# Stochastic dynamics for adaptation and evolution of microorganisms

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CEMRACS Numerical and mathematical modeling for biological and medical applications: deterministic, probabilistic and statistical descriptions, CIRM, July 2018

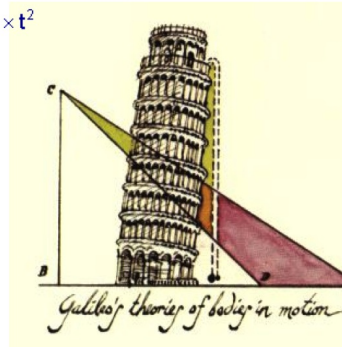


# A long history to address evolution

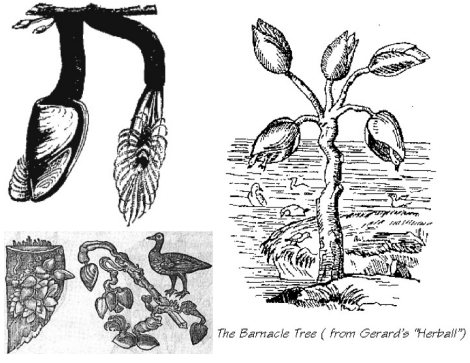
In 1604, Galilée understands the mathematical law of falling bodies.

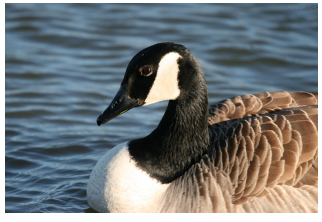
$$\vec{d} = \frac{1}{2} \times 9{,}8 \frac{m}{s^2} \times t^2$$

$$\vec{d} = 4{,}9 \frac{m}{s^2} t^2$$



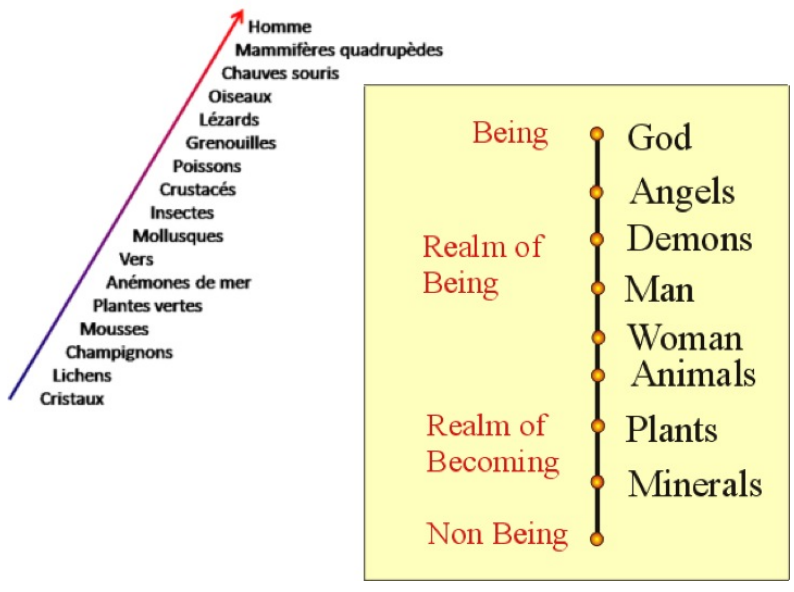

*In biology, knowledge is still close to stone age....*

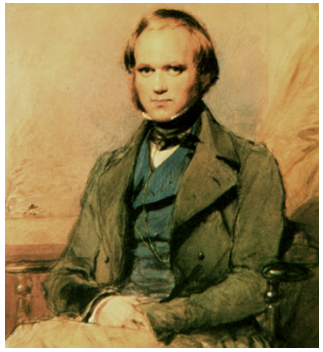
# What is a species?

Until the end of *XVIII* century: a linear image of the great chain of living Beings.

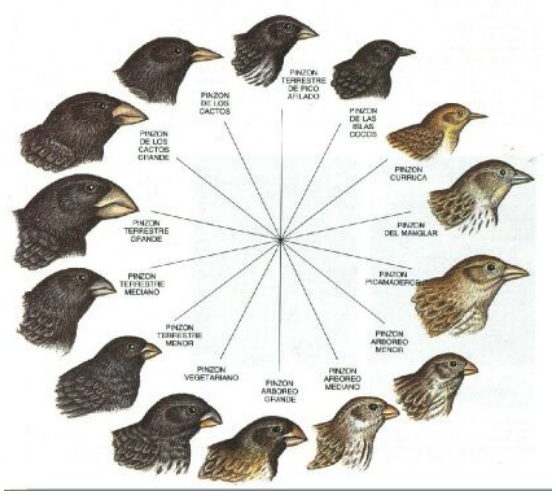


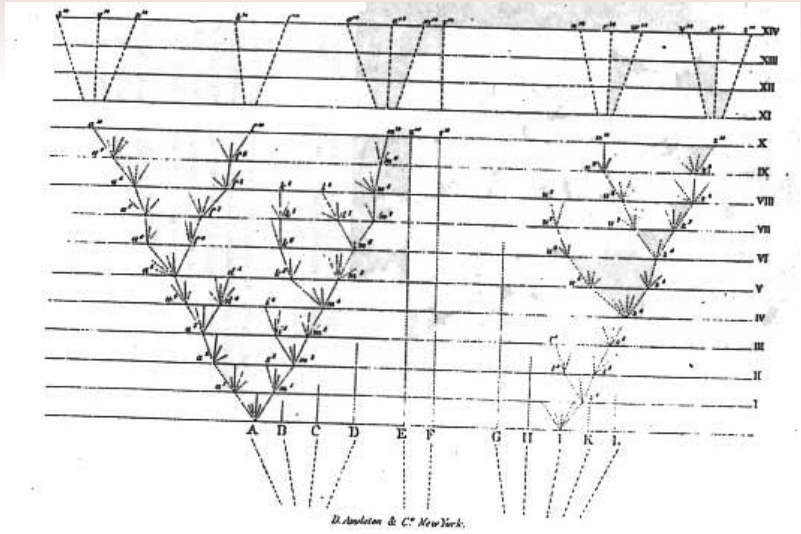
# Theory of Evolution (1859)

