0^t \int_{\mathcal{X}^2} \big(f(T_1(x,y)) + f(T_2(x,y)) - f(x) - f(y)\big) \frac{\tau(x,y)}{\beta + \mu\langle \xi_s, 1\rangle} \xi_s(dy)\xi_s(dx)ds.\end{aligned}$$

Mutations disappear at this time scale.
Proof: usual compactness-uniqueness argument using moment estimates. Identification of the limit.

The specific case of bacteria conjugation.

Introduce the transfer flux $\alpha(x,y) = \tau(x,y) - \tau(y,x)$, (positive or negative).

1) *Density case*

Proposition: *Assume that* $\xi_0 \ll \lambda$ (λ *Lebesgue measure), then for any* $t > 0$, $\xi_t(dx) = u(t,x)dx$ *and*

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

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

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

2) *two types case:* $\mathcal{X} = \{x,y\}$. Set $X_t^K = \nu_t^K(\{x\})$; $Y_t^K = \nu_t^K(\{y\})$.

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

$$\frac{dn^x}{dt} = \Big(r(x) - C(x,x)n^x - C(x,y)n^y + \frac{\alpha(x,y)}{\beta + \mu\,(n^x + n^y)}\,n^y\Big)n^x$$

$$\frac{dn^y}{dt} = \Big(r(y) - C(y,x)n^x - C(y,y)n^y - \frac{\alpha(x,y)}{\beta + \mu\,(n^x + n^y)}\,n^x\Big)n^y.$$

Stability Analysis

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

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

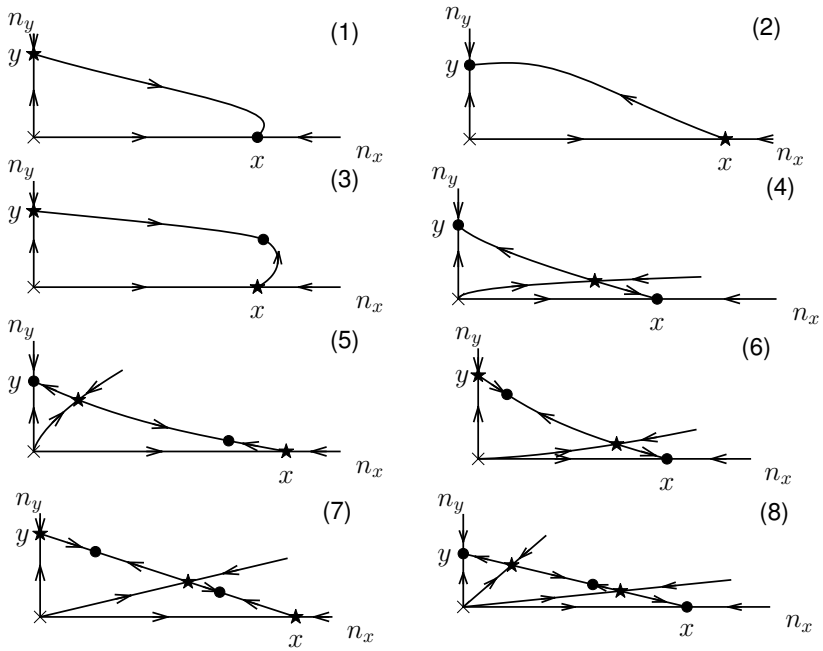
governs the stability.

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

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

Figures (1)-(4) are possible for all forms of HGT rates,
Figures (5)-(6) for DD and BDA
while Figures (7)-(8) for BDA.

Compared to the classical two-species Lotka-Volterra system, 4 new phase diagrams are possible: Figures (5)-(8).

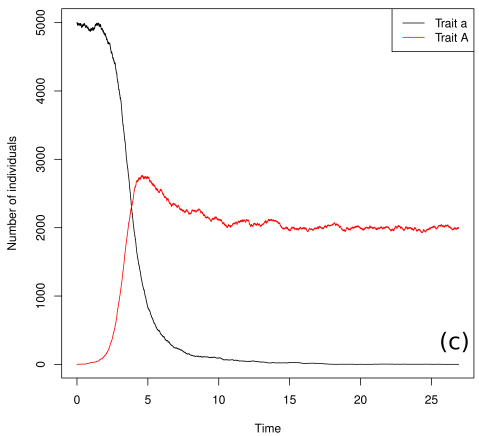


- Invasion fitness of individuals with trait y in the x-resident population:

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

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

Example: Invasion-fixation of a costly plasmid (unilateral transfer)



$b(y) = 0.8$, $b(x) = 1$, $d \equiv 0$,
$\tau(y,x) = \alpha(y,x) = 5$, $K = 10000$,
$C_{y,x} = C_{x,x} = 2$, $C_{y,y} = 4$, $C_{x,y} = 1$.

