Competitive populations with vertical and horizontal transmissions

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CIRM 2015, Marseille, June 2015

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Vertical and Horizontal Gene Transfers for Micro-organisms

The ability of a bacteria to survive and reproduce depends on its genes.

The evolution results from the basic mechanisms.

- Heredity. (Vertical) transmission of the ancestral trait to the offsprings.
- Mutation. Generates variability in the trait values.
- Selection. Acts on the death rates as the result of competition between individuals.
- Horizontal Gene Transfer (HGT): the bacteria exchange genetic information.

Horizontal Gene Transfer

- HGT is recognized as a major process in the evolution and adaptation of population, especially for micro-organisms.
- *HGT plays a main role in the evolution, maintenance, and transmission of virulence.*

  It is the primary reason for bacterial antibiotic resistance.

  It plays an important role in the evolution of bacteria that can degrade novel compounds such as human-created pesticides.
- There are several mechanisms for horizontal gene transfer.
  - Transformation: some DNA filaments directly enter the cell.
  - Transduction: DNA is carried by some viruses (phages) which affect the cell.
  - Conjugation: plasmids: circular DNA replicates from a cell to another one, independently of the chromosome.
- We will focus on Conjugation.

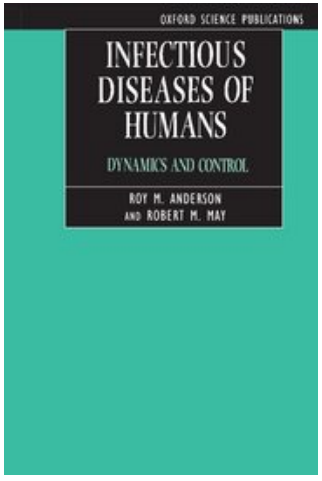
Biological and Medicine context

- The spread of antibiotic resistances among bacterial pathogens becomes very concerning.
- Urgent to develop new technologies to fight bacterial infections.
- Use of the plasmid transfer to destroy pathogenic bacteria within complex microbial populations.
- A technique which will not destroy the ecosystem and will weaken the resistance.

Our aim

- To propose a general stochastic eco-evolutionary model of population dynamics with horizontal and vertical transfers, inspired by the transfer of plasmids in bacteria.
- To study different transfer rates: either density-dependent or frequence-dependent or Beddington-deAngelis horizontal gene transfer (HGT) rates.
- To study the impact of HGT on the maintenance of polymorphism and the invasion or elimination of pathogens strains
- To study the impact of HGT on the evolution and to show how it can drastically affect the evolutionary outcomes.

- A large literature from the seminal work of Anderson-May, on the population dynamics of host-pathogens, but no general models of gene transfer.



- Previous models are either deterministic (epidemiological models) or stochastic (population genetics models with constant population size).

Individual-based model: a 2-traits population

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

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

  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 $u \in \{A, a\}$: $b_K(u)$.

  With probability p_K, the offspring carries the trait u, with probability $1 - p_K$, its trait is in $\{A, a\} \setminus \{u\}$.
- Death rate of an individual u at time t:

$$d_K(u) + \frac{C(u,u)}{K} N_t^{u,K} + \frac{C(u,v)}{K} N_t^{v,K}.$$

Modeling of the HGT at the individual scale

- In a population (x, y), a donor transfers its trait u to a recipient with trait v at rate $\tau_K(u, v, x, y)$.The recipient becomes u. (bacteria conjugation).
- We will denote the difference between the two transfer rates by

$$\alpha_K(A, a, x, y) = \tau_K(A, a, x, y) - \tau_K(a, A, x, y).$$

- Observations: HGT rate is *density-dependent when the population size is low* and *frequency-dependent when the population is close to its carrying capacity*.
- Here, we consider the general form: for $x, y \in \frac{\mathbb{N}}{K}$,

$$\tau_K(u, v, x, y) = \frac{\psi_K(u, v) E_K(u, v)}{E_K(u, v) + K\, \psi_K(u, v)\, (x + y)}.$$

- $E_K(u, v)$: quantity of resources useable for HGT which are shared among individuals.
  $\psi_K(u, v)$: maximal quantity of resources one individual can use per time unit to perform HGT.

Three interesting cases

- Density-Dependent transfer rate (DD): If
  $\lim_{K\to+\infty} \frac{E_K}{K\psi_K(u,v)} = +\infty$ and $\lim_{K\to+\infty} \psi_K(u,v) = \psi(u,v)$,

$$\tau_K(u,v,x,y) = \psi(u,v).$$

- Frequency-Dependent transfer rate (FD): If
  $\lim_{K\to+\infty} \frac{E_K}{K\psi_K(u,v)} = 0$ and $\lim_{K\to+\infty} \frac{E_K(u,v)}{K} = E(u,v)$,

$$\tau_K(u,v,x,y) = \frac{E(u,v)}{x+y}.$$

- Beddington-deAngelis transfer rate (BA): If
  $\lim_{K\to+\infty} \psi_K(u,v) = \psi(u,v)$ and $\lim_{K\to+\infty} \frac{E_K(u,v)}{K} = E(u,v)$,

