Metastability between the clicks of the Muller ratchet

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Deleterious mutations invade any population,
-> How efficiently regulated are the events of fixation
in an **asexual** reproduction mode ?

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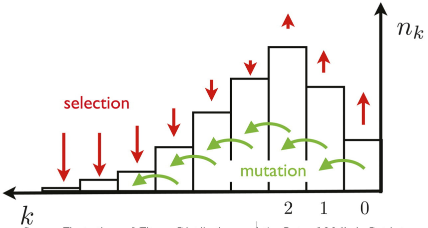
-> How efficiently regulated are the events of fixation
in an **asexual** reproduction mode ?

Muller's ratchet model

A simplified description:

- purely **deleterious** mutations
- **offspring number** simply prescribed through the **number of mutations** carried by the parent
- deleterious mutations **added independently** at each generation

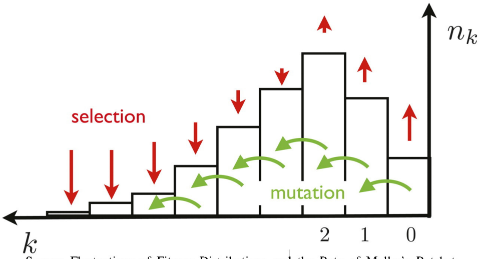


Click and survival

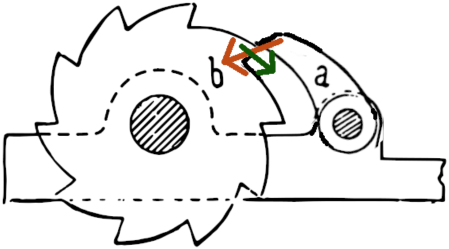
Survival: individuals without mutations can be found

⇒ no click up to the observation time

Click: punctual event at which the last individual carrying no mutation dies without similar offspring



Source: Fluctuations of Fitness Distributions and the Rate of Muller's Ratchet, by Richard A. Neher and Boris I. Shraiman



The intuition behind the term of ratchet

mullersratchet.wordpress.com/2012/08/14/why-mullers-ratchet/

Asymptotic Comparison of Survival

$$\limsup_{t\to\infty} \sup_{x\in\mathbb{X}} \frac{\mathbb{P}_x(t<\tau_\partial)}{\mathbb{P}_\zeta(t<\tau_\partial)} < \infty.$$

- Start with a stochastic model with a notion of **survival**
- Compare the probability of survival at time t (denoted as the event $\{t<\tau_\partial\}$)

Crucial step in the proof of quasi-stationarity:

$$\mathbb{P}_x(X_t\in dy,\ t<\tau_\partial) \sim e^{-\rho t} h(x)\,\nu(dy).$$

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- Start with a stochastic model with a notion of **survival**
- Compare the probability of survival at time t

  (denoted as the event $\{t < \tau_\partial\}$)

  as time **t** goes to infinity

  between several initial conditions:

  $x \in \mathbb{X}$ (**generic**) compared to ζ (fixed **reference** measure)

Crucial step in the proof of quasi-stationarity:

$$\mathbb{P}_x(X_t \in dy,\ t < \tau_\partial) \sim e^{-\rho t} h(x)\, \nu(dy).$$

Context in my research

- Overview
- Contributions already obtained, in two main directions
- Large time asymptotic

Muller's ratchet model in detail

- The discrete model
- The infinite-dimensional diffusion model
- The finite-dimensional diffusion model

Elements of proof

’17-20 PhD in Mathematics, **I2M**, Aix-Marseille Univ.
E. Pardoux, *M. Kopp* (AMU), *D. Kim* (Kumamoto)

’15-16 M2: **Mathematics for Life Sciences** (Orsay)

2013-17 Student at **Ecole Normale Supérieure** (Paris)

4 postdoctoral positions:

'25- at **LaMME**, University of Evry Paris-Saclay
D. Loukianova (LaMME), *E. Löcherbach* (SAMM)

'23-24 **MaIAGE**, Inrae, Jouy-en-Josas
V. Bansaye (CMAP), *P. Hoscheit* (MaIAGE), *G. Pang* (Rice, USA)

'22-23 **LAMA**, Gustave Eiffel University, Marne-la-Vallée
P-A. Zitt (LAMA), *J.-F. Delmas* (Ponts) *C. Tran* (Iria de Lille)
P. Frasca, F. Garin (Gispa-Lab in Grenoble)

'20-21 Institute for Mathematics, **Goethe University**, Frankfurt
C. Pokalyuk (Lübeck), *T. Krueger* (Wroclaw, Poland)