Fixation of a deleterious and very consuming mutant.

- **Invasion**: $S(y;x) > 0$.
- **Invasion Probability:**

$$\frac{[S(y;x)]_+}{b(y) + h(y,x,\overline{n^x})\,\overline{n^x}}.$$

For FD transfer with constant C:

$$\frac{r(y) - r(x) + \alpha(y,x)}{b(y) + \tau(y,x)}.$$

Time for the population with trait y to be of order K: $\dfrac{\log K}{S(y;x)}$.

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

- **Fixation** (when the deterministic system converges to $(0, \overline{n^y})$): birth-death process with negative fitness $S(x;y) < 0$.

Duration of the competition phasis $\dfrac{\log K}{|S(x;y)|}$.

Invasion implies fixation: when a mutation occurs, cases (1) or (2). (No coexistence).

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

We come back to the continuum of traits $x \in \mathcal{X}$.

We assume rare mutations:

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

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

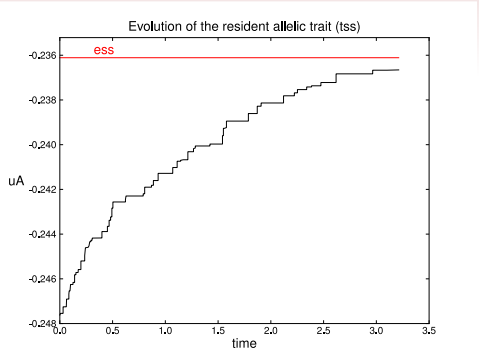
Theorem (TSS Approximation)

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

As soon as Invasion-implies-fixation, the sequence $\left(\nu^K_{\frac{t}{Kp_K}}, t \geq 0\right)_{K \geq 1}$

converges in law to the jump process $(V_t = \overline{n^{Z_t}} \delta_{Z_t}, t \geq 0)$, *where the process* Z *jumps from* x *to* y *with the jump measure*

$$b(x)\,\overline{n^x}\,\frac{[S(y;x)]_+}{b(y) + h(y,x,\overline{n^x})\overline{n^x}}\,m(x,y)dy \quad \text{with} \quad \overline{n^x} = \frac{r(x)}{C(x,x)}.$$



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

Proof: Adaptation of Champagnat 2006. (Heuristics in Metz et al. 1996).

- $\frac{1}{Kp_K} \ll e^{KV}$, 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 $\log K$.
- $\log K \ll \frac{1}{Kp_K}$: 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 $\overline{n^x}$ bacteria with trait x to $\overline{n^y}$ bacteria with trait y.
- Succession of phases of trait mutant invasion, and phases of competition between traits.

Main Fact: transfer events may drastically change the evolution.

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

(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.

The canonical equation - Small mutation steps

The mutation measure has steps 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.

Let us denote by Z^σ the associated TSS.

Theorem *The processes* $(Z^\sigma_{t/\sigma^2}, t \geq 0)$ *converge when* $\sigma \to 0$, *to 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:

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

yields the optimal nil trait which maximizes the birth rate.

With transfer:

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

The evolution decreases the reproduction rate until it vanishes and therefore may lead the population to evolutive suicide.

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.