$$\tau_K(u,v,x,y) = \frac{\psi(u,v)E(u,v)}{E(u,v)+\psi(u,v)\,(x+y)}.$$

The Stochastic process

Recall that we focus on conversion. Let us consider test functions $F \in \mathcal{C}_b(\mathbb{R}^2,\ \mathbb{R})$. The generator of the process $(X_t^K,\ Y^K)_{t\geq 0}$ is:

$$
\begin{aligned}
LF(x,y) &= K\big((1-p_K)b_K(A)x + p_K b_K(a)y\big)\Big(F\big(x+\frac{1}{K},y\big) - F(x,y)\Big) \\
&+ K\big(p_K b_K(A)x + (1-p_K)b_K(a)y\big)\Big(F\big(x,y+\frac{1}{K}\big) - F(x,y)\Big) \\
&- K\left(d_K(A) + C(A,A)\,x + C(A,a)\,y\right)x\,\Big(F\big(x-\frac{1}{K},y\big) - F(x,y)\Big) \\
&- K\left(d_K(a) + C(a,A)\,x + C(a,a)\,y\right)y\,\Big(F\big(x,y-\frac{1}{K}\big) - F(x,y)\Big) \qquad (1) \\
&+ K\,\tau_K(A,a,x,y)\,x\,y\,\Big(F\big(x+\frac{1}{K},y-\frac{1}{K}\big) - F(x,y)\Big) \\
&+ K\,\tau_K(a,A,x,y)\,x\,y\,\Big(F\big(x-\frac{1}{K},y+\frac{1}{K}\big) - F(x,y)\Big).
\end{aligned}
$$

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

Large population limit with no mutation

- We assume that $b_K(u) = b(u)$, $d_K(u) = d(u)$ and that $p_k \longrightarrow 0$.

We set $b(u) - d(u) = r(u)$.

- To fix ideas, we also assume that

$$\lim_{K\to\infty} \tau_K(A, a, x, y) = \frac{\tau(A, a)}{\beta + \mu\,(x + y)} \quad .$$

- For $\beta = 1, \mu = 0$ or $\beta = 0, \mu = 1$ or $\beta, \mu \neq 0$, one gets the three cases of DD, FD or BA horizontal transfer rates.

- Denote $\alpha(A, a) = \tau(A, a) - \tau(a, A)$, (positive or negative).

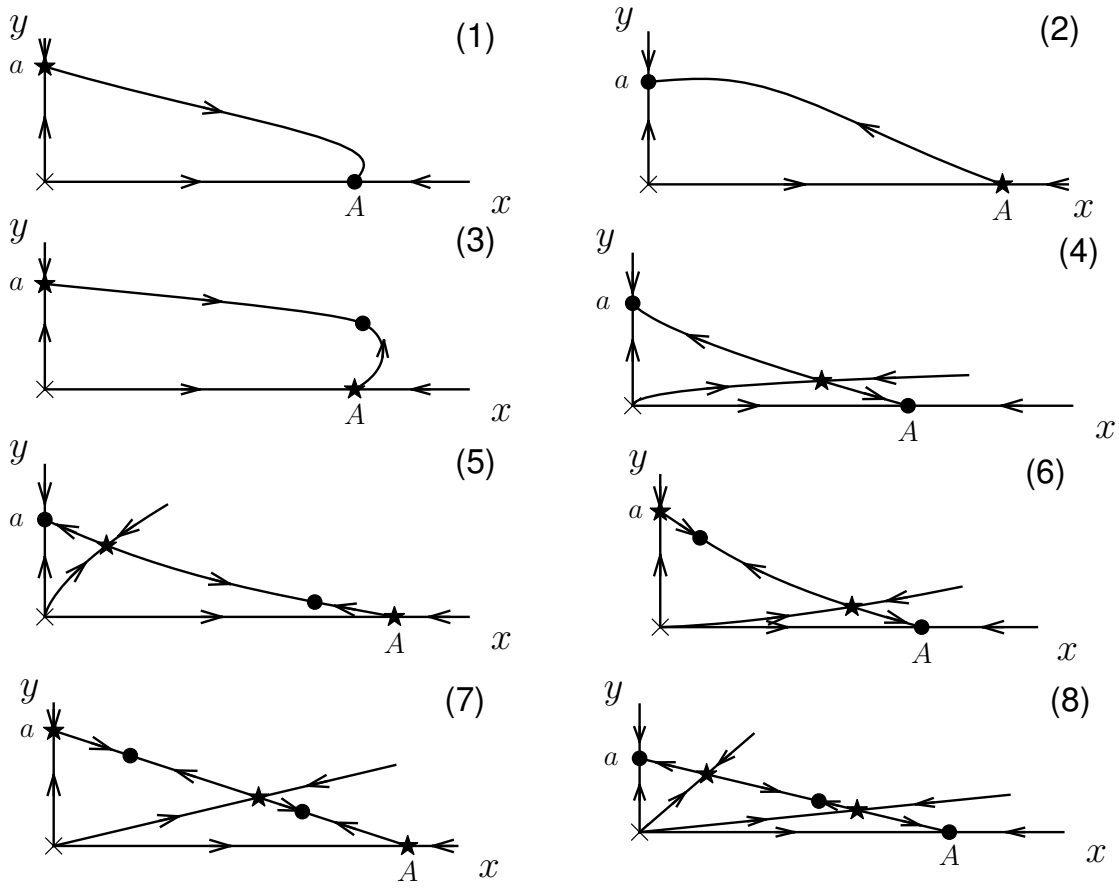
Theorem

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

$$\frac{dx}{dt} = \Big(r(A) - C(A, A)x - C(A, a)y + \frac{\alpha(A, a)}{\beta + \mu\,(x + y)}\, y\Big)x$$

$$\frac{dy}{dt} = \Big(r(a) - C(a, A)x - C(a, a)y - \frac{\alpha(A, a)}{\beta + \mu\,(x + y)}\, x\Big)y.$$