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1. Velleret, A.; Individual-based models under various time scales; **ESAIM:Proceedings and Surveys**, 2020
2. Velleret, A.; Unique Quasi-Stationary Distribution, with a stabilizing extinction, **Stochastic Processes and Applications**, 2022
3. Velleret, A.; Exponential quasi-ergodicity for processes with discontinuous trajectories, **ESAIM: Probability and Statistics**, 2023
4. Velleret, A.; Adaptation of a population to a changing environment in the light of quasi-stationarity, **Advances in Applied Probability**, 2024
5. Velleret, A.; Two-level natural selection with a quasi-stationarity approach; **Discrete and Continuous Dynamical Systems Series B**, 2024
6. *with* Delmas, J-F., Frasca, P., Garin, F., Tran, C., Zitt, P-A.; Individual-based SIS models on (not so) dense large random networks, **ALEA: Probab. Math. Stat.**, 2024
7. *with* Mariani, M., Pardoux, E.; Metastability between the clicks of the Muller ratchet; **Probab. Theory Related Fields**, in press
8. *with* Bezborodov, V., Krueger, T., Pokalyuk, C., Szymanski, P.; Inter-city infections and the role of size heterogeneity in containment strategies. revision submitted to Journal of Theoretical Biology,
9. *with* Kim, D. and Tagawa, T.; Quasi-ergodic limits for Feynman-Kac semigroups and large deviations for additive functionals, submitted
10. *with* Pang, G., Pardoux, E.; SIR model on inhomogeneous graphs with infection-age dependent infectivity, submitted

I. Large time asymptotic

Quasi-stationarity, ergodicity, metastability
and large deviations of stochastic processes:
such as Brownian diffusion,
EDS driven by Poisson point processes,
including PDMP (pure jump processes, growth-fragmentation)
Applications: Theoretical ecology (notion of adaptation)

II. Large population limits of particle systems

- Convergence of measure-valued processes
  empirical measure at time t over the entire population
- Random graphs (of interaction)
- Propagation of chaos, coupling (of point processes..)

Applications: Epidemiology, Neuroscience

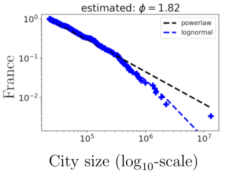
III. The Address of Reality

- Simulation of stochastic processes
- Manipulation and analysis of real data
- Synthesis and model reduction
- Visualization of results
  (convergence properties and representation of emerging structures)

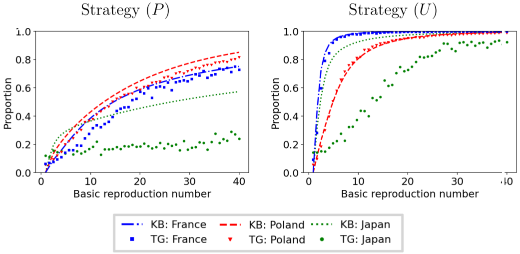
One preprint in revision at Journal Theoretical Biology,

regarding the representation of regional regulation strategies on a country-level

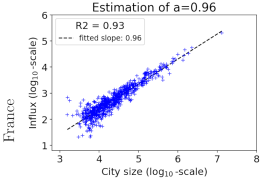
Estimation of the power-law coefficient



Mean proportion of people under isolation



Influx



Exponential quasi-stationary convergence

There exist characteristics (ρ, h, ν) and constants $C, \gamma > 0$ such that:

$$\left\| \exp(\rho t) \cdot \int_{\mathbb{X}} \mathbb{P}_y\Big(X_t \in dx \ ; \ t < \tau_\partial\Big)\mu(dy) - \Big(\int_{\mathbb{X}} h(y)\mu(dy)\Big) \cdot \nu(dx) \right\|_{TV} \leq C \cdot \exp(-\gamma t),$$

for any **probability measure** μ on $\mathbb{X}$ as an **initial condition**

and for all time $t > 0$, where τ_∂ is the **extinction time**.

(ρ, h, ν) important for applications

Establishment of new criteria specifically tailored

notably to the three previous adaptation issues

Velleret 2022 Stoch. Proc. Appl.

Velleret 2023 ESAIM Probab. Stats.

