Exponent dynamics for branching processes
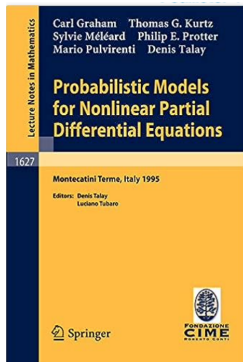
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A Random Walk in the Land of Stochastic Analysis and Numerical Probability, in honor of Denis Talay, CIRM 2023

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

A long friendship but no photos!

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, Diekmann 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.
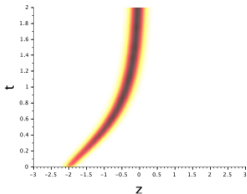
- **Stochastic individual-based processes** (birth and death processes with mutation and selection) :
  (Bolker-Pacala 97, Kisdi 99, Dieckmann-Law 00, Fournier-M. 04, Ferrière-Champagnat-M. 06, Champagnat 06, Champagnat-M. 10).

  Concentration phenomenon on advantageous mutants but evolution seems too slow (time scale separation between competition phases and mutation arrivals).
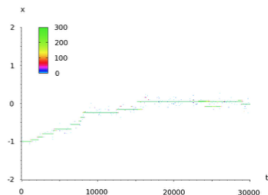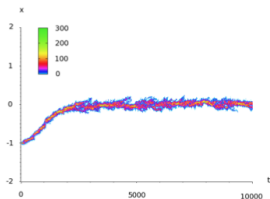
It is not clear how these models are related.

- 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^β, on the time scale $\log K$.

  ($\beta = 0$ means "extinction").

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

- First model : a joint work with N. Champagnat and V.C. Tran.

- The mutations are rare but not small ; The discretization mesh is fixed.

- Second model : a joint work with N. Champagnat, S. Mirrahimi and V.C. Tran.

- The mutations are small but not rare; The 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.

$$x = i\delta \in [0, 1], \qquad i \in \left\{0, \ldots \lfloor \frac{1}{\delta} \rfloor\right\}.$$

- **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 $d(x) = d + C \dfrac{N^K}{K}$; $d < 1$.

- **Unilateral transfer**: $(x, y) \to (y, y)$ at rate $\dfrac{\tau}{N^K} \mathbf{1}_{y > x}$.

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.

- It is well known that, when K tends to infinity, the total population size can be approximated by $K\,n(t)$ where $n(.)$ solves the ODE

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

  whose unique positive stable equilibrium is given by
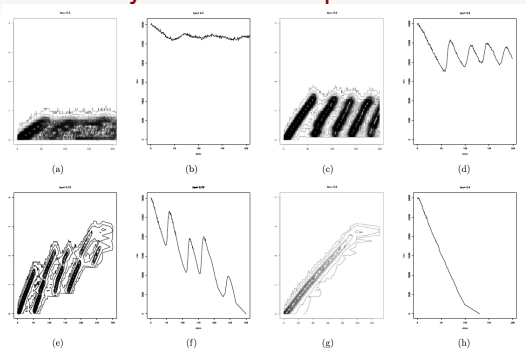
$$\overline{n}(x) = \frac{1 - d - x}{C}.$$

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

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

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

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

Dynamics of the process

(a)   (b)   (c)   (d)

(e)   (f)   (g)   (h)

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

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): $\tau = 0.6$: cycli 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.

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

Then we study, for all $i \in \{0, 1, \ldots, \lfloor 1/\delta \rfloor\}$, 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 $K \to +\infty$.

Exponents for 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,*

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

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

Note that

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

Therefore,

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

Exponents for birth and death processes with immigration

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:

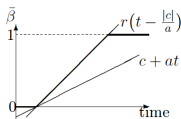$$4 - y + \tau \quad \text{et} \quad 1 + \frac{CN_x^K(t)}{K}.$$

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

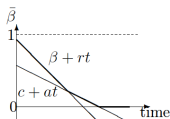Previous lemma : $N_x^K(s \log K)K^{-\alpha}$ behaves as K^{c+as} with $a, c \in \mathbb{R}$.

