Stochastic dynamics for adaptation and evolution of microorganisms

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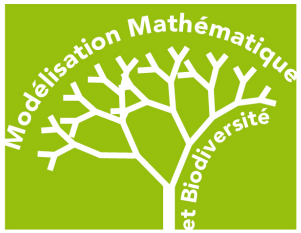


Anton and the Adaptive Biology

CAPTION

Professor Dr. Anton Bovier with his co-authors Martina Baar, Hannah Mayer, and Loren Coquille (from the left) of the Institute of Applied Mathematics.

Mathematics to fight cancer

UNIVERSITY OF BONN

Adaptive Biology

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:

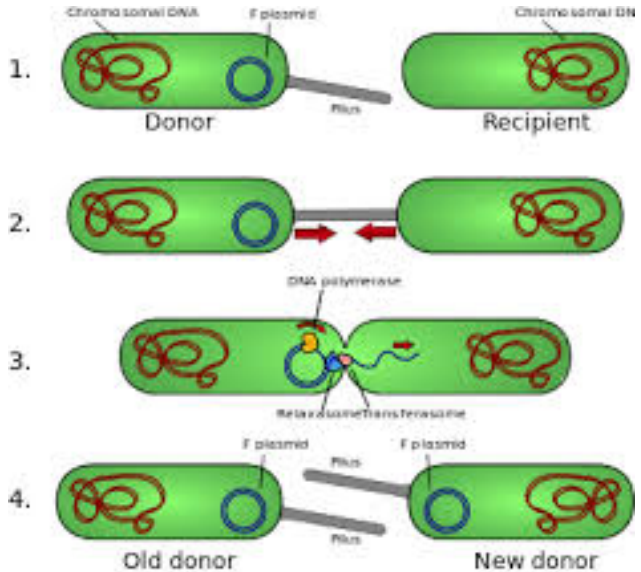
- Heredity. (Vertical) transmission of the ancestral trait to the offsprings.
- Mutation. Generates variability in the trait values.
- Selection. Individuals with traits increasing their survival probability or their reproduction ability will spread through the population over time. The variability can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

Horizontal Gene Transfer

There are several mechanisms for horizontal gene transfer: transformation, transduction and conjugation.

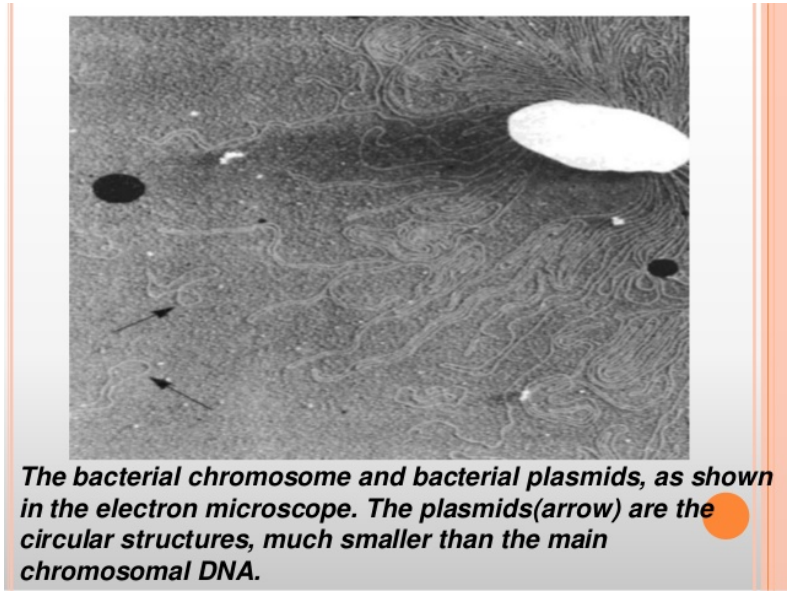
Conjugation : transfer of genetic material between bacteria cells by direct cell-to-cell contact. We will focus on plasmid conjugation.

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

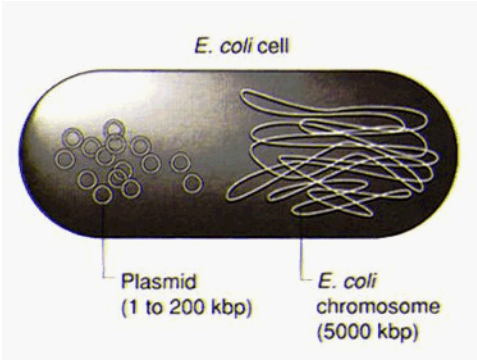


Plasmids in E-Coli

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



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)

The plasmids are costy and the cells with plasmids are less efficient for reproduction.