Generic property crucial in the next 3 publications

More conventional formulation:

Quasi-stationary convergence

$$\left\| \mathbb{P}_{\mu}\left(X_t \in dx \,\middle|\, t < \tau_\partial\right) - \nu(dx) \right\|_{TV} \leq \frac{C}{\int_{\mathbb{X}} h(y)\mu(dx)} \cdot \exp(-\gamma t).$$

Contribution: denominator with an interpretation

Justification of quasi-stationarity

Coupling of marginal laws **according to the initial condition**:

- $(A1)$ **Mixing**, by local lower-bound on the semigroup via a reference measure ζ (related to Doeblin estimates)
- $(A2)$ **Escape from the transient domain**, distance from the boundary (by repulsion or counter-absorption), in comparison with an estimate of survival rate
- $(A3)$ **Asymptotic comparison of survival**, estimate in the long term $$\limsup_{t\to\infty} \sup_{x\in\mathbb{X}} \frac{\mathbb{P}_x(t<\tau_\partial)}{\mathbb{P}_\zeta(t<\tau_\partial)} < \infty.$$
    - $(A3_F)$ **Almost perfect harvest**, the events to be controlled occur over a finite time period.

Applications: 3 stakes of adaptation under consideration

demographic dynamics associated with selective processes:

- ▷ Resilience to environmental change

  Velleret 2024 Adv. Appl. Probab.

- ▷ Perenity of collaboration within groups

  Velleret 2024 Disc. Cont. Dyn. Sys.-B

- ▷ Counter-selection of deleterious mutations

  Mariani, Pardoux, Velleret, in press PTRF

The notion of adaptation is related to that of metastability
via the results of quasi-stationarity

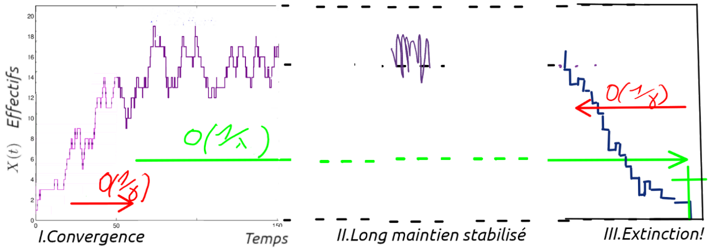
What does it mean for a population to **adapt**?

Motivation from theoretical ecology hard to translate mathematically

Characteristics of the quasi-stationary regime

- $\rho > 0$: the **extinction rate**
- $\gamma > 0$: delicate quantification, partially clarified by theoretical proofs
  comparison with ρ: criterion of **adaptation**, of **metastability**
- $h(x)$
- $\nu(dx)$

$$\left\| e^{\rho t} \cdot \int_{\mathbb{X}} \mathbb{P}_y\Big(X_t \in dx \;;\; t < \tau_\partial\Big)\mu(dy) - \Big(\int_{\mathbb{X}} h(y)\mu(dy)\Big) \cdot \nu(dx) \right\|_{TV} \leq C \cdot e^{-\gamma \cdot t},$$

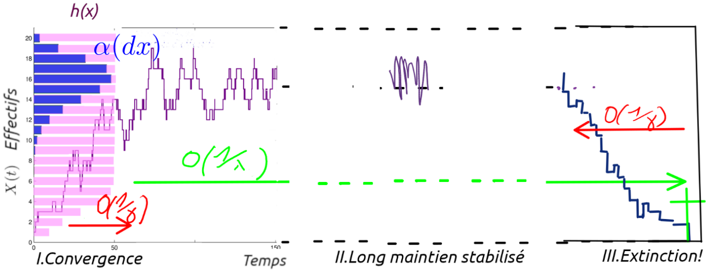


Characteristics of the quasi-stationary regime

- ▷ $\rho > 0$: the **extinction rate**
- ▷ $\gamma > 0$: delicate quantification, partially clarified by theoretical proofs
  comparison with ρ: criterion of **adaptation**, of **metastability**
- ▷ $h(x)$: summarizes the dependence on the **initial condition**
  with respect to the survival of the process *(as a function)*
- ▷ $\nu(dx)$: summarizes the dependence on the **final state** of the process

Typical configuration conditioned on survival *(as a probability measure)*

$$\left\| e^{\rho t} \cdot \int_{\mathbb{X}} \mathbb{P}_y\Big(X_t \in dx \; ; \; t < \tau_\partial\Big)\mu(dy) - \Big(\int_{\mathbb{X}} h(y)\mu(dy)\Big) \cdot \nu(dx) \right\|_{TV} \leq C \cdot e^{-\gamma \cdot t},$$



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The discrete model

The illustrative setting in the PTRF paper:

- N individuals at each generation

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- N individuals at each generation
- each offspring chooses independently its parent:
  the probability of choosing parent ℓ with i mutations
  is proportional to $e^{-\alpha i}$
- the mutations of the parent are given to the offspring
- Poisson number of mutations added

Main setting in the PTRF paper:
individuals have almost identical life-expectancies

Extension :

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Extension :