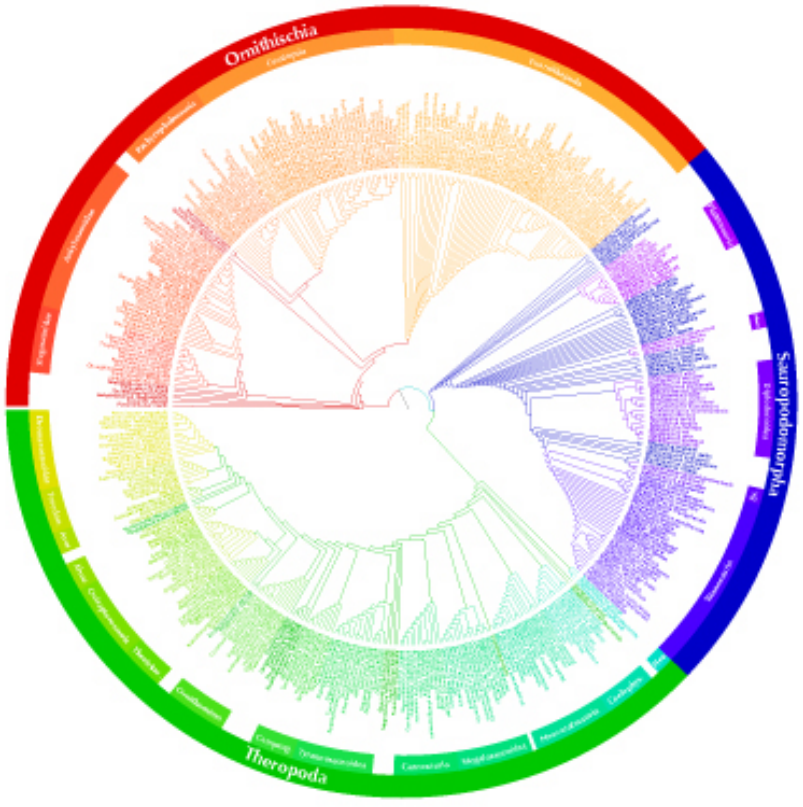
DARWIN (1809-1882).
His work on the evolution of living species revolutionized biology.



He formulates the hypothesis that all living species have evolved over time from a single or a few common ancestors through the **natural selection process**.




A B C D E F G H I K L
D. Appleton & Co. New York.


Ornithischia
Sauropodomorpha
Theropoda

# 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".

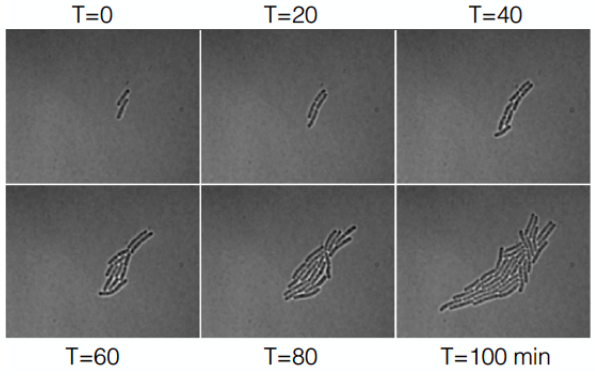
Charles Darwin, On the origin of species, 1859.

# Micro-organisms

We focus on bacteria cells.

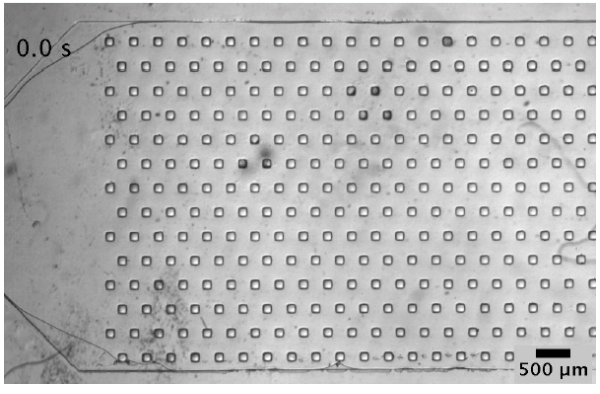
(M. El Karoui - C. Baroud - J. Harmand)

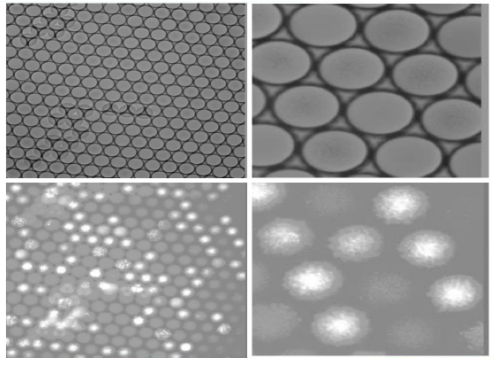
Binary division: birth and death process in continuous time.

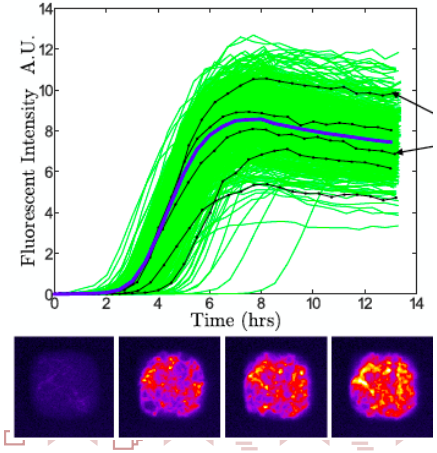



Understanding the population development.