$\tau = 0$

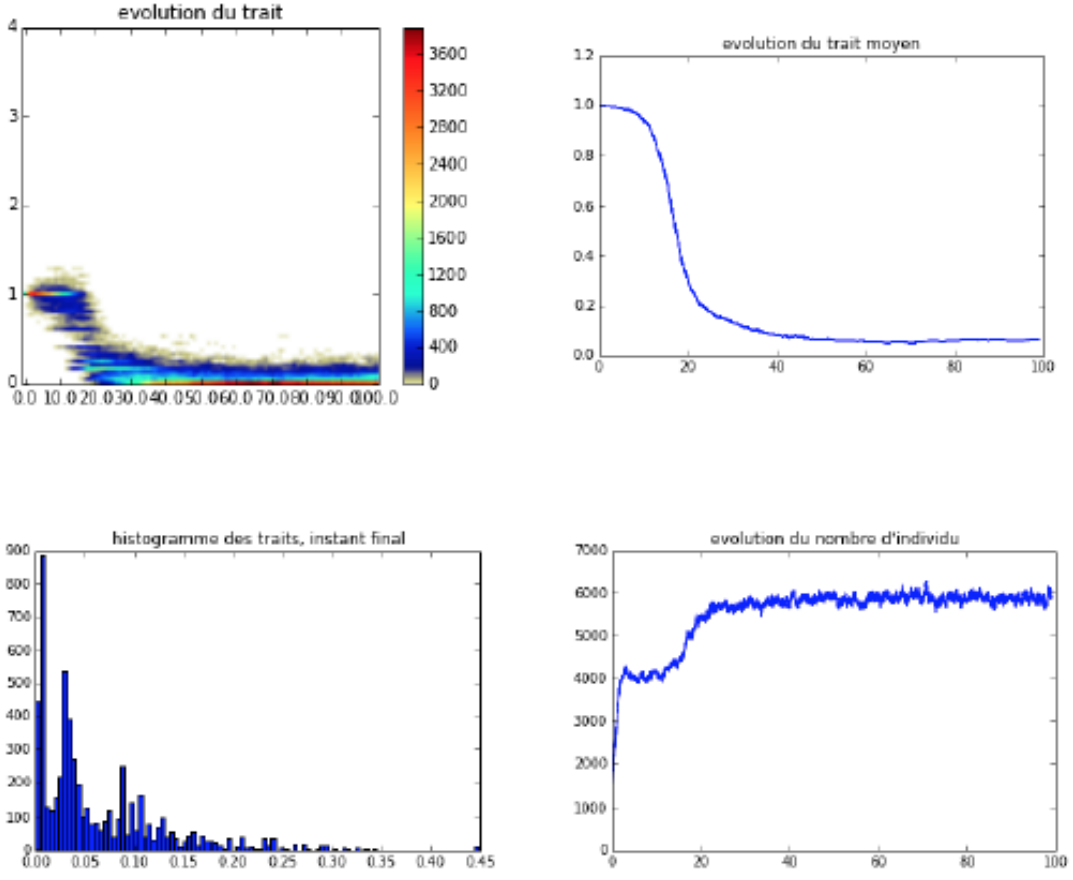


FIGURE 7 – Simulations pour $\tau = 0$.