The eight possible phase diagrams



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

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

$$S_{Aa} = r(A) + (\alpha(A,a,0,\overline{y}) - C(A,a))\,\overline{y} \quad \text{and} \quad \overline{y} = \frac{r(a)}{C(a,a)}$$
$$= r(A) + \frac{\alpha(A,a)r(a)}{\beta C(a,a) + \mu r(a)} - \frac{C(A,a))r(a)}{C(a,a)}.$$

- Compared to the classical two-species Lotka-Volterra system, 4 new phase diagrams are possible: Figures (5)-(8).
- Figures (1)-(6) are possible for all forms of HGT rates while Figures (7)-(8) are not possible when the HGT rate is DD.
- 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 drastically the picture: a stable polymorphic state can exist whatever the sign of the fitness.

Population size and Frequencies

Let us consider

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

Then the coupled system writes

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

The case of small mutations

Let introduce $\varepsilon > 0$ and assume that mutation A brings only little changes in demographic and ecological parameters.

We set $r(a) = 1$; $C_{a,a} = C$; $\alpha(a,a) = 0$, thus

$r(A) = 1 + s\,\varepsilon$,
$C(A,a) = C + d_1\,\varepsilon$; $C(a,A) = C + d_2\,\varepsilon$, $C_{AA} = C + d_1\,\varepsilon + d_2\,\varepsilon$,
$\alpha(A,a) = \lambda\,\varepsilon$.

Theorem

Assume s, d_1 , d_2 *and* λ *are randomly chosen on* $[-1,1]$.

Then, with probability of order $1-\varepsilon$, *we fall in cases (1)-(4),*
with probability between ε *and* ε^2 *in the cases (5)-(6),*
with probability between ε^2 *and* ε^3 *in the case (7)*
and with probability lower than ε^3 *in the case (8).*

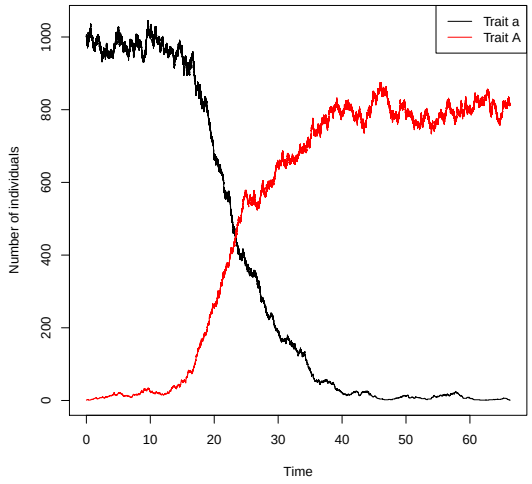
Idea of the proof: expansion in ε of the stationary points.

$$0 = \varepsilon\,\overline{q}\,(1-\overline{q})\Big(H_0 + \varepsilon\,q\,H_1 + \varepsilon^2\,q^2\,H_2 + \varepsilon^3\,q^3\,H_3\Big).$$

Probability and time of invasion-fixation with HGT

Fate of the mutant with trait A in the resident population a.

If $S_{Aa} > 0$, the stochastic dynamics can be decomposed in three phrases (as in Champagnat 2006).



Unilateral DD transfer:
$\tau = \alpha = 5.10^{-4}$, $K = 1000$,
$C = 1$, $b(A) = 0.8$, $b(a) = 1$,
$d \equiv 0$. Without transfer, the mutant couldn't invade and fix.

First phase (stochastic): the number of A-mutants reaches a threshold ϵK. It occurs with probability

$$P(A,a) = \frac{S_{Aa}}{b(A) + \tau(A,a,0,\overline{y})\,\overline{y}} = \frac{b(A) - d(A) + \left(\alpha(A,a,0,\overline{y}) - C(A,a)\right)\overline{y}}{b(A) + \tau(A,a,0,\overline{y})\,\overline{y}}.$$

The first phase has a duration of order $\log K/S_{Aa}$.

Second phase (deterministic): follows the EDOs system - Duration of order 1.

Third phase (the latter case): birth-death process until A is fixed and a is lost - Duration of order $\log K/S_{aA}$.