Understanding its heterogeneity.





# Adaptive biology for micro-organisms

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

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

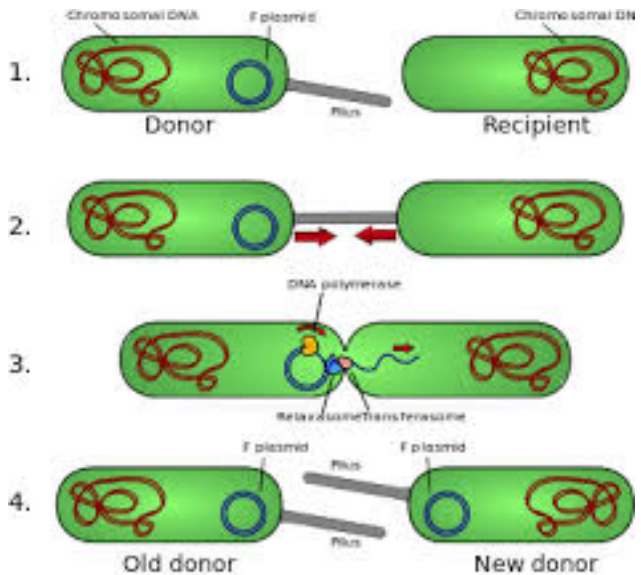
The evolution of the trait distribution results from the following mechanisms:

- 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

Major process in the evolution and adaptation of micro-organisms.

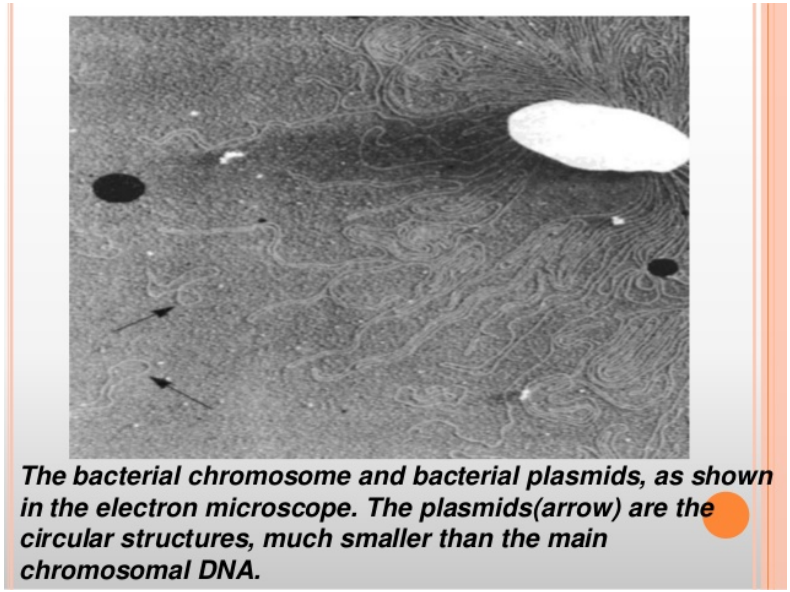
Plasmids: small circular double-stranded DNA, physically separated from the chromosonal DNA.



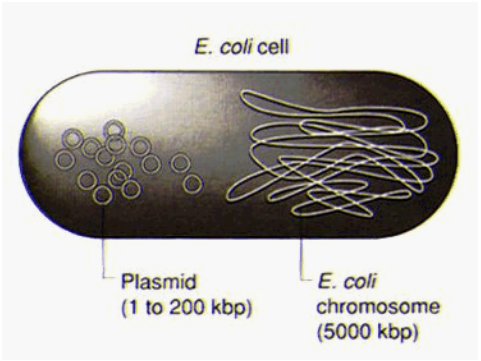
# Plasmids in E-Coli

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)

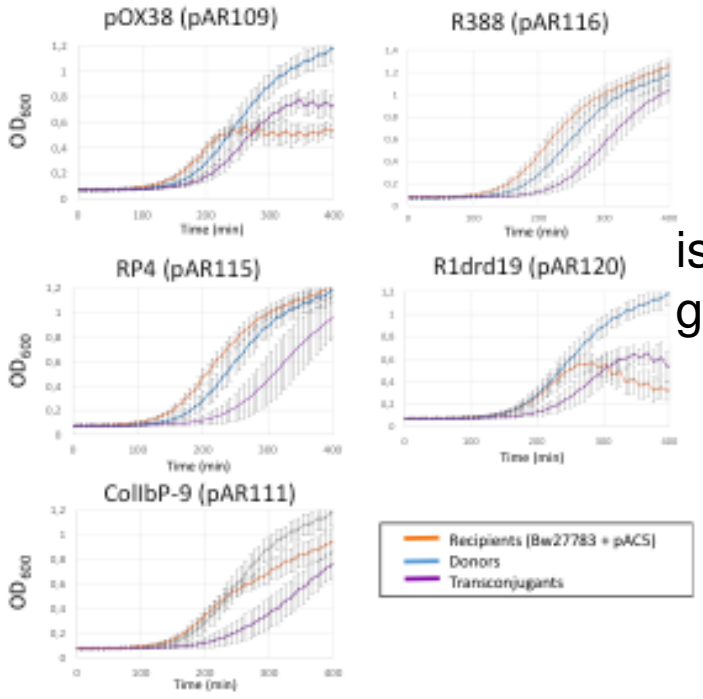
The plasmids are costy and the cells with plasmids are less efficient for reproduction.
How the demographic parameters, the transfer rate and the environment do interplay in the evolution mechanism?

