

# Exponent dynamics for branching processes

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30 ans du Laboratoire Manceau de Mathématiques :  
Probabilités - Statistique - Risque, 2024

Joint works with N. Champagnat (Nancy), S. Mirrahimi (Montpellier) and V.C. Tran (Marne-la-Vallée).



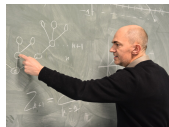
Funded by the  
European Union

## Le Mans- 1984-1989

Two fantastic colleagues :



Two excellent students :



## Adaptation and Evolution for asexual populations

*Individuals are characterized by genetic or phenotypic information (trait) that influences their ability to reproduce and their probability of survival.*

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

- **Heredity.** (Vertical) transmission of the ancestral trait to the offsprings.
- **Mutation.** Creates variability in the trait values.
- **Selection.** Individuals with a higher probability of survival or a better ability to reproduce will invade the population over time (genetical selection), as will those most able to survive in competition with others (ecological selection).
- **Horizontal Gene Transfer (HGT):** the bacteria exchange genetic information.

*HGT has a main role in the evolution of virulence and is considered as the primary reason for bacterial antibiotic resistance.*

Asexual populations (cells, bacteria).

Usual biological assumptions:

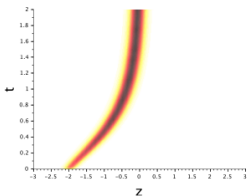
- large populations
- rare mutations
- small mutation steps
- long (evolutionary) time scale.

The main goal:

- predict the long term evolutionary dynamics.
- model and quantify the successive invasions of successful mutants: by mutation-selection, the population concentrates on advantageous mutants.

That is a multi-scale question : different mathematical approaches using different analytical tools.

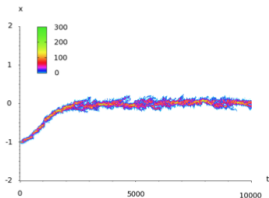
- **Game Theory - Dynamical Systems:**  
Maynard-Smith 1974, Hofbauer-Sigmund 1990, Marrow-Law-Cannings 1992, Metz-Geritz-Meszéna et al. 1992, 1996, Dieckmann-Law 1996, Dieckmann 2004.
- **Partial or integro-differential and Hamilton-Jacobi equations (Hopf-Cole transformation):**  
Perthame-Barles-Mirrahimi 07-10, Jabin, Desvillettes, Raoul, Mischler 08-10.  
Concentration phenomenon on advantageous mutants but evolution seems too fast.



- **Stochastic individual-based processes** (birth and death processes with mutation and selection) :

(Bolker-Pacala 97, Kisdi 99, Dieckmann-Law 00, Fournier-M. 04, Ferrière-Champagnat-M. 06, Champagnat 06, Champagnat-M. 10).

**Concentration phenomenon on advantageous mutants but evolution seems too slow** (time scale separation between competition phases and mutation arrivals).



It is not clear how these models are related.

## Some motivating questions

- Mutations rare but not so rare.
- How to interpret the results of the Hamilton-Jacobi approach with regard to the initial individual based model.
- What new behaviours does horizontal transfer entail?
- How to keep track of small subpopulations in large population approximations?

## Two discrete models

- The trait space is a discretized version of  $[0, 1]$ .
- In both cases, there is a scaling parameter  $K$ : order of magnitude of the population size or of the resources amount.
- We will follow the populations of size  $K^\beta$ , on the time scale  $\log K$ .  
( $\beta = 0$  means "extinction").

$$\text{If } N^K(t \log K) \sim K^{\beta^K(t)}, \quad \text{then } \beta^K(t) \sim \frac{\log(1 + N^K(t \log K))}{\log K}.$$

- **First model** : a joint work with N. Champagnat and V.C. Tran.  
 $\rightsquigarrow$  Mutations are rare but not small ; discretization mesh is fixed.
- **Second model** : a joint work with N. Champagnat, S. Mirrahimi and V.C. Tran.  
 $\rightsquigarrow$  Mutations are small but not rare; discretization mesh is going to 0.



## A discrete model - Rare mutations

(Durrett, Mayberry 2011 - Bovier, Coquille, Smadi 2019).

- The trait space  $[0, 1]$  is discretized :  $\delta > 0$  is fixed.

$$x = i\delta \in [0, 1], \quad i \in \{0, \dots, \lfloor \frac{1}{\delta} \rfloor\}.$$

- **Divisions:** rate  $b(x) = 1 - x$ 
  - Probability  $p_K = K^{-\alpha}$  with  $0 < \alpha < 1$ : mutant trait  $x + \delta$ .
  - Probability  $1 - K^{-\alpha}$ : clonal reproduction.