HGT increases the probability of invasion of a mutant $\Longleftrightarrow$

$$\frac{b(A) - d(A) - C(A,a)\bar{y}}{b(A)} < 1 - \frac{\tau(a,A,0,\bar{y})}{\tau(A,a,0,\bar{y})}.$$

- If **HGT is symmetrical**, $\tau(A,a,0,\bar{y}) = \tau(a,A,0,\bar{y})$, HGT decreases the probability of invasion of A.
- If **HGT is unilateral**, $\tau(A,a,0,\bar{y}) > 0$ *and* $\tau(a,A,0,\bar{y}) = 0$, HGT increases the probability of invasion of A.
- If $\alpha(A,a,0,\bar{y}) > 0$, (**HGT biased towards** A), invasion and fixation times are decreased by HGT.

A diffusive equation with HGT - Frequency-Dependent case

We assume that birth, death and transfer rates have allometric forms:

$$\begin{aligned} b_K(u) &= K\gamma(u) + \eta(u), \\ d_K(u) &= K\gamma(u) + \rho(u), \\ \tau_K(u,v) &= K\, s(u,v) + h(u,v), \end{aligned}$$

where $s(u,v) = s(v,u)$. (Small perturbations of a critical population with symmetric transfer). Moreover,

$$p_K = \frac{p}{K}, \qquad C_K(u,v) = \frac{C(u,v)}{K}.$$

Theorem

Under those assumptions, the stochastic process $\left(\left(X_t^K + Y_t^K, \frac{X_t^K}{X_t^K + Y_t^K}\right), t \geq 0\right)$ *converges in law, as* K *tends to infinity, to the diffusion process* $((N_t, Q_t), t \geq 0)$*, defined as follows.*

A generalized Wright-Fisher equation

$$
\begin{aligned}
N_t =& N_0 + \int_0^t \Big\{ (\eta_A - \rho_A) Q_s - (\eta_a - \rho_a)(1 - Q_s) \\
&\qquad - N_s \Big(C_{AA} Q_s^2 + C_{aa}(1 - Q_s)^2 + (C_{Aa} + C_{aA}) Q_s (1 - Q_s) \Big) \Big\} N_s \, ds \\
&+ \int_0^t \sqrt{2\gamma_A N_s Q_s} \, dW_s^A + \int_0^t \sqrt{2\gamma_a N_s (1 - Q_s)} \, dW_s^a \\
Q_t =& Q_0 + \int_0^t \Big\{ p\gamma_a (1 - Q_s) - p\gamma_A Q_s \\
&+ Q_s (1 - Q_s) \Big[(\eta_A - \rho_A) - (\eta_a - \rho_a) + (h_{Aa} - h_{aA}) \\
&\qquad + N_s \big((C_{aA} - C_{AA}) Q_s + (C_{aa} - C_{Aa})(1 - Q_s) \big) \Big] \Big\} ds \\
&+ \int_0^t (1 - Q_s) \sqrt{2\gamma_A \frac{Q_s}{N_s}} \, dW_s^A - \int_0^t Q_s \sqrt{2\gamma_a \frac{1 - Q_s}{N_s}} \, dW_s^a \\
&+ \int_0^t \sqrt{2 s_{Aa} \frac{Q_s (1 - Q_s)}{N_s}} \, dB_s. \qquad (2)
\end{aligned}
$$

Remark that if $\gamma(A) = \gamma(a) = \gamma$, then Equation (2) writes

$$\begin{aligned} Q_t = & Q_0 + \int_0^t \Big\{ Q_s(1-Q_s)\Big[(\eta_A - \rho_A) - (\eta_a - \rho_a) + (h_{Aa} - h_{aA}) \\ & + p\gamma(1-2Q_s) + N_s\big((C_{aA} - C_{AA})Q_s + (C_{aa} - C_{Aa})(1-Q_s)\big)\Big]\Big\} ds \\ & + \int_0^t \sqrt{2(\gamma + s_{Aa})\,\frac{Q_s(1-Q_s)}{N_s}}\, d\widetilde{W}_s, \end{aligned}$$

where $\widetilde{W}$ is a Brownian motion.

Expression close to the one established by Tazzyman-Bonhoeffer (discrete time, unilateral transfer, fixed population size, no competition).

HGT has the same quantitative effect on genetic drift than demographic stochasticity.

Evolution - Rare mutations - Logistic Competition

We assume now that there is a continuum of traits $u \in U \subset \mathbb{R}$.

The population is described by $\nu_t^K = \frac{1}{K} \sum_{i \in N_t} \delta_{U_t^i}$. Rates are given by

$$b(u)\,,\ d(u)\,,\ \frac{C}{K}\,,\ p_K\,,\ \tau(u,v,x,y) = \frac{\tau(u,v)}{\beta + \mu\,(x+y)}.$$

Mutation with probability p_K *: mutation law* $m_\sigma(u,h)dh$ *for an ancestor with trait* u *to give an offspring* $u+h$.

We assume rare mutations:

$$\forall V > 0\ ,\ \lim_{K\to\infty} p_K\, e^{VK} = +\infty\ ;\quad \lim_{K\to\infty} p_K\,(K \log K) = 0.$$

It results a separation of time scales, between competition phases and mutation arrivals (cf. Champagnat 2006).

The evolution at time scale $\dfrac{t}{K\,p_K}$ can be approximated by a TSS.

(Cf. Metz et al.)