# 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

**Our goal**

- To propose a general stochastic eco-evolutionary model of population dynamics with birth, death, mutation, transfer and competition
- 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, Novozhilov-Karev-Koonin 2005, Tazzyman-Bonhoeffer 2013, Billiard-Collet-Ferrière-M.-Tran 2016, 2018.

# 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

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

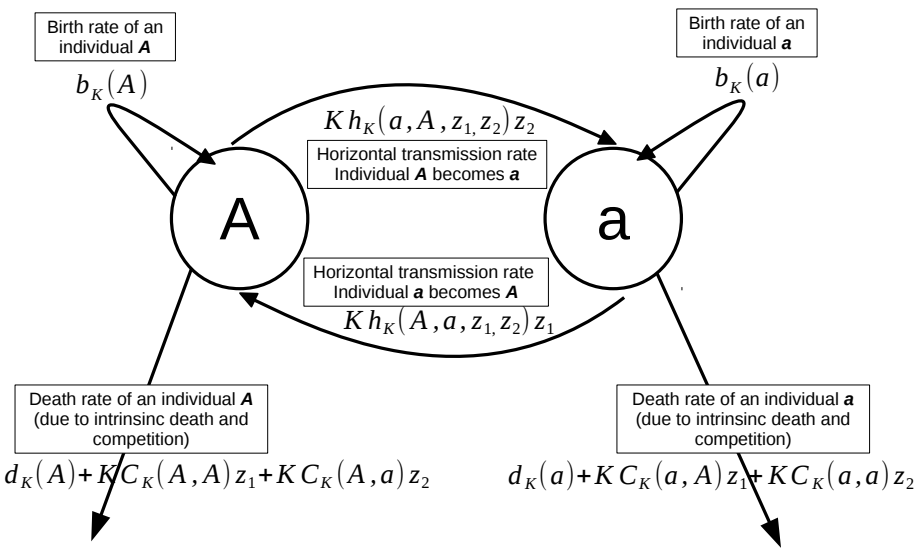
  where $N_t^{A,K}$ and $N_t^{a,K}$ the numbers of individuals with alleles respectively $A$ and $a$.
- Birth rate of an individual with trait $x \in \{A, a\}$: $b_K(x)$.
- Death rate of an individual with trait $x \in \{A, a\}$ at time $t$; $y \in \{A, a\}$ is the other trait:

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

# 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:

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

# 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 $x, y \in \{a, A\}$,

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

Experimental remark: *HGT rate is density-dependent when the population size is low* and *frequency-dependent when the population size 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. our proof in dimension 1).

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

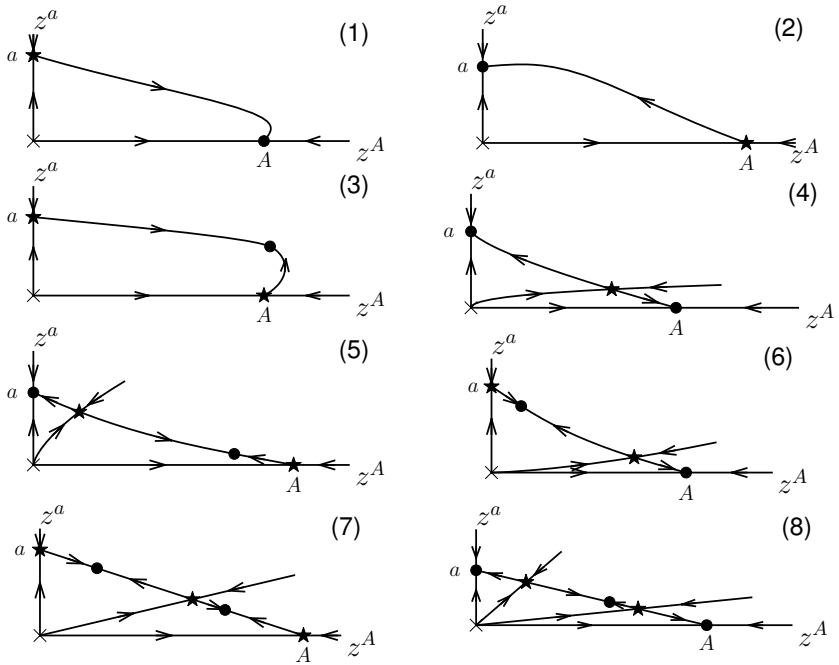
When $\alpha(x, y) \equiv 0$: classical Lotka-Volterra system. The stability is governed by the sign of the invasion fitness function

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

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.

# 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.
- 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".

$$n(t) = z^1(t) +^2 (t) \quad ; \quad q(t) = \frac{z^1(t)}{z^1(t) +^2 (t)}.$$

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

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

# Constant competition case

Assume that $C$ is constant.

Then the system reduces to

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

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 $A$ in a resident population $a$.

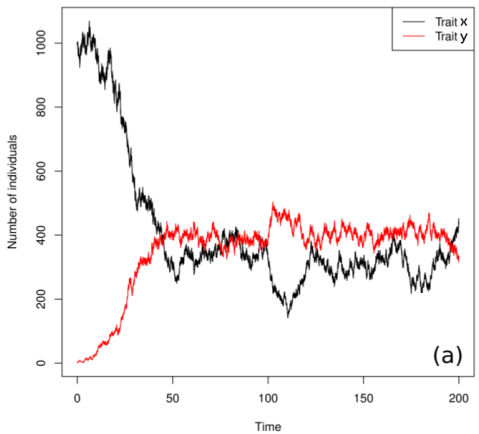
Here the usual fitness is negative and the transfer is unilateral.