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,*

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

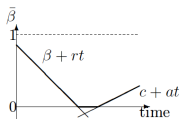$$s \in [0, T]),$$

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

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

First step:
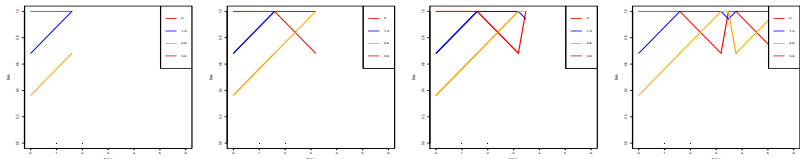- **Trait** δ: $\beta_1(0) = 1 - \alpha$ and $S(\delta;0) = \tau - \delta > 0$: then
$$\beta_1(s) = (1 - \alpha) + (\tau - \delta)s \qquad (\geq 1 - \alpha).$$

- **Trait** 2δ : $\beta_2(0) = 1 - 2\alpha$ and $S(2\delta;0) = \tau - 2\delta < 0$ but there are mutations from trait δ: $\beta_2(s) = (1 - 2\alpha) + (\tau - \delta)s$.
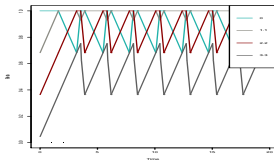
Second step: δ becomes dominant. We compute the fitnesses, and so on...

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

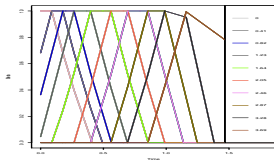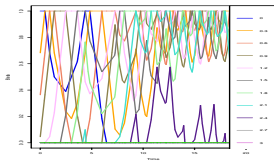The system is periodic.

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 $i \in \{0, 1, \ldots, \lfloor 1/\delta \rfloor\}$,*

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

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

where β_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 $(\beta_0(s), \ldots, \beta_{\lfloor 1/\delta \rfloor}(s))$ can occur at times where

- *a new exponent reaches 1 ⤳ change of resident trait*

- *a new exponent reaches 0 ⤳ extinction of the trait*

- *The slope of an exponent which was driven by its fitness becomes driven by its mutations*

Dynamics of $\beta_0(s)$

The function $\beta_0(s)$ is piecewise affine and the slopes are defined by their values at points $s_i = \frac{i\alpha}{\tau - \delta}$, ($\tau > \delta$).

$\beta_0\left(s_i\right) = 1 - \frac{\alpha(i-1)}{\tau - \delta}\left(\tau - \frac{i}{2}\delta\right)$; minimal value for $i^* := \lceil \frac{\tau}{\delta} \rceil$, equal to

$M_0 = 1 - \frac{\alpha(i^* - 1)}{\tau - \delta}\left(\tau - \frac{i^*}{2}\delta\right)$.

Theorem.

- If $M_0 > 0$ and $i^* < \lceil \frac{3}{\delta} \rceil$, *There is resurgence of trait* 0.
  [open question: is there a periodic solution?]

- If $M_0 < 0$ and $i^* < \lceil \frac{3}{\delta} \rceil$, *trait* 0 *is lost and we have extinction.*

- If $i^* \geq \lceil \frac{3}{\delta} \rceil$, $\rightsquigarrow$ *Case not yet fully understood.*

• It seems really difficult to go further with probabilistic tools.

• Alternative approach: to derive a Hamilton-Jacobi equation when $\delta \to 0$ and work with analytical tools.

A discrete model - Small discretization mesh and mutation steps

- $C = \tau = 0$.

- For any K, the trait space is a discretization of the torus $\mathbb{T}$:
$$\mathcal{X}_K := \left\{ i\delta_K : i \in \{0, 1, \cdots, \lfloor \tfrac{1}{\delta_K} \rfloor\} \right\}.$$

- 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

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

- 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 $\mathcal{O}(1)$:

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

The different scalings:

- Large population : $K \to +\infty$.

- 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 $K \to +\infty$, of the exponent processes $(\beta_i^K(t), i \in \{0, 1, \cdots, \lfloor \frac{1}{\delta_K} \rfloor\})_{t \geq 0}$, 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

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

Assumptions:

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

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

A Hamilton-Jacobi equation from the individual-based model

Theorem

Assume that $(\widetilde{\beta}^K(0, \cdot))_K$ converges to a deterministic function $\beta_0(\cdot)$ and assumptions above. Then the processes $\widetilde{\beta}^K$ 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.*
$\widetilde{\beta}^K(t, x)$ 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).

Cher Denis,