Monomorphic Equilibrium with trait u: $\overline{x}_u = \dfrac{r(u)}{C}$.

Invasion Fitness Function:

$$S(u+h;u) = r(u+h) - r(u) + \frac{\alpha(u+h,u)\, r(u)}{\beta\, C + \mu\, r(u)}.$$

Theorem

Invasion-implies-fixation assumption. The initial conditions $\nu_0^K = x_0^K\, \delta_{u_0}(du)$ *converge to* $\overline{x}_{u_0}\delta_{u_0}(du)$.

Then the sequence $\left(\nu^K_{./Kp_K}\right)_{K\geq 1}$ *converges in law to the process* $(V_t(du) = \overline{x}_{Y_t}\delta_{Y_t}(du), t \geq 0)$, *where the process* Y *jumps from* u *to* $u+h$ *with the jump measure*

$$b(u)\,\overline{x}_u\, \frac{[S(u+h;u)]_+}{b(u+h) + \tau(u+h,u,0,\overline{x}_u)}\, m_\sigma(u,h)dh.$$

Proof: direct adaptation of Champagnat 2006.

Main Fact: transfer events may drastically change the evolution.

Exemple: $u \in [0, 4]$. A frequency-dependence HGT case.

$$b(u) = 4 - u \; ; \; d \equiv 1 \; , \; C(u, v) \equiv C \; ; \; \tau(u, v) = e^{u-v} \; , \; \beta = 0 \; , \; \mu = 1.$$

Then, $\overline{x}_u = \dfrac{3-u}{C}$ and if $h > 0$,

$$\begin{aligned} S(u+h; u) &= r(u+h) - r(u) + \tau(u+h, u) - \tau(u, u+h) \\ &= -h + e^h - e^{-h} > 0 \\ &\iff h > 0. \end{aligned}$$

The evolution will lead to larger and larger traits.

Without HGT: the fitness function equals $r(u+h) - r(u)$ and is negative when $h > 0$: a mutant with trait $u + h$ cannot invade the population.

The canonical equation - $\sigma \to 0$

We assume that $\int g(h)m_\sigma(u,h)dh = \int g(\sigma h)m(u,h)dh$. Let us denote by Y^σ the associated TSS.

Theorem

The processes $(\frac{1}{\sigma^2} Y_t^\sigma, t \geq 0)$ *converge when* $\sigma \to 0$*, to the solution of the deterministic equation*

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

In the example, $r'(u) = -1$ and $\partial_1\tau(u,u) = -\partial_2\tau(u,u) = 1$. Then

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

The evolution with transfer decreases the reproduction rate until it vanishes and therefore yields the population to evolutive suicide.

Without transfer: EC: $u'(t) = -\frac{3-u(t)}{C} \int h^2 m(u(t),h)dh$ yields the optimal nil trait which maximizes the birth rate.

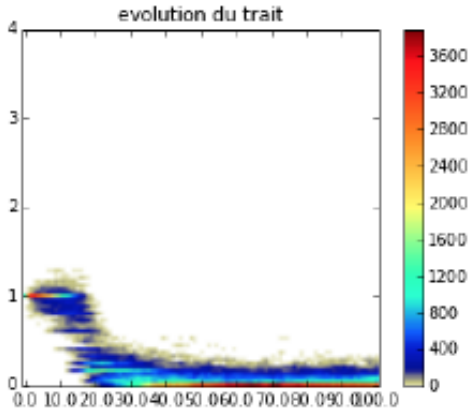
Simulations - Case of Frequency-Dependence

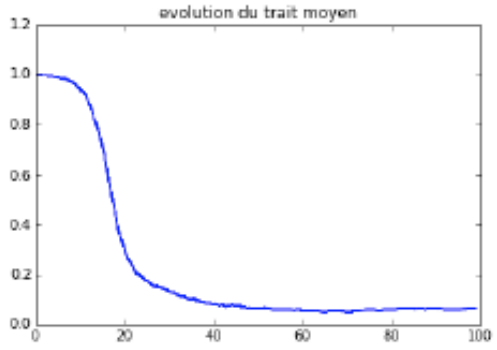
Two students: Lucie Desfontaines and Stéphane Krystal.

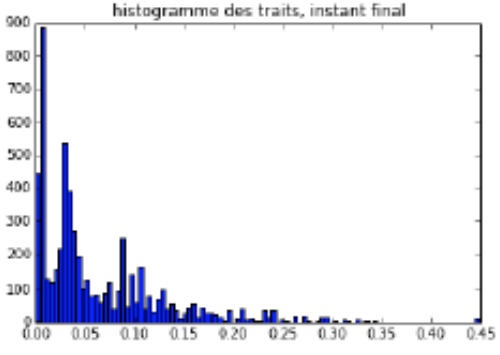
- $u \in [0,4],\ m(u,h)dh = \mathcal{N}(0,\sigma^2)$.
- Frequency-dependent unilateral HGT model. $\tau(u,v,x,y) = \frac{\tau \mathbf{1}_{u>v}}{x+y}$. The constant τ will be the varying parameter.
- $b(u) = 4-u\ ;\ d(u) = 1\ ;\ C = 0,5\ ;\ p = 0,03\ ;\ \sigma = 0,1\ ;\ K = 1000$.
- Initial state: 1000 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.