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

Our goal

- To propose a general stochastic eco-evolutionary model of population dynamics with birth, death, mutation, transfer and competition
- To integrate the different size and time scales.
- Understanding the trade-offs between intrinsic growth, competition and transfer in evolutionary mechanisms.
- Focus on the interplay between ecology 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.

Adaptive Biology

How to describe and quantify the successive invasions of successful mutants?

Three biological assumptions:

- large populations
- rare mutations
- small mutation steps

and long (evolutive) time scale.

Remark: The evolution time scale can be very fast (with respect to the human time scale . . .).

For example, bacteria E. Coli become resistant to an antibiotic by an evolutive procedure after $\sim$ 5 years.

From a virus, its shorter ($\sim$ 6 months).

Some references

- either deterministic:

Game theory and dynamical systems:
Levin-Stewart-Rice 1979, Anderson-May 1979,
Hofbauer-Sigmund 1990, Marrw-Law-Cannings 1992
Metz-Geritz-Meszéna et al. 1992, 1996, Diekmann 2004.

PDE:
Perthame-Barles-Mirrahimi 2007, 2009, Desvillettes-Jabin-Mischler-Raoul 2008,
Hinow-Le Foll-Magal-Webb 2009, Magal-Raoul 2015.

- or stochastic:
Dieckmann-Law 1996, 2000, Bolker-Paccala 1997, Kisdi 1999 Fournier-M. 2004, Champagnat-Ferrière-M. 2006, Champagnat 06, Champagnat-M. 2010, ...
Bovier et al. 2012, 2015, 2017, 2018

Novozhilov-Karev-Koonin 2005, Tazzyman-Bonhoeffer 2013,
Billiard-Collet-Ferrière-M.-Tran 2016, 2018.

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).
- 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 trait of the individual 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)

Bacteria conjugation: the donor transfers its trait to the recipient.

- 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 (x, x).

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

DEATHS:

- Each individual with characteristics x dies at rate

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

- $\frac{C(x, x_i)}{K}$: competition pressure between two individuals.
- The functions d and C are bounded continuous and

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

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

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

Large population, time scale $O(1)$

$K \to \infty$, $p_K \to p$ and.

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

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

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* $T > 0$. *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*

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

Proof: 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.**

Two traits case $\mathcal{X} = \{x, y\}$ and rare mutations: $p_K \to 0$.

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:

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

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

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

$$\frac{dn^x}{dt} = \left(r(x) - C(x,x)n^x\right) n^x .$$

A unique stable equilibrium:

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

Stability Analysis

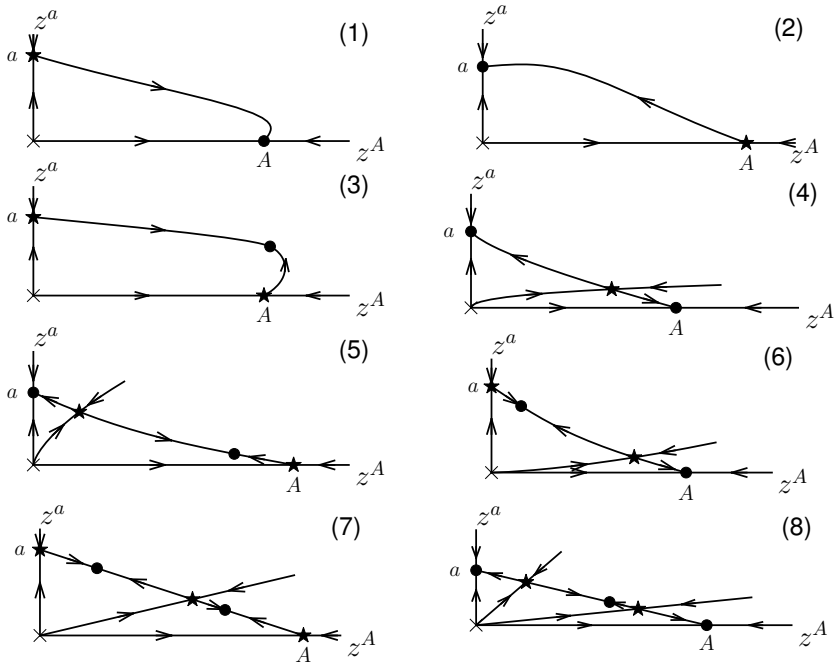
When $\alpha(x, y) \equiv 0$: classical Lotka-Volterra system. The stability is governed by the sign of the invasion fitness function

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

For C constant and r monotone, $f(y; x) = r(y) - r(x)$: 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 y in the x-resident population:

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

- 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.