- consider small selective effects ($\alpha \to 0$), considered with a large number of generations
- only keep track of the proportion X_i of individuals carrying i mutations ($i \in \mathbb{Z}_+$)
- adjust the small rate of mutations -> λ
- large population limit ($N \to \infty$), with still demographic fluctuations remaining

The infinite dimensional model

For $i \in \mathbb{Z}_+$:

$$\begin{aligned} dX_i(t) = \alpha(M_1(t) - i)\, X_i(t)\, dt + \lambda(X_{i-1}(t) - X_i(t))\, dt \\ + \sqrt{X_i(t)}\, dW_t^i - X_i(t)\, dW_t \end{aligned}$$

where $W_t := \sum_{j=0}^{\infty} \int_0^t \sqrt{X_j(s)} dW_s^j, \quad M_1(t) := \sum_{i=0}^{\infty} i\, X_i(t),$

with $(W^i)_{i \geq 0}$ a family of mutually independent Brownian Motions.

State space $\mathbb{X}$: configuration with a finite six-order moment $(x_i)_{i \in [\![0,d]\!]} \in [0,1]^{d+1}$, with $x_0 > 0$, $\sum_{i=0}^{d} x_i = 1$ and $\sum_{i=0}^{d} i^6\, x_i < \infty$.

Truncation at a maximum of d mutations:

The finite dimensional model

For $i \in [\![0, d]\!]$:

$$dX_i(t) = \alpha(M_1(t) - i)\, X_i(t)\, dt + \lambda(X_{i-1}(t) - 1_{\{i<d\}} X_i(t))\, dt \\ + \sqrt{X_i(t)}\, dW_t^i - X_i(t)\, dW_t$$

where $W_t := \sum_{j=0}^{d} \int_0^t \sqrt{X_j(s)} dW_s^j, \quad M_1(t) := \sum_{i=0}^{d} i\, X_i(t),$

with $(W^i)_{i\geq 0}$ a family of mutually independent Brownian Motions.

State space: any configuration $(x_i)_{i\in[\![0,d]\!]} \in [0,1]^{d+1}$, with $x_0 > 0$ and $\sum_{i=0}^{d} x_i = 1$.

We aim for the following implication for all $t > 0$ and $\mu \in \mathcal{M}_1(\mathbb{X})$:

$$\frac{\mu P_t(dx)}{\mathbb{P}_\mu(t < \tau_\partial)} \geq c \cdot \zeta(dx)$$

$$\Rightarrow \forall\, s > 0,\ \frac{\mu P_{t+s}(dx)}{\mathbb{P}_\mu(t + s < \tau_\partial)} \geq c \cdot c_* \cdot \frac{\zeta P_s(dx)}{\mathbb{P}_\zeta(s < \tau_\partial)}.$$

Non-degeneracy to justify:
the contribution of the coupling step

must be non-negligible in the long term.

A3: Asymptotic comparison of survival

$$\limsup_{t\to\infty} \sup_{x\in\mathbb{X}} \frac{\mathbb{P}_x(t < \tau_\partial)}{\mathbb{P}_\zeta(t < \tau_\partial)} < \infty.$$

How to prove the asymptotic comparison of survival?

$$\limsup_{t\to\infty} \sup_{x\in\mathbb{X}} \frac{\mathbb{P}_x(t<\tau_\partial)}{\mathbb{P}_\zeta(t<\tau_\partial)} < \infty?$$

Discrete model:

If the process can (effectively) reach a state x from the initial condition ζ,

then the survival from x entails the survival from ζ.

In particular, for any finite set F:

$$\limsup_{t\to\infty} \sup_{x\in F} \frac{\mathbb{P}_x(t<\tau_\partial)}{\mathbb{P}_\zeta(t<\tau_\partial)} < \infty.$$

Finite set F: the number of mutations
carried by one individual stays bounded.

τ_E : first hitting time of :

$$E := \{ \text{ no individual with more than } L \text{ mutations}\}.$$

$\tau_\partial \wedge \tau_E$ has fine exponential moment for $L \geq 1$ large enough
exponent larger than the asymptotic rate of survival from ζ.