We will make τ increase.

$\tau = 0$







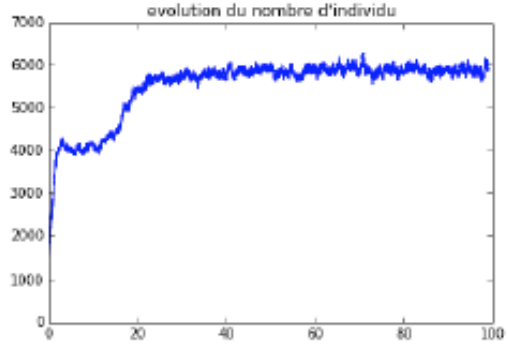


FIGURE 7 – Simulations pour $\tau = 0$.

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

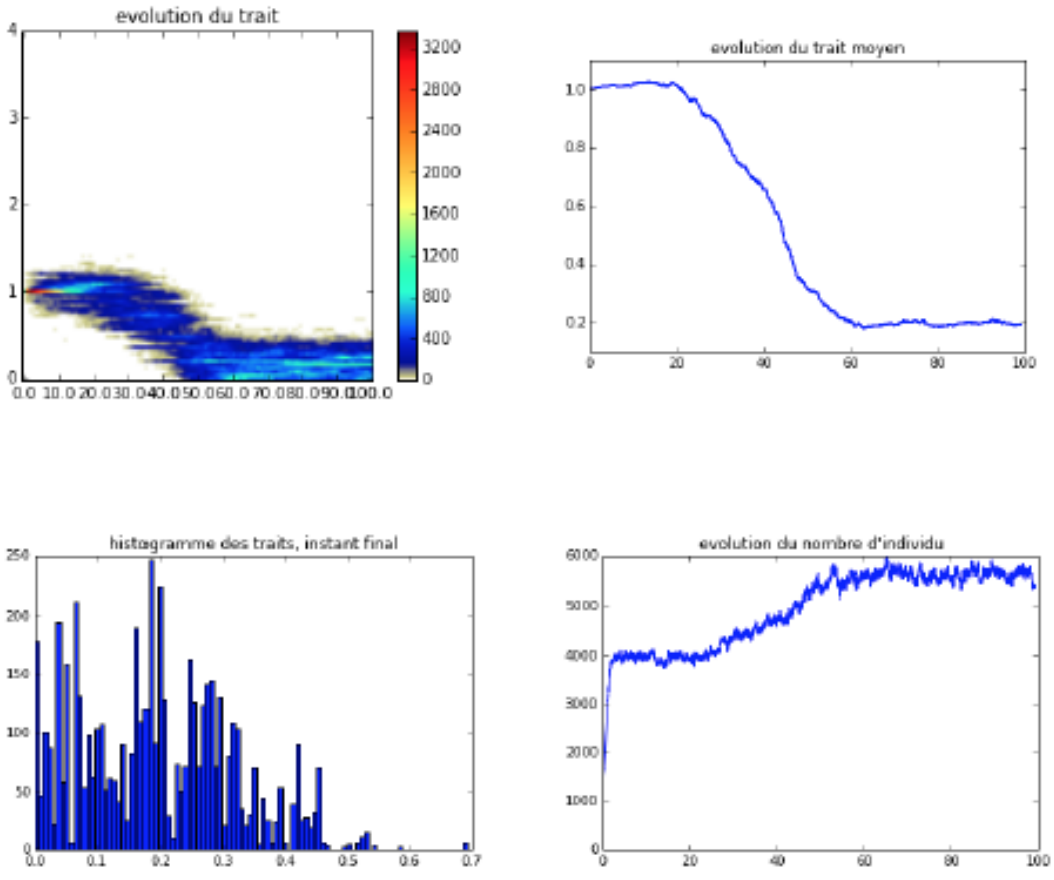


FIGURE 8 – Simulations pour $\tau = 0.2$

$\tau = 0,6$ - Stepwise Evolution

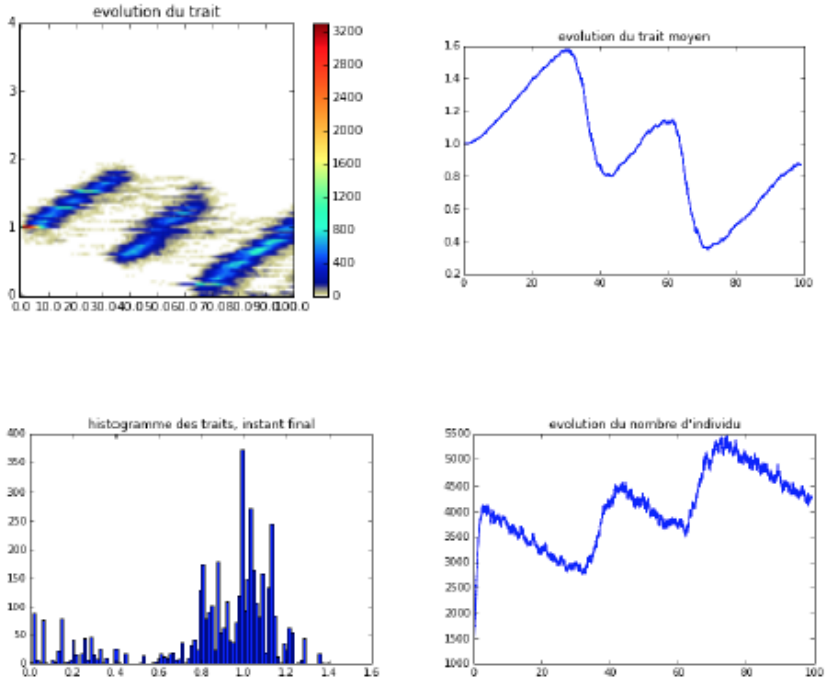


FIGURE 9 – Simulations pour $\tau = 0.6$ sur un temps de 100

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

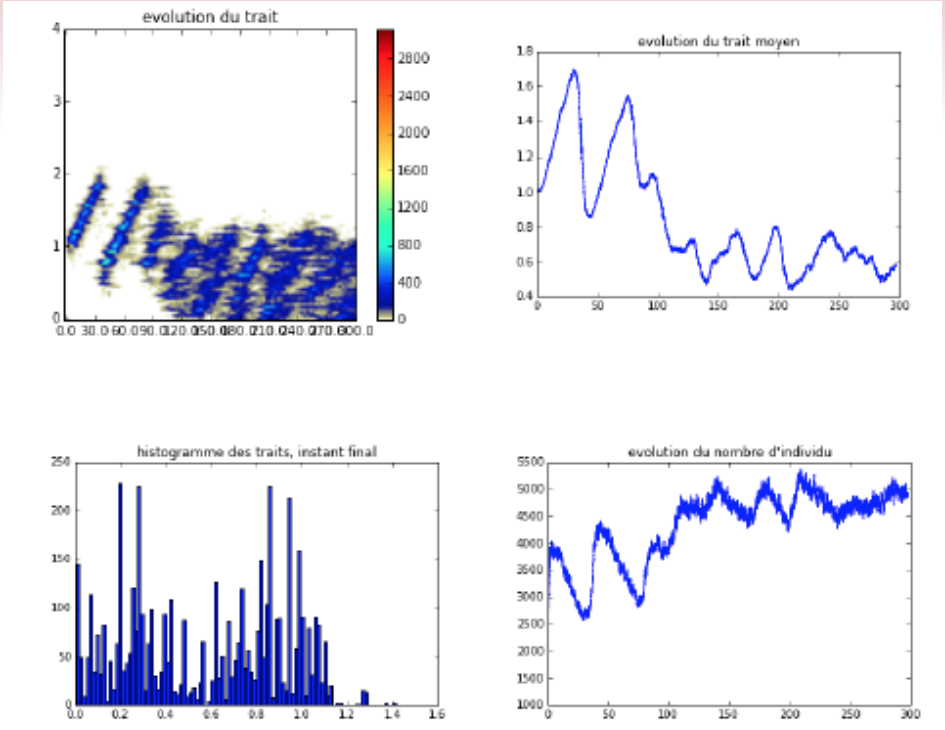


FIGURE 10 – Simulations pour $\tau = 0.6$ sur un temps de 300