Study of the dynamical system

- If $C(y,y) > 0$ and $C(x,x) > 0$, then $\phi(n^x, n^y) = \frac{1}{n^x n^y}$ is a Dulac function.
- Bendixson-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".

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

$$\begin{aligned}\frac{dn}{dt} &= n\Big(q\,r(y) + (1-q)\,r(x) - C_{yy}\,q^2 n - (C_{yx} + C_{xy})\,q(1-q)n \\ &\qquad - C_{xx}\,(1-q)^2 n\Big) \\ \frac{dq}{dt} &= q\,(1-q)\Big(r(y) - r(x) + nq(C_{xy} - C_{yy}) + n(1-q)(C_{xx} - C_{yx}) + \\ &\qquad + \alpha(x,y)\frac{n}{\beta + \mu n}\Big).\end{aligned}$$

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

Constant competition case

Assume that C is constant.

Then the system reduces to

$$\frac{dn}{dt} = n\left(q\, r(y) + (1-q)\, r(x) - Cn\right)$$
$$\frac{dq}{dt} = q\,(1-q)\left(r(y) - r(x) + \alpha(x,y)\frac{n}{\beta + \mu n}\right).$$

In the particular case of frequency-dependent transfer rate ($\mu = 1$, $\beta = 0$), we cannot obtain co-existence.

We have the "Invasion-implies-Fixation" principle.

Invasion, fixation or polymorphism persistence of a costly plasmid

Our results show that the horizontal transfer can dramatically change the usual picture.

Fate of a deleterious mutant y in a resident population x.

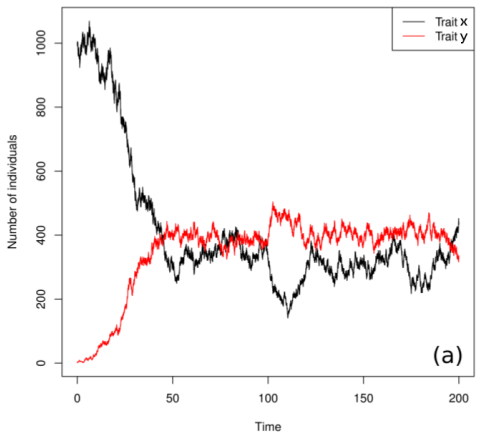
Here the usual fitness is negative and the transfer is unilateral.

$$f(y;x) < 0 \quad ; \quad \tau(y,x) > 0 \quad ; \quad \tau(x,y) = 0.$$

Cases where C is constant:

- **Unilateral DD transfer.**

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

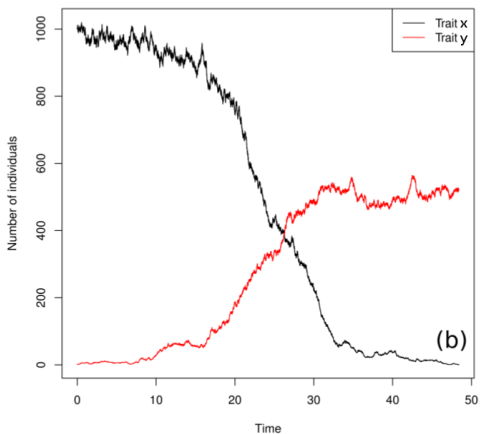


$b(y) = 0.5\ ;\ b(x) = 1\ ;\ \tau(y,x) = \alpha(y,x) = 0,7\ ;\ K = 1000\ ;\ C = 1\ ;\ d \equiv 0.$

Polymorphism with C constant.