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

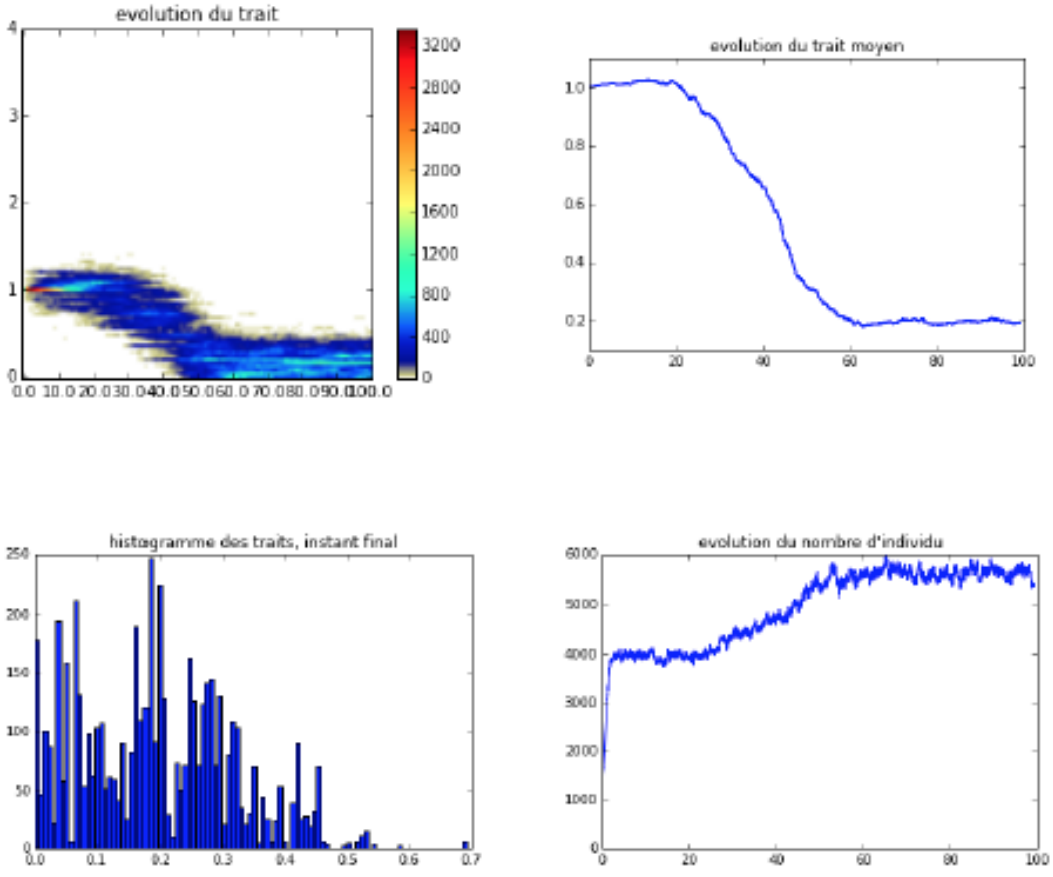


FIGURE 8 – Simulations pour $\tau = 0.2$

$\tau = 0,6$ - Stepwise Evolution

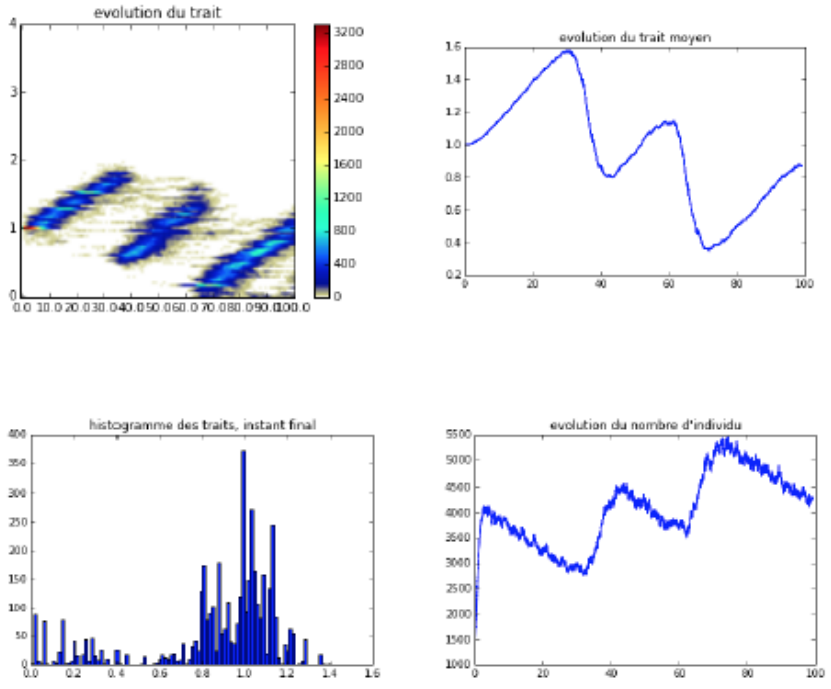


FIGURE 9 – Simulations pour $\tau = 0.6$ sur un temps de 100

- 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.