- Mutants with small trait u_{small} appear in the resident population with trait $\overline{u}$. Invasion fitness:

$$S(u_{small}; \overline{u}) = \overline{u} - u_{small} - \tau.$$

- Thus, mutants will survive $\iff \overline{u} - u_{small} > \tau$.
- If such a mutant appears, it reproduces faster and its subpopulation kills the population with trait $\overline{u}$.

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

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

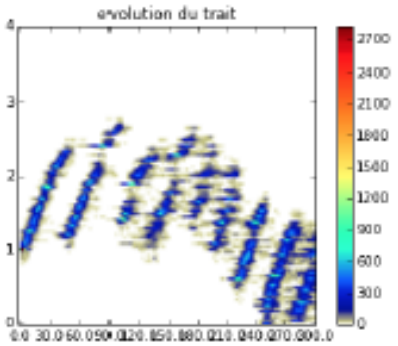


FIGURE 12 – simulation 1

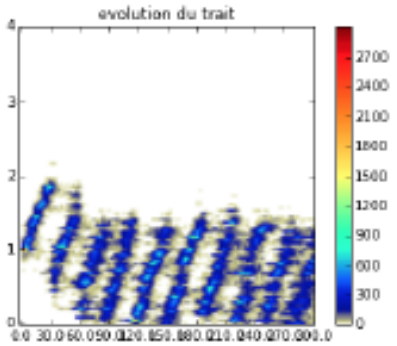
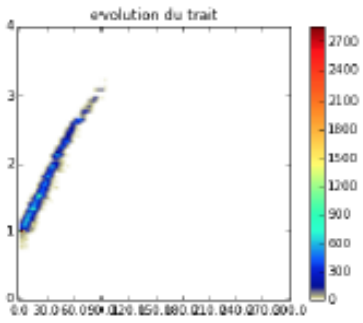
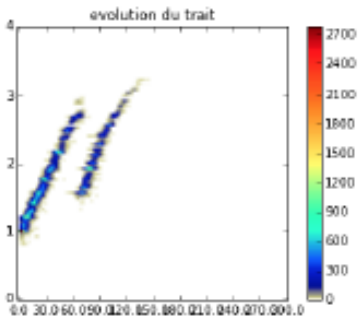