- **Unilateral FD transfer.**

$$S(y;x) = r(y) - r(x) + \tau(y,x)\ ;\ S(x;y) = -S(y;x).$$

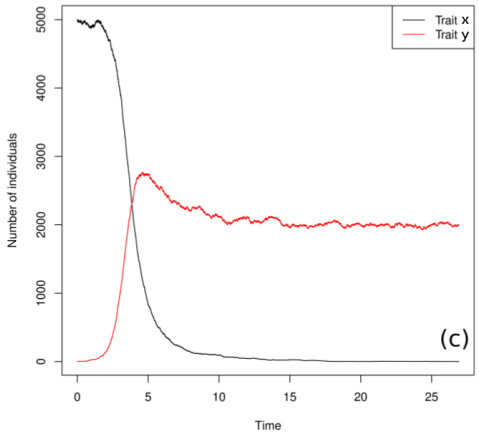


$b(y) = 0.5\ ;\ b(x) = 1\ ;\ \tau(y,x) = \alpha(y,x) = 0,7\ ;\ K = 1000\ ;\ C = 1\ ;\ d \equiv 0.$

Fixation of a deleterious mutant.

The case of a very consuming mutant $(x = a, y = A)$.

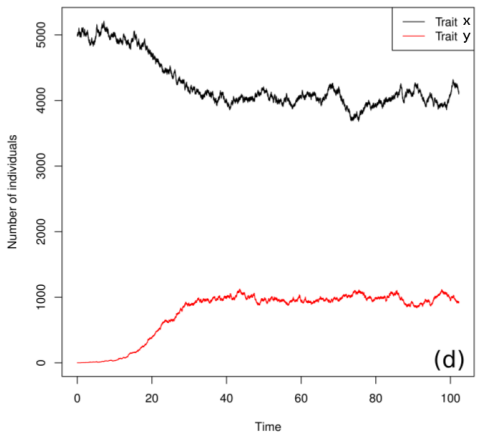
- **Unilateral DD transfer.**



$b(y) = 0.8$; $b(x) = 1$; $\tau(y, x) = \alpha(y, x) = 0.5$; $K = 5000$, $C_{yx} = C_{xx} = 2$; $C_{yy} = 4$; $C_{xy} = 1$; $d \equiv 0$.

Fixation of a deleterious and very consuming mutant.

- **Unilateral FD transfer.**



$b(y) = 0.8$; $b(x) = 1$; $\tau(y, x) = \alpha(y, x) = 0.5$; $K = 5000$; $C_{yx} = C_{xx} = 2$; $C_{yy} = 4$; $C_{xy} = 1$; $d \equiv 0$.

Polymorphism with a deleterious and very consuming mutant.

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

$$P_{yx} = \frac{[S(y;x)]_+}{b(y) + \tau(y,x,0,\bar{n}^x)\,\bar{n}^x} = \frac{[b(y) - d(y) + \left(\tau(y,x,0,\bar{n}^x) - C_{yx}\right)\bar{n}^x]_+}{b(y) + \tau(y,x,0,\bar{n}^x)\,\bar{n}^x}.$$

  Unilateral horizontal transfer increases the probability of invasion of y.

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

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

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

  Duration of order $\frac{\log K}{|S(x;y)|}$.

  Fixation times are decreased by transfer.

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

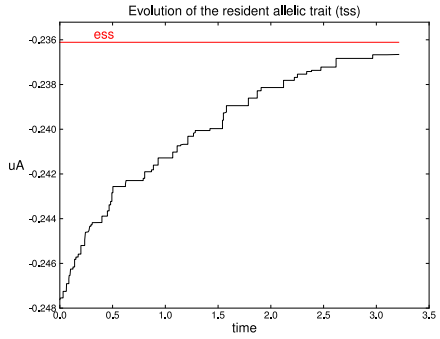
We come back to the continuum of traits $x \in \mathcal{X}$.

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. (Adaptation of Champagnat 2006, heuristics in Metz et al. 1996).

- $\log K \ll \frac{1}{Kp_K}$: the selection process has sufficient time to eliminate disadvantaged trait before the next mutation event arrives with high probability.
- Succession of phases of trait mutant invasion, and phases of competition between traits.
- **At the mutation time scale**: we will only see jumps from $\overline{n^x}$ bacteria with trait x to $\overline{n^y}$ bacteria with trait y.



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

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 $\left(\nu^K_{\frac{t}{K p_K}}, t \geq 0 \right)_{K \geq 1}$

converges in law to a jump process which jumps from $\overline{n^x} \, \delta_x$ *to* $\overline{n^y} \, \delta_y$ *with the jump measure*

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

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 - FD HGT

When the mutation step tends to zero and in a longer time scale, the trait dynamics is given by 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.