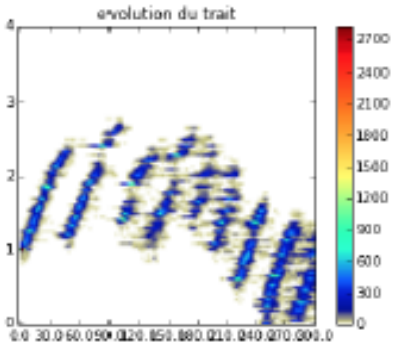


FIGURE 12 – simulation 1

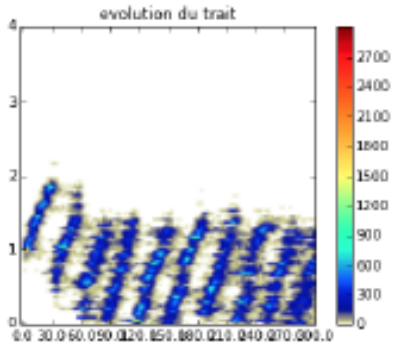
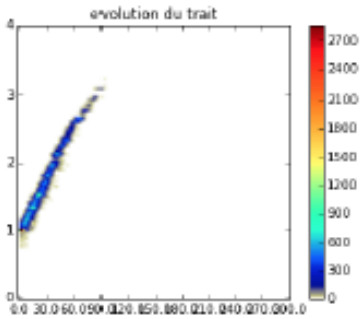
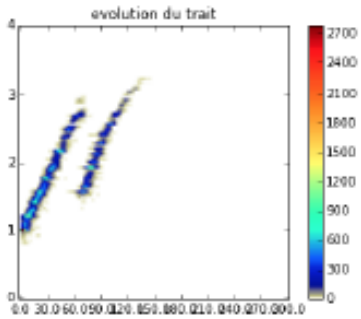


FIGURE 13 – simulation 2





$\tau = 1$ - Evolutive Suicide

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

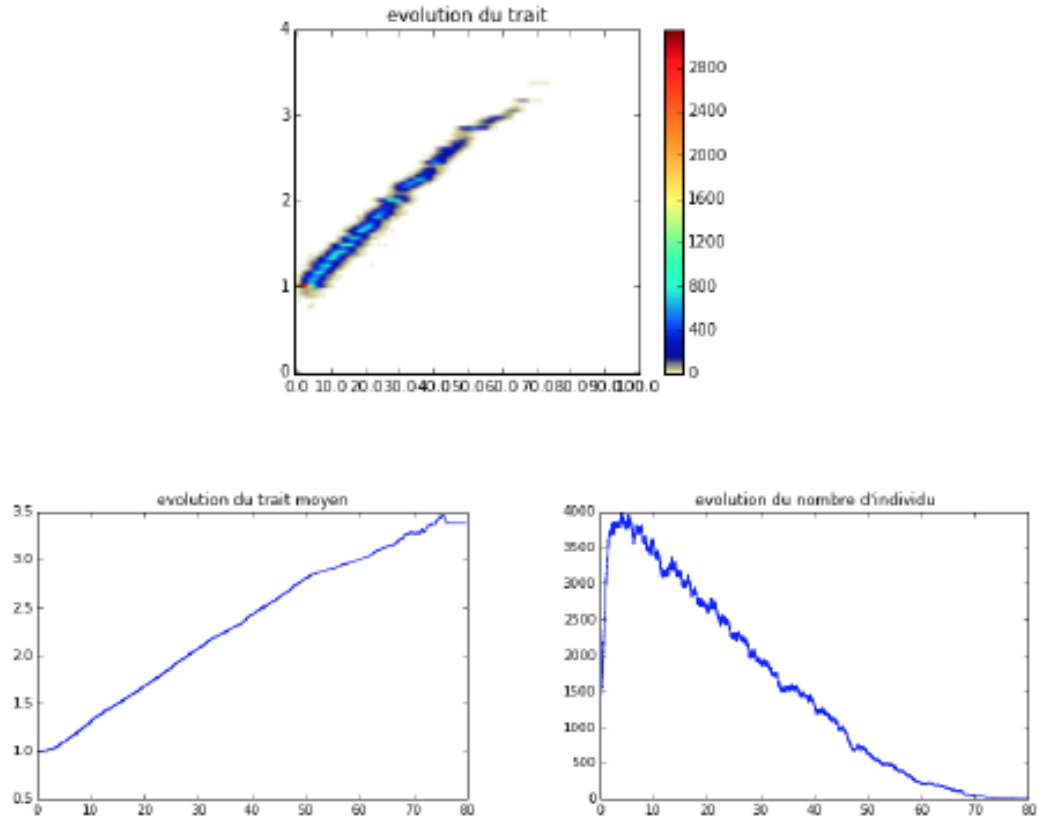


FIGURE 17 – Simulations pour $\tau = 1$

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Master students (simulations): L. Desfontaines, S. Krystal.

Thank you for your attention!