$$f(A;a) < 0 \quad ; \quad \tau(A,a) > 0 \quad ; \quad \tau(a,A) = 0.$$

## Cases where $C$ is constant ($x = a, y = A$):

- **Unilateral DD transfer.**

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

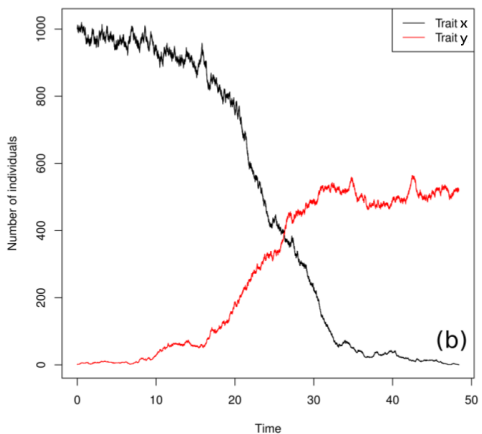



$b(A) = 0.5\ ;\ b(a) = 1\ ;\ \tau(A,a) = \alpha(A,a) = 0,7\ ;\ K = 1000\ ;\ C = 1\ ;\ d \equiv 0.$

Polymorphism with $C$ constant.

- **Unilateral FD transfer.**

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

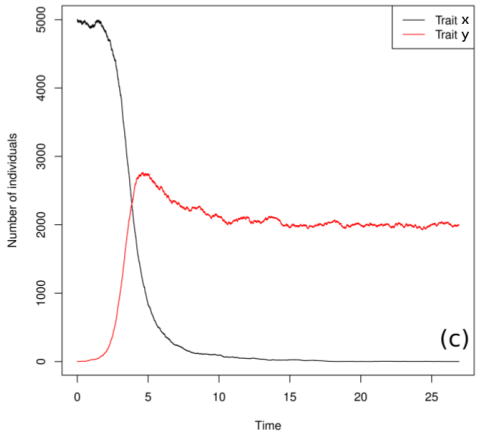



$b(A) = 0.5\ ;\ b(a) = 1\ ;\ \tau(A,a) = \alpha(A,a) = 0,7\ ;\ K = 1000\ ;\ C = 1\ ;\ d \equiv 0.$

Fixation of a deleterious mutant.

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

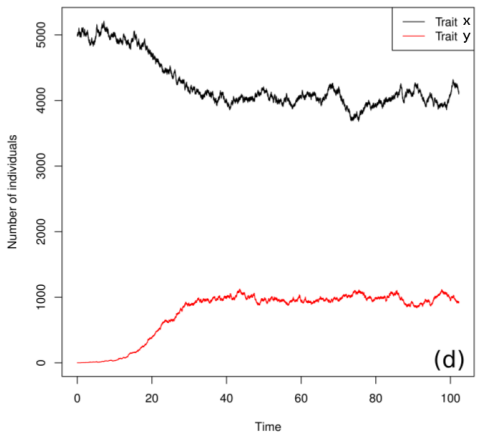
- **Unilateral DD transfer.**




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

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 horizontal transfer 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 transfer.

# Evolution: mutations of traits

- The trait values belong to a continuum.
- Phenotypic trait under selection $x$ in a compact subset $\mathcal{X}$ of $\mathbb{R}^d$.
- $K$ 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

Individuals exchange information by conjugation. In the population $\nu$, 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

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

# Large population, time scale $O(1)$

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

where $\tau$ 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*

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

**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).

The main example is the case of FD transfer rate ($\beta = 0, \mu = 1$) with $C$ constant.

- The initial population is monotype: all individuals at time 0 have the same trait.

- **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.

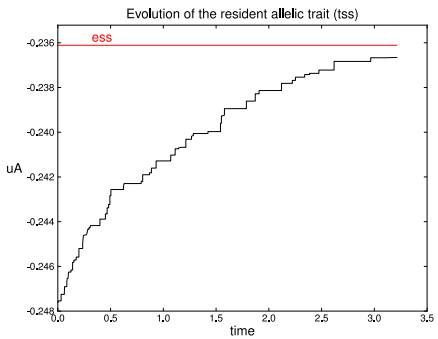
## Theorem (TSS Approximation)

*Assume: the initial conditions* $\nu_0^K = z_0^K \, \delta_{x_0}(dx)$ *converge to* $\bar{z}^{x_0} \delta_{x_0}(dx)$.

*As soon as Invasion-Implies-Fixation, 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.

**Example**.

- Constant competition pressure $C$:

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

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

(i) **Without transfer**: 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 FD transfer**: 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 $\sigma$:
$\int g(z)\, m_\sigma(x,z)dz = \int g(x+\sigma h)\, \overline{m}(x,h)dh$, where $\overline{m}$ independent of $\sigma$.

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

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

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).*

- $x \in [0,4]$; $m(x,z)dz = \mathcal{N}(x,\sigma^2)$.
- FD **unilateral** transfer 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.