$\tau = 0$

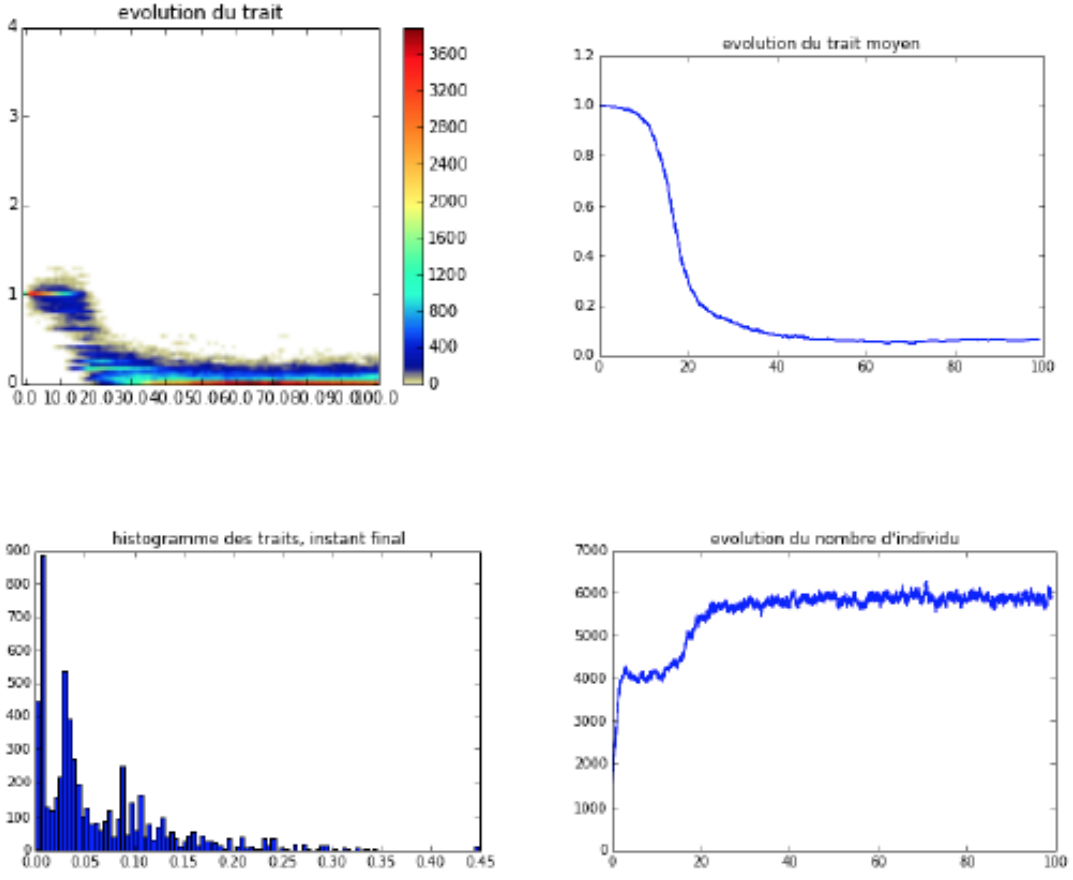


FIGURE 7 – Simulations pour $\tau = 0$.