FIGURE 13 – simulation 2





$\tau = 1$ - Evolutive Suicide

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

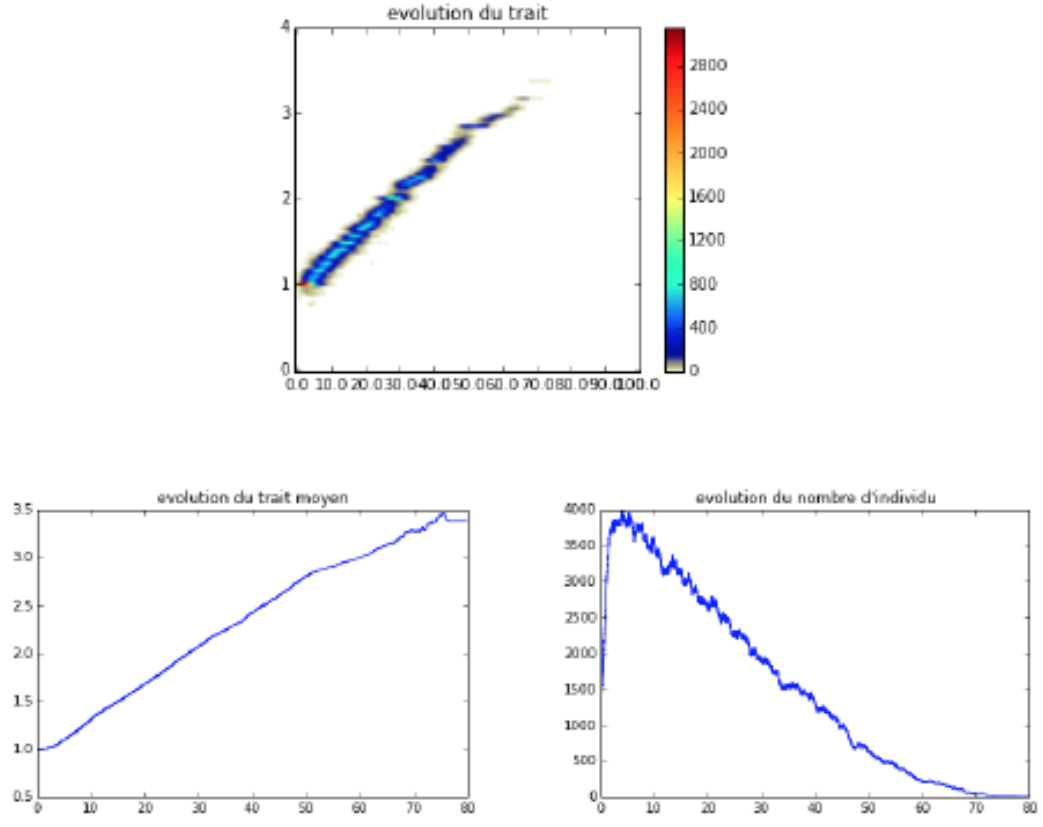
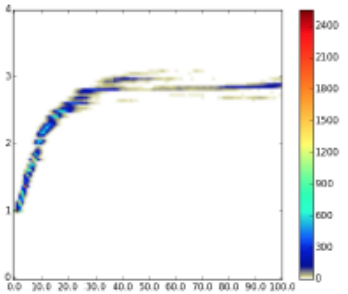
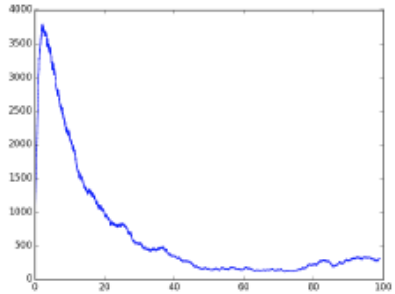


FIGURE 17 – Simulations pour $\tau = 1$

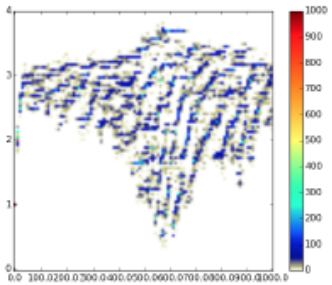
Density-Dependence Case

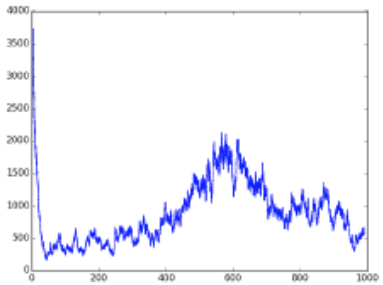
The transfer rate is proportional to $\tau \mathbf{1}_{u>v} N^u$, where N^u is the number of individuals with trait u.





$\tau = \frac{1}{K}$ and $time = 100$.





$\tau = \frac{1}{K}$ and $time = 1000$.

For transfer rates larger than $\frac{2}{K}$, one observes the evolutive suicide.