# $\tau = 0$

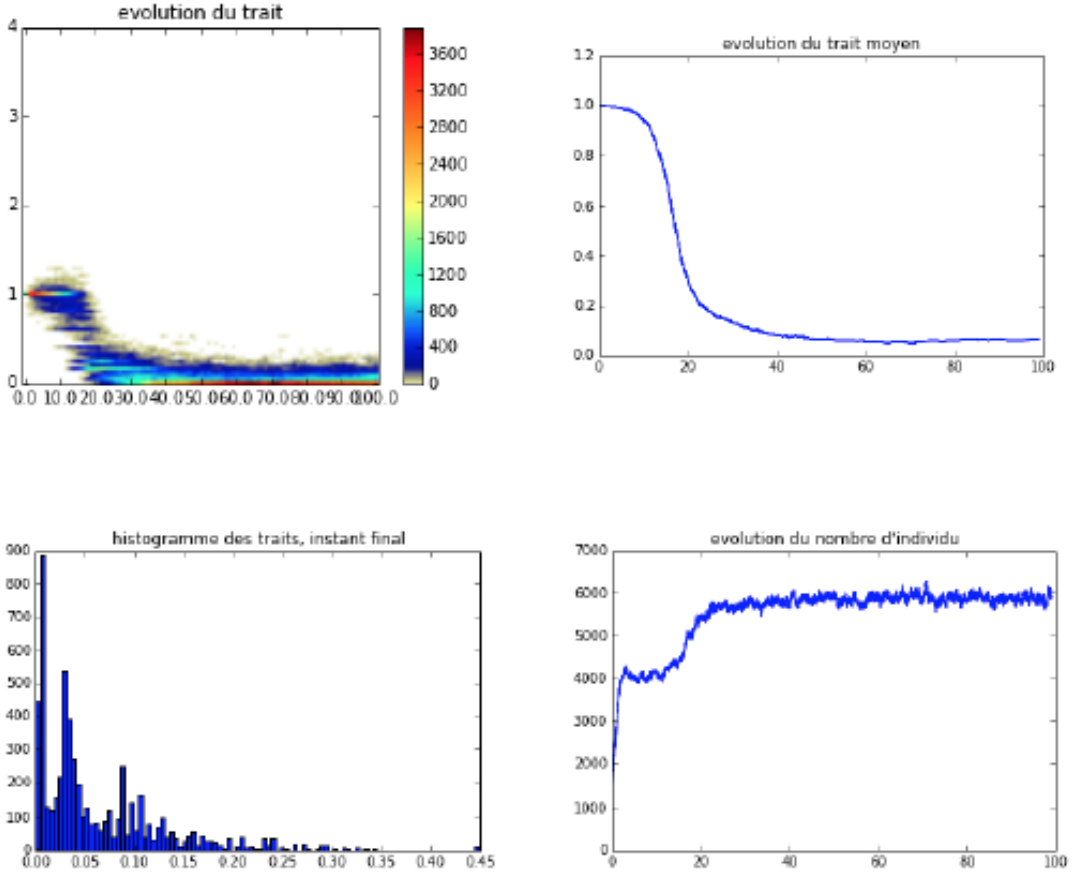



FIGURE 7 – Simulations pour $\tau = 0$.