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

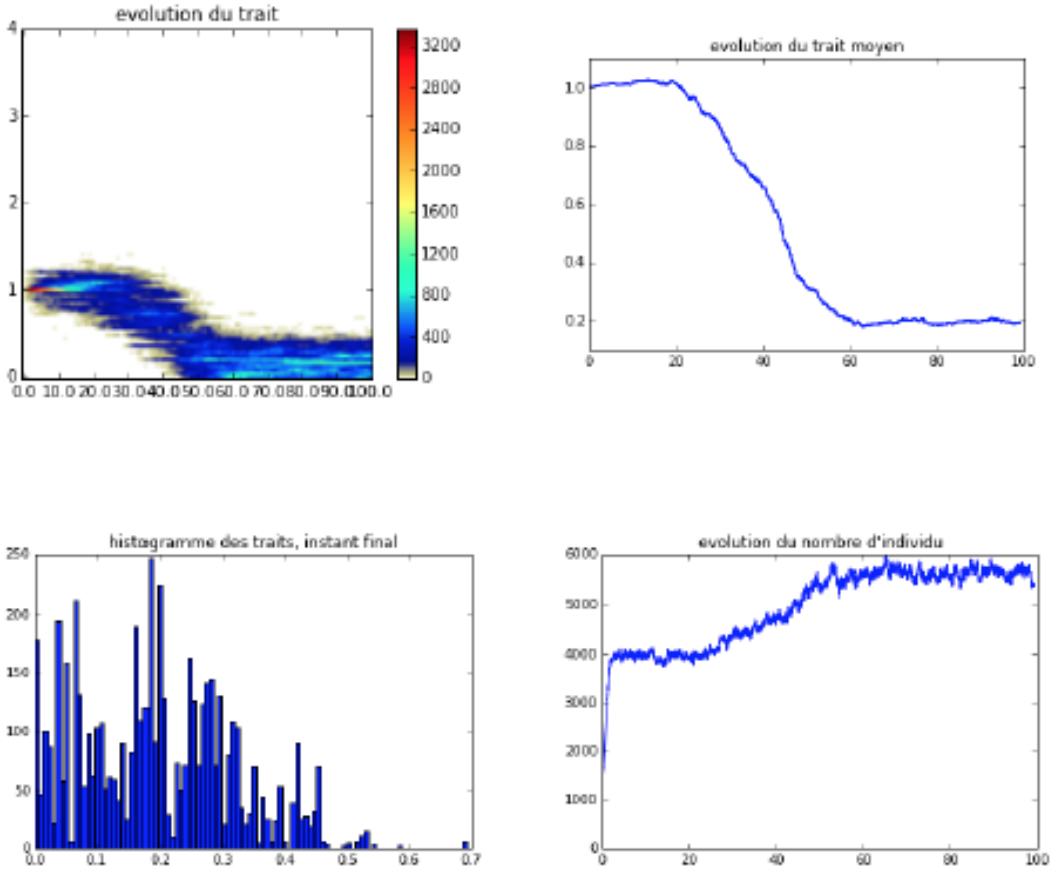


FIGURE 8 – Simulations pour $\tau = 0.2$

$\tau = 0,6$ - Stepwise Evolution

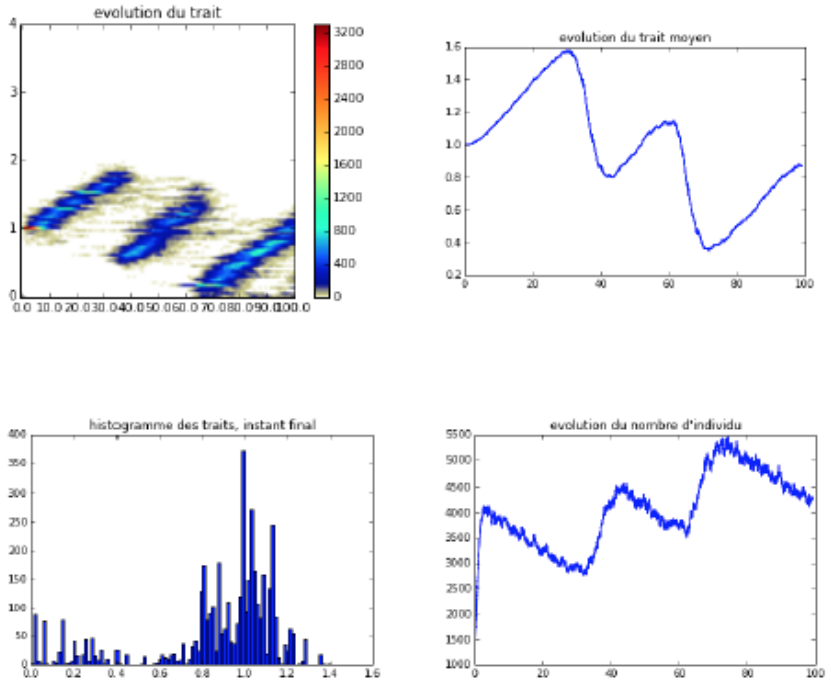


FIGURE 9 – Simulations pour $\tau = 0.6$ sur un temps de 100

- 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.