Complexity of the infinite dimensional model

- Continuum of states
- Density not tractable in infinite dimension
- Gather $(X_i)_{i \geq k}$ into $X_{(k)} := \sum_{i \geq k} X_i$
  and control the discrepancies
- Almost perfect harvest

  to be deduced with the Girsanov transform, with comparison properties between processes and with known properties of one-dimensional diffusions

$(A3_H)$: Almost perfect harvest

E to be adjusted for convenience
ζ, and $\rho > \rho_S[\zeta]$ from elsewhere

For all $\epsilon \in (0,\ 1)$, there exist $t, c > 0$
with the following property for all $x \in E$.
There exist two stopping times U_H and V such that:

$$\mathbb{P}_x\big(X(U_H) \in dx'\,;\ U_H < \tau_\partial\big) \leq c\,\mathbb{P}_\zeta\big(X(V) \in dx'\,;\ V < \tau_\partial\big),$$
$$\{U_H > \tau_\partial \wedge t_F\} = \{U_H = \infty\},$$
$$\mathbb{P}_x(U_H = \infty,\ t_F < \tau_\partial) \leq \epsilon\, \exp(-\rho\, t_F).$$

+ regularity conditions (on U_H)
automatic if Ω is pathwise (Markov property)

Harvest: what can be achieved with the first estimate between densities

Confined regions, for $\ell \geq 1$:

$$\mathcal{D}_\ell := \left\{ x \in \mathcal{X}_d \,;\; x_0 \geq \frac{1}{2\ell} \right\},$$

$$\zeta(\mathrm{d}x) := \int_{\mathbb{X}_d} \mathbb{P}_z \left(X(1) \in \mathrm{d}x \,\middle|\, \tau_0^{(2)} < 1 < T_{\mathcal{D}_3} \right) \nu(\mathrm{d}z)\,,$$

where the measure ν is defined as follows:

$$\nu(\mathrm{d}z) := \frac{1_{\{z \in \mathcal{R}_y\}}}{\mathcal{Z}} \mathbb{P}_z \Big(\pi_2(X(2)) \in \mathrm{d}z \,;\; 1 < T_y^2 \wedge T_{m_D}^{(3)} \Big),$$

$$\mathcal{R}_y := \Big\{ z = (z_0, z_1, 1 - z_0 - z_1) \,;\; z_0 \in (1 - 5y, 1 - 4y)\,,\; z_1 \in (2y, 3y) \Big\}.$$

while $z \in \mathcal{R}_y$ is seen as an element of $\mathbb{X}_d$ by defining $z_k = 0$ for any $k \in [\![3, d]\!]$, $\mathcal{Z}$ a normalizing constant.

Given ϵ, 6 parameters to be adjusted (here E depends on ϵ)

- small times $t_H, t_B \in (0, 1/3)$
- small $z > 0$: vicinity of extinction for 1D diffusion
- large m_M: which level for the third moment
- large J : up to how many classes of mutations
- small y: distance to the boundary

U_H: the harvesting time

$$\widehat{\tau}_0^{(J)} := \inf\Big\{t \geq \tau_E + t_H \,;\; X_{(J)}(t) = 0\Big\}.$$

$U_H := \widehat{\tau}_0^{(J)}$ on the following event:

$$\Big\{\tau_E < \tfrac{1}{3}\Big\} \cap \Big\{\tau_E + t_H < \widehat{T}^J_{y/2}\Big\} \cap \Big\{\widehat{\tau}_0^{(J)} < (\tau_E + t_H + t_B) \wedge \widehat{T}^{(3)}_{m_M} \wedge \tau_\partial\Big\}$$

and otherwise $U_H := \infty$, where:

$$\widehat{T}^J_{y/2} := \inf\Big\{t \geq \tau_E \,;\; \pi_J(X(t)) \notin \mathcal{Y}_J(y/2)\Big\},$$

$$\widehat{T}^{(3)}_{m_M} := \inf\Big\{t \geq \tau_E + t_H \,;\; M_3(t) \geq m_M\Big\}.$$

Conclusion

Exponential quasi-stationary convergence

There exist $C, \gamma > 0$ such that the following characterizing property of (ρ_d, h_d, ν_d) holds for any $d \in [\![3, \infty]\!]$:

$$\left\|\exp(\rho_d t) \cdot \mathbb{P}_\mu\left(X_t^{(d)} \in dx \ ; \ t < \tau_\partial^{(d)}\right) - \left(\int_{\mathbb{X}_d} h_d(y)\mu(dy)\right) \cdot \nu_d(dx)\right\|_{TV} \leq C \cdot \exp(-\gamma t),$$

for any **probability measure** μ on $\mathbb{X}_d$ as an **initial condition**

and for all time $t > 0$, where τ_∂ is the **extinction time**.

In addition, for any $y_0 \in (0,1)$, $h^{(\infty)}$ is lower-bounded by a positive constant on $\{x \in \mathbb{X}_\infty \ ; \ x_0 \geq y_0\}$.

The criterion $\rho_d < \gamma$ for metastability has a reasonable meaning even for large d (possibly infinite).