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

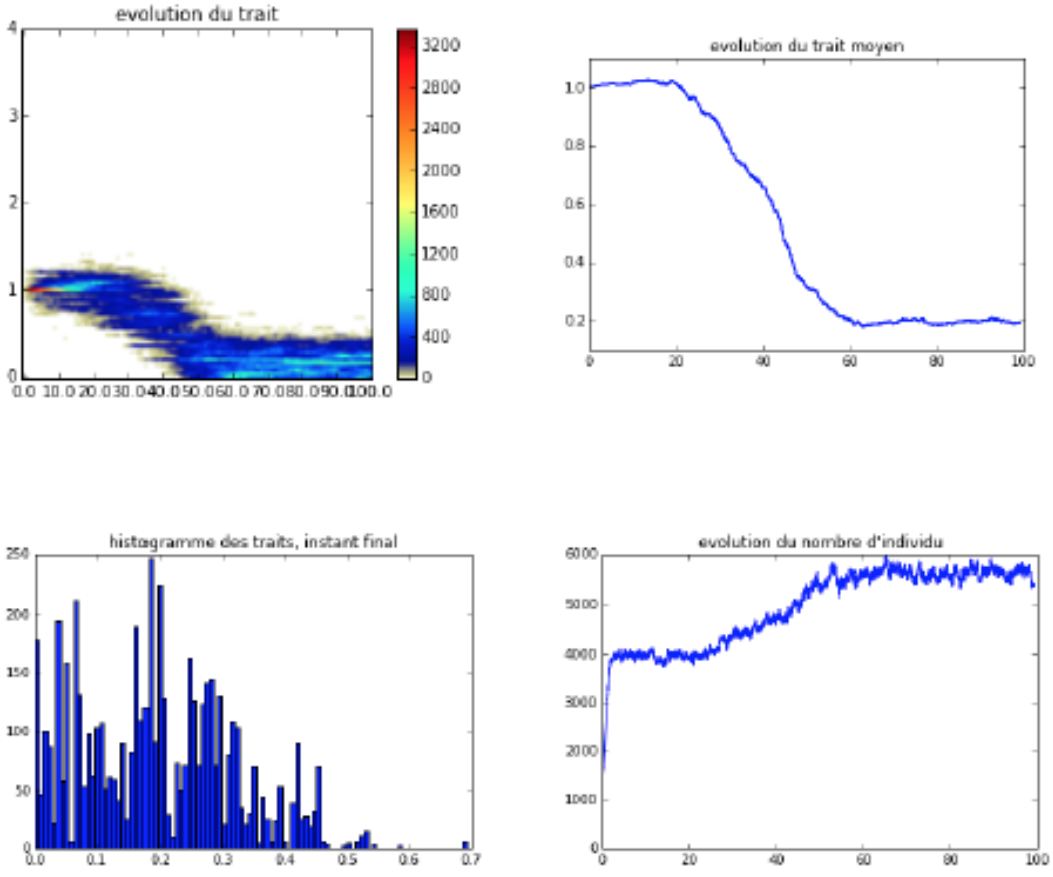



FIGURE 8 – Simulations pour $\tau = 0.2$

# $\tau = 0,6$ - Stepwise Evolution

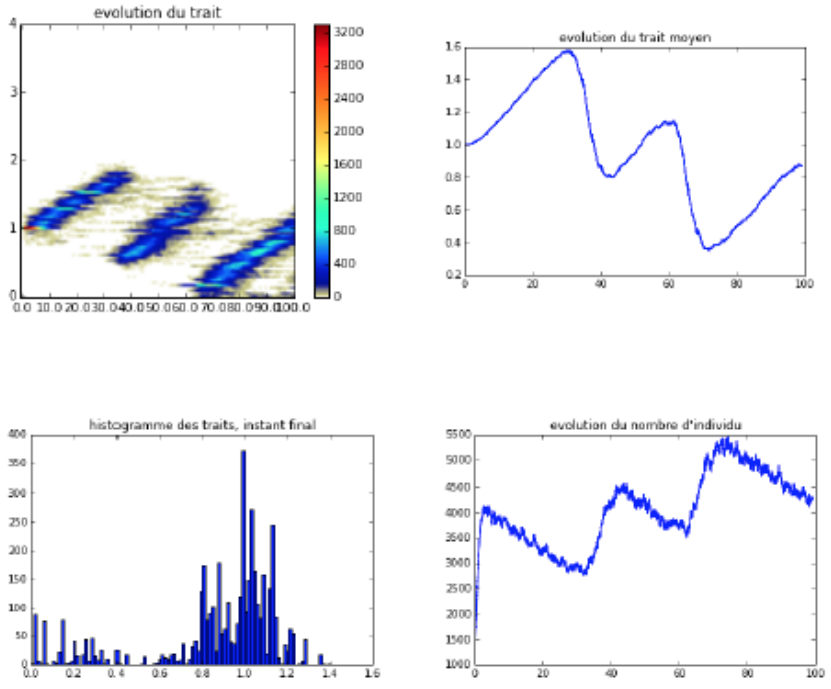



FIGURE 9 – Simulations pour $\tau = 0.6$ sur un temps de 100

- 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.

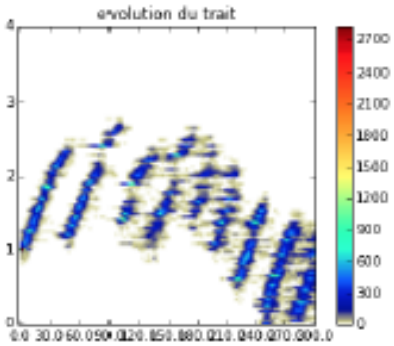



FIGURE 12 – simulation 1

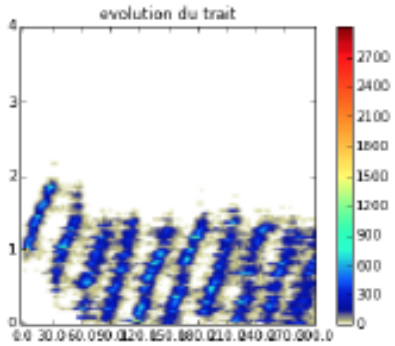
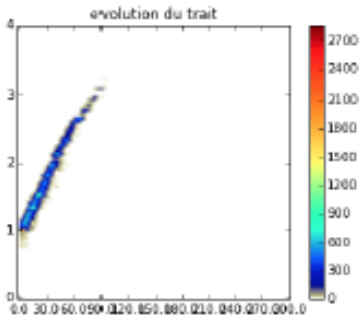
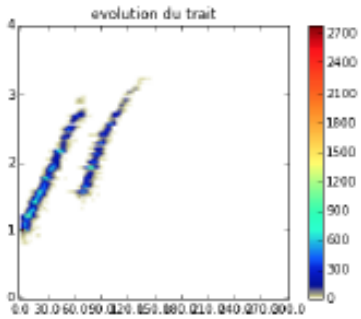



FIGURE 13 – simulation 2



# $\tau = 1$ - Evolutive Suicide

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

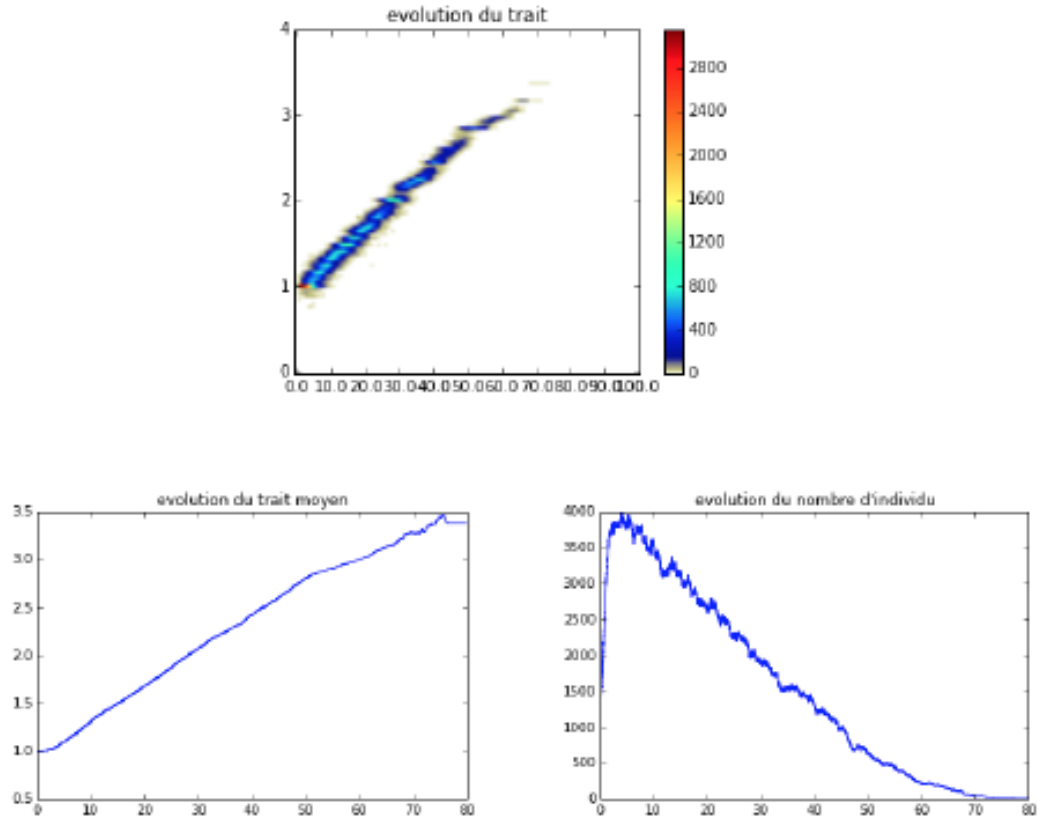



FIGURE 17 – Simulations pour $\tau = 1$

# 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 $\varepsilon^2$ and long time $t/\varepsilon$.

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

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:

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

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

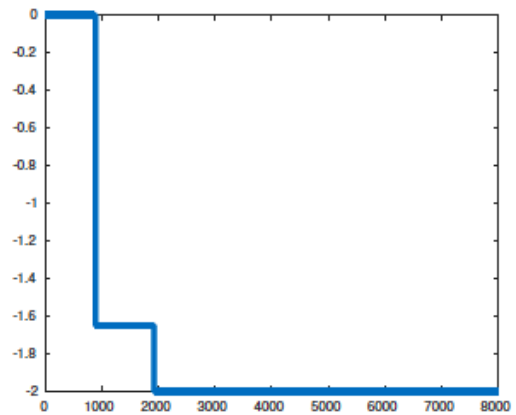
$$\begin{cases} \lambda = b - \bar{x} + \alpha(\bar{x}, \bar{x}) \\ 0 = -1 + \partial_x \alpha(\bar{x}, \bar{x}) \end{cases} \tag{3}$$

Moreover, the following nonnegativity constraint must be satisfied everywhere:

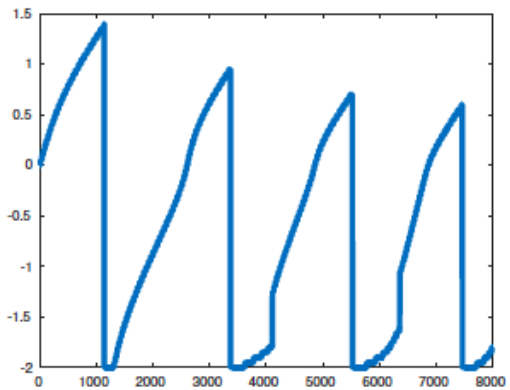
$$(\forall x) \quad \lambda - b + x - \alpha(x, \bar{x}) \geq 0 \tag{4}$$

This is where interesting things happen depending on the shape of $\alpha$ (the value of $\tau$): 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)

$\tau$ small $\tau$ large.

## 2 - Work in progress with N. Champagnat and C.V. Tran

Trait space $\mathcal{X} = \{0, \Delta, \cdots, \bar{\ell}\Delta\}$ with $\bar{\ell} = 4/\Delta$.

We assume that $b(x) = 4 - x$; $d(x) = 1 + C(N/K)$. Then $\bar{z}^x = (3 - x)/C$.

Mutation probability: $p_K = K^{-\alpha}$, $0 < \alpha < 1$ and if $x = \ell\Delta$, a mutant will be $(\ell + 1)\Delta$.

Assume that
$(N_0^K(0), \cdots, N_\ell^K(0), \cdots, N_{\bar{k}}^K(0)) = (\frac{3K}{C}, K^{1-\alpha}, \cdots, K^{1-\ell\alpha}, \cdots, 0 \cdots, 0)$.

The fitness is given by $S(y; x) = s(\frac{x-y}{\Delta})$, with $s(z) = \Delta z - \tau sign(z)$.

Then

$$N^K_{t \log K}(\ell\Delta) = K^{\beta^K_\ell(t)}$$

and

$$\lim_{K\to\infty} \beta^K_\ell(t) = \beta_\ell(t),$$

with

$$\beta_\ell(t) = \beta_\ell(t) + t\, s(\ell - \ell^*(t))$$

where $\ell^*(t)$ is the dominant trait at time $t$.

# Co-authors and biologists collaborators

Figure: S. Billiard , N. Champagnat , P. Collet , R. Ferrière, C.V. Tran

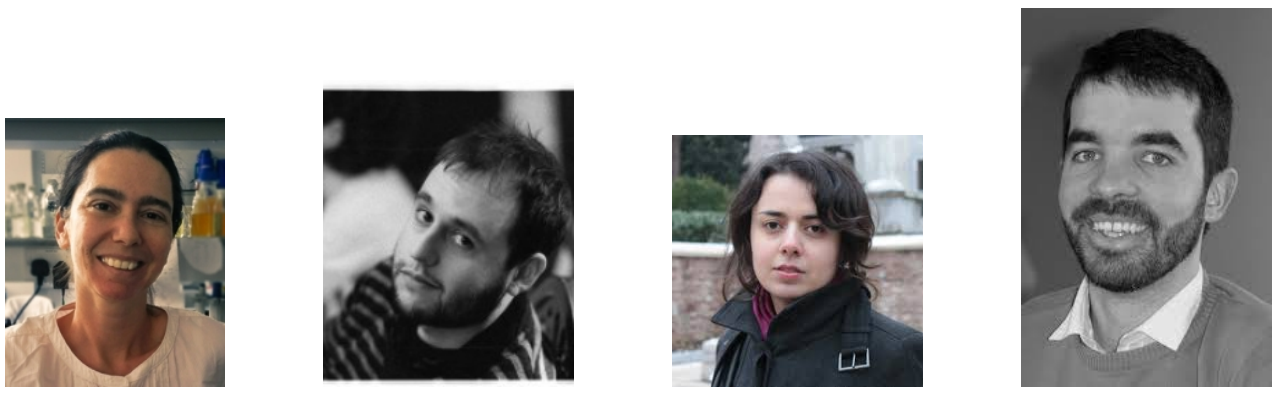


Figure: M. El Karoui, R. Fernandez-Lopez , S. Mirrahimi, V. Calvez

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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.

# Thank you for your attention!