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

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

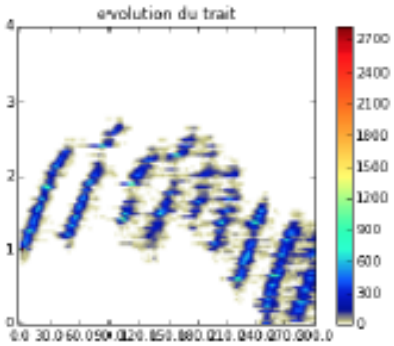


FIGURE 12 – simulation 1

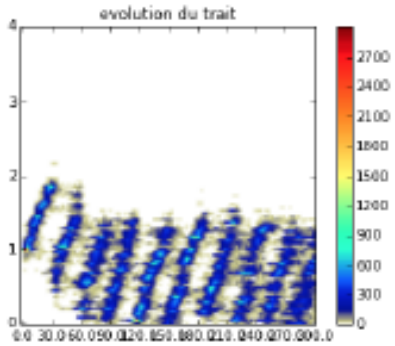
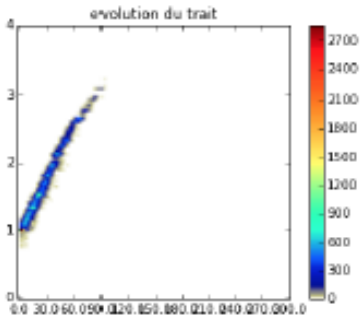
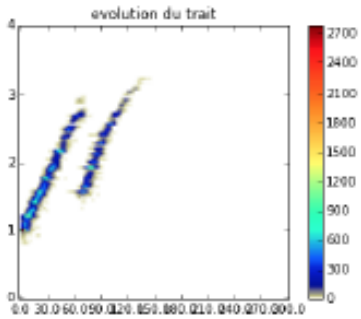


FIGURE 13 – simulation 2





$\tau = 1$ - Evolutive Suicide

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

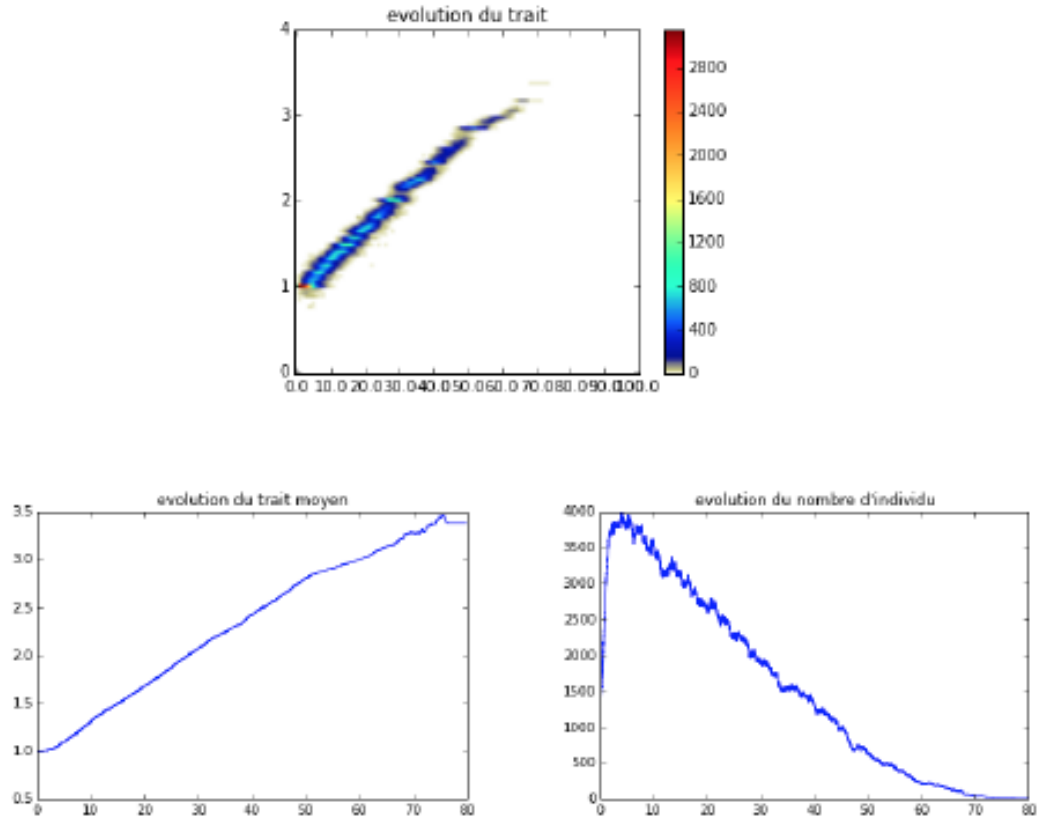


FIGURE 17 – Simulations pour $\tau = 1$

Happy Birthday, Anton!