Note that  $K p_K = K^{1-\alpha}$  tends to infinity.

- **Deaths:** rate  $d(x) = d + C \frac{N^K}{K}$  ;  $d < 1$ .
- **Unilateral transfer:**  $(x, y) \rightarrow (y, y)$  at rate  $\frac{\tau}{NK} \mathbf{1}_{y>x}$ .

## Evolutionary point of view

- The population is at equilibrium, with a single trait  $x$  and population size of order  $K$ . The trait  $x$  is called resident trait.
- When  $K$  tends to infinity, the total population size  $N^K$  can be approximated by  $Kn(t)$  where  $n(\cdot)$  solves the ODE

$$n'(t) = n(t)(1 - d - x - Cn(t)),$$

whose unique positive stable equilibrium is given by

$$\bar{n}(x) = \frac{1 - d - x}{C}.$$

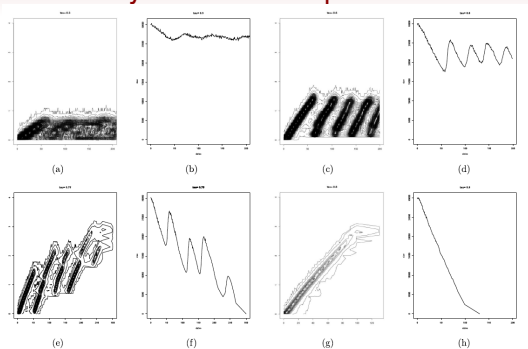
- When a single mutant with trait  $y$  appears, its growth rate is approximatively the invasion fitness, given by

$$S(y; x) = (1 - d - y) - C\bar{n}(x) + \left( \frac{\tau}{\bar{n}(x)} (\mathbf{1}_{y>x} - \mathbf{1}_{x>y}) \right) \bar{n}(x);$$

$$S(y; x) = x - y + \tau \text{sign}(y - x).$$

The sign of  $S(y; x)$  will impact the mutant dynamics: trade-off between demography and transfer.

## Dynamics of the process



$K = 10000$ ;  $d = 0.25$ ;  $\delta = 0.1$ ;  $\alpha = 0.5$ ;  $C = 1$ ;

Initial subpopulation sizes: 0 is the resident trait.

$$N_0^K(0) = \frac{(1-d)K}{C} ; N_{i\delta}^K(0) = K^{1-i\alpha} \vee 0.$$

(a)-(b):  $\tau = 0.3$  : equilibrium near 0;

(c)-(d):  $\tau = 0.6$ : cyclical re-emergences of the fittest traits;

(e)-(f):  $\tau = 0.75$ : re-emergence towards higher and less fit trait values;

(g)-(h):  $\tau = 0.8$  : evolutionary suicide.

### Possible resurgences :

For any  $i \in \{0, \dots, \lfloor \frac{1}{\delta} \rfloor\}$ , we follow the small populations  $N_{i\delta}^K \sim K^{\beta_i^K}$  at the logarithm time scale.

Then we study, for all  $i \in \{0, 1, \dots, \lfloor 1/\delta \rfloor\}$ , the asymptotic behaviour of the process

$$\left( \frac{\log(1 + N_{i\delta}^K(s \log K))}{\log K}, s \in [0, T] \right)$$

when  $K \rightarrow +\infty$ .

## Two Lemmas for exponents of birth and death processes

A small population with trait  $y$  in a resident population with trait  $x$  with  $y < x$  behaves as a branching process with birth and death rates respectively:

$$4 - y \quad \text{and} \quad 1 + \frac{CN_x^K(t)}{K} + \tau.$$

**Lemma** *Let us consider a linear birth and death process  $(Z_t^K)_{t \geq 0}$  with rates  $b$  and  $d$ , starting from the initial condition  $[K^\beta - 1]$  (avec  $\beta \leq 1$ ).*

*Then,*

$$\left( \frac{\log(1 + Z_{s \log K}^K)}{\log K}, s \in [0, T] \right) \xrightarrow{K \rightarrow +\infty} ((\beta + s(b - d)) \vee 0, s \in [0, T]),$$

*uniformly on  $[0, T]$ , in probability.*

Note that

$$\mathbb{E}[Z^K(t)] = \mathbb{E}[Z^K(0)]e^{(b-d)t}.$$

Therefore,

$$\mathbb{E}[Z^K(s \log K)] = [K^\beta - 1] K^{(b-d)s}.$$

A small population with trait  $y$  in a resident population with trait  $x$ , with  $y = x + \delta$ , behaves as a branching process with birth and death rates respectively:

$$4 - y + \tau \quad \text{et} \quad 1 + \frac{CN_x^K(t)}{K}.$$

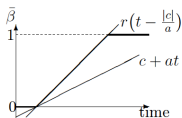
But  $y$  can also receive a contribution from  $x$  due to mutations:  $N_x^K(t)K^{-\alpha}$ .