Rare or small mutations and long time scale

1 - Work in progress (with V. Calvez and S. Mirrahimi)

We consider a close equation with Gaussian mutations at rate ε^2 and long time t/ε.

$$\partial_t n_\varepsilon = (b-x)\frac{n_\varepsilon}{\varepsilon} + \varepsilon\, b\, \partial_x^2 n_\varepsilon + \frac{n_\varepsilon}{\varepsilon \int n_\varepsilon(t,y)dy} \int \alpha(x,y) n_\varepsilon(t,y)dy.$$

One introduces $u_\varepsilon(t,x) = \varepsilon \log n_\varepsilon(t,x)$.

Then

$$\partial_t u_\varepsilon = b - x + \varepsilon b \partial_x^2 u_\varepsilon + b\,|\partial_x u_\varepsilon|^2 + \frac{\int \alpha(x,y) n_\varepsilon(t,y)dy}{\int n_\varepsilon(t,y)dy}.$$

Assume that $n_\varepsilon \to n$, $\int \alpha(x,y) n_\varepsilon(t,y)dy \to I_\alpha(t) = \int \alpha(x,y) n(t,y)dy$ and $\int n_\varepsilon(t,y)dy \to I(t) = \int n(t,y)dy$.

One obtains the limiting equation

$$\partial_t u(t,x) = b - x + b\,|\partial_x u|^2 + \frac{I_\alpha(t)}{I(t)}.$$

Assume now that for any t, there exists a unique dominant trait: $\operatorname{argmax} u(t,x) = \{\bar{x}(t)\}$.

Then the equation is

$$\partial_t u(t,x) = b - x + b\,|\partial_x u|^2 + \alpha(x, x(t)).$$

Seeking a stationary equation of the form $u(t,x) = \lambda t + U(x)$ is equivalent to solving:

$$\lambda = b - x + b|\partial_x U(x)|^2 + \alpha(x, \bar{x}) \tag{1}$$

where $\bar{x}$ is the dominant trait: $\operatorname{argmax} U = \{\bar{x}\}$. There are two *macroscopic equations* for the two unknowns $(\lambda, \bar{x})$:

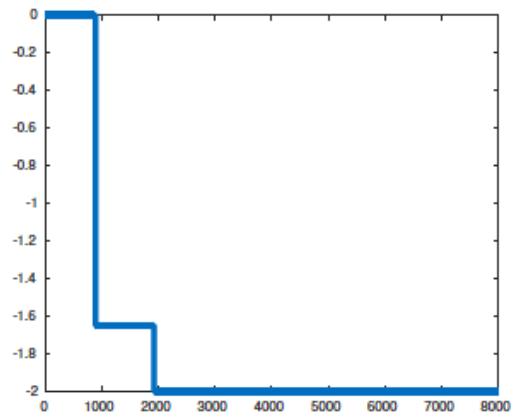
$$\begin{cases} \lambda = b - \bar{x} + \alpha(\bar{x}, \bar{x}) \\ 0 = -1 + \partial_x \alpha(\bar{x}, \bar{x}) \end{cases} \tag{2}$$

Moreover, the following nonnegativity constraint must be satisfied everywhere:

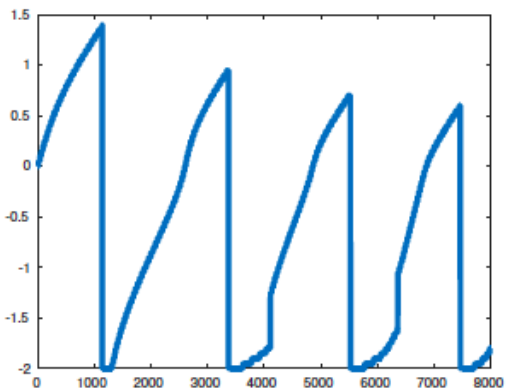
$$(\forall x) \quad \lambda - b + x - \alpha(x, \bar{x}) \geq 0 \tag{3}$$

This is where interesting things happen depending on the shape of α (the value of τ): it can happen than the solution $(\lambda, \bar{x})$ violates the last condition. Then, things are going to oscillate...

For $\alpha(x, y) = \phi(x - y)$, where $\phi(z) = \tau \tanh(z)$, the dominant trait follows the following dynamics:



(a)



(b)

τ small τ large.