**Previous lemma** :  $N_x^K(s \log K)K^{-\alpha}$  behaves as  $K^{c+as}$  with  $a, c \in \mathbb{R}$ .

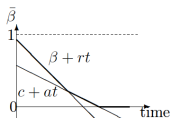
**Lemma** *Hypotheses of previous lemma* + *immigration* at rate  $K^c e^{at}$ , for  $a, c \in \mathbb{R}$ . Assume that  $c \leq \beta$  and either  $\beta > 0$  or  $c \neq 0$ . Then,

$$\left( \frac{\log(1 + \frac{Z_{s \log K}^K}{\log K})}{\log K}, s \in [0, T] \right) \xrightarrow{K \rightarrow +\infty} ((\beta + s(b-d)) \vee (c + as) \vee 0, s \in [0, T]),$$

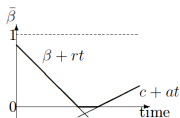
uniformly on any  $[0, T]$  and in probability.



(a):  $c < \beta = 0, 0 < a < r$



(b):  $0 < c < \beta, r < a < 0$



(c):  $c < 0 < \beta, r < 0 < a$

## Case of three traits

Three traits:  $0, \delta, 2\delta$  satisfying  $\delta < \tau < 2\delta < 3$ .

Recall that  $0 < \alpha < 1/2$  and that  $S(y; x) = x - y + \tau \text{sign}(y - x)$ .

At time 0,  $\beta^K(0) = (1, 1 - \alpha, 1 - 2\alpha)$ ,  $N_0^K(0) = \frac{3K}{C}$ .

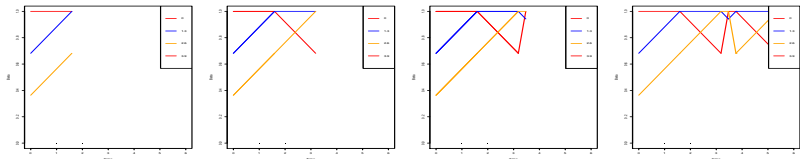
*First step:*

- **Trait  $\delta$ :**  $\beta_1(0) = 1 - \alpha$  and  $S(\delta; 0) = \tau - \delta > 0$ : then  

$$\beta_1(\mathbf{s}) = (1 - \alpha) + (\tau - \delta)\mathbf{s} \quad (\geq 1 - \alpha).$$
- **Trait  $2\delta$ :**  $\beta_2(0) = 1 - 2\alpha$  and  $S(2\delta; 0) = \tau - 2\delta < 0$  but there are mutations from trait  $\delta$ :  $\beta_2(\mathbf{s}) = (1 - 2\alpha) + (\tau - \delta)\mathbf{s}$ .

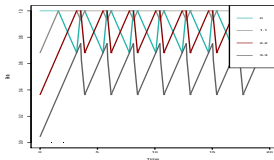
*Second step:*  $\delta$  becomes dominant. We compute the fitnesses, and so on...

For  $\delta = 1.3$ ,  $\alpha = 0.32$ ,  $\tau = 1.5$ :

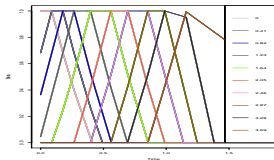


The system is periodic.

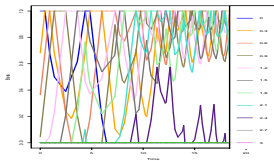
## Asymptotic behaviours



$\delta = 1.1, \alpha = 0.32, \tau = 1.3.$



$\delta = 0.41, \alpha = 0.32, \tau = 4.$



$\delta = 0.3, \alpha = 0.32, \tau = 1.$



## Main result

**Theorem** For  $i \in \{0, 1, \dots, \lfloor 1/\delta \rfloor\}$ ,

$$\left( \frac{\log(1 + N_{i\delta}(s \log K))}{\log K}, s \in [0, T] \right) \xrightarrow{K \rightarrow +\infty} (\beta_i(s), s \in [0, T])$$

uniformly on  $[0, T]$ , in probability,

where  $\beta_i$  is *continuous, piecewise affine and solution of a ODEs system* with  $\beta_i(0) = (1 - i\alpha) \vee 0$

and where *changes of slopes* of the exponents  $(\beta_0(s), \dots, \beta_{\lfloor 1/\delta \rfloor}(s))$  can occur at times where

- a new exponent reaches 1  $\rightsquigarrow$  *change of resident trait*
- a new exponent reaches 0  $\rightsquigarrow$  *extinction of the trait*
- The slope of an exponent which was driven by its fitness becomes driven by its mutations

## A discrete model - Small discretization mesh and mutation steps

- $C = \tau = 0$ .
- For any  $K$ , the trait space is a discretization of the torus  $\mathbb{T}$  :

$$\mathcal{X}_K := \left\{ i\delta_K : i \in \{0, 1, \dots, \lfloor \frac{1}{\delta_K} \rfloor\} \right\}.$$

- Birth rate :  $b(x)$  .
- Death rate :  $d(x)$ .

$b, d$  are Lipschitz continuous on  $\mathbb{T}$  and  $\forall x \in \mathbb{T}, b(x) > d(x)$ .

- **Small mutations**: an individual with trait  $x \in \mathcal{X}_K$  gives birth to a mutant with trait  $y \in \mathcal{X}_K$  at rate

$$p(x)\delta_K \log K G(\log K(x - y)) \text{ with } p \text{ positive and Lipschitz.}$$

- Discretization mesh  $\ll$  mutation scale:  $h^K := \delta_K \log K \ll 1$ .

- Mutation rate from an individual with trait  $x_K = [x/\delta_K]\delta_K$  of order  $\mathcal{O}(1)$ :

$$\lim_{K \rightarrow +\infty} p(x_K) \sum_{j=0}^{\frac{1}{\delta_K} - 1} h_K G(h_K([x/\delta_K] - j)) = p(x) \int_{\mathbb{R}} G(y) dy = p(x).$$

The different scalings:

- Large population :  $K \rightarrow +\infty$ .
- The individual mutations are not rare: individual mutation rate  $p(x)$ .
- The mutation steps are small: scale  $\frac{1}{\log K}$ .
- Long time scale:  $\log K$ .
- Discretization mesh  $\ll$  mutation scale.

Convergence, as  $K \rightarrow +\infty$ , of the exponent processes  $(\beta_i^K(t), i \in \{0, 1, \dots, \lfloor \frac{1}{\delta_K} \rfloor\})_{t \geq 0}$ , with

$$\beta_i^K(t) = \frac{\log(N_i^K(t \log K))}{\log(K)}.$$

For all  $x \in \mathbb{T}$  and  $K \geq 1$ , let  $i$  be such that  $x \in [i\delta_K, (i+1)\delta_K)$  and define

$$\tilde{\beta}^K(t, x) = \beta_i^K(t)(1 - \frac{x}{\delta_K} + i) + \beta_{i+1}^K(t)(\frac{x}{\delta_K} - i).$$

*Assumptions:*

(i)  $\exists a_1 > 0$  such that  $\forall K$  and  $\forall i \in \{0, 1, \dots, \frac{1}{\delta_K} - 1\}$ :  $\beta_i^K(0) \geq a_1$ .

(ii)  $\exists A > 0$ , such that  $\lim_{K \rightarrow \infty} \mathbb{P}\left(\sup_{i \neq j} \frac{|\beta_i^K(0) - \beta_j^K(0)|}{\rho(i\delta_K, j\delta_K)} > A\right) = 0$ .

## A Hamilton-Jacobi equation from the individual-based model

### Theorem

Assume that  $(\tilde{\beta}^K(0, \cdot))_K$  converges to a deterministic function  $\beta_0(\cdot)$  and assumptions above. Then the processes  $\tilde{\beta}^K$  converge in probability in  $\mathbb{D}([0, T], C(\mathbb{T}, \mathbb{R}))$  to the unique Lipschitz viscosity solution of the Hamilton-Jacobi equation (HJ)

$$\begin{cases} \frac{\partial}{\partial t} \beta(t, x) = b(x) - d(x) + p(x) \int_{\mathbb{R}} G(h) e^{h \partial_x \beta(t, x)} dh, & (t, x) \in \mathbb{R}_+ \times \mathbb{T} \\ \beta(0, x) = \beta_0(x), & x \in \mathbb{T}. \end{cases}$$

**Steps of the proof:** Compactness (tightness) - uniqueness argument.  
 $\tilde{\beta}^K(t, x)$  has a semi-martingale decomposition.

Control of the martingale increments.

Almost sure maximum principle on the increments of the finite variation part.

Almost sure identification of the limit as viscosity solution of (HJ).

**Thank you for your attention !**

