Piecewise Deterministic Markov Processes and Bacterial Growth

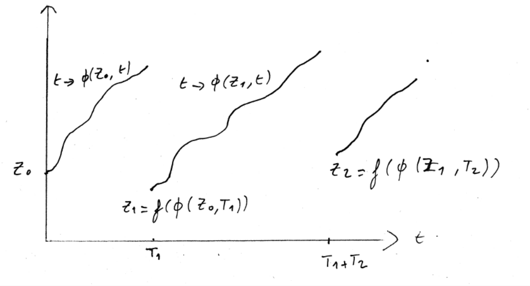
B. Cloez, B. De Saporta, M. Doumic, M. Hoffmann, N. K., L. Robert , T. Roget and Emeline Schmisser

Montpellier, INRIA, Dauphine, Rennes 2, INRA, Lille

MaSeMo, 1st July, 2025

Table of contents

The PDMP $(X(t))_{t\geq 0}$ depends on the jump rate λ, the flow ϕ and a deterministic increasing function f.



$$\mathbb{P}_x(T_1 > t) = e^{-\int_0^t \lambda(\phi(x,s))ds}$$

and Z_i the post jump location after the i-th jump.

✏K. ESAIM : P.S. 2016.

Some references

Fujii Journal of Applied Probability 2013.

Azaïs, Dufour, Gégout-Petit. Scand. J. Stat. 2014.

Bouguet. ESAIM: P.S. 2015.

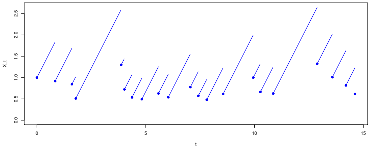
Azaïs, Muller-Gueudin. Electron. J. Stat. 2016.

Azaïs, Genadot. Comm. Statist. Theory Methods. 2018.

Azaïs, and Denis arXiv 2025.

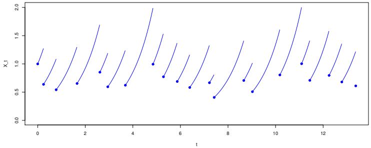
Figure: Exemples of simulations of processes (X) et (Z_k) for $f(x) = x/2$

TCP protocol



$\phi(x,t) = x + t,\ \lambda(x) = \sqrt{x}$

Bacterial growth



$\phi(x,t) = xe^t,\ \lambda(x) = x^2$

• : process Z_k $\quad$ – : process X

Table of contents

Statistical estimation

- To the Piecewise Deterministic Markov processes, we associate the microscopic model

$$\big(Z_n, T_n, n \in \mathbb{N}\big).$$

- The dynamic is determined by the jump rate $\lambda(x)$, the flow ϕ, and the division function f.
- We want to estimate nonparametrically $x \rightsquigarrow \lambda(x)$.
- We observe the process until its n-th jump.
- Observation scheme

$$\boxed{\big\{(Z_i, T_i), \quad i \leq n.\big\}}$$

- Asymptotics taken as $n \to \infty$.

Statistical estimation

We have

$$\mathbb{P}(T_n \in [t, t+dt] \,|\, T_n \geq t, Z_n = x) = \lambda(\phi(x,t))dt$$

from which we obtain the density of the jump time T_n conditional on $Z_n = x$:

$$\boxed{t \rightsquigarrow \lambda(\phi(x,t)) \exp\Big(- \int_0^t \lambda(\phi(x,v))dv \Big).}$$

The explicit transition

- Using $Z_{n+1} = f(\phi(Z_n, T_n))$, we further infer

$$\mathcal{P}_\lambda(x,y) = \lambda(f^{-1}(y))e^{-\int_{f(x)}^{y} \lambda(f^{-1}(s))g_x(s)ds} g_x(y)\mathbb{1}_{\{y \geq f(x)\}}$$

  where

$$g_x(y) = \left[(f \circ \phi_x)' \left((f \circ \phi_x)^{-1}(y)\right)\right]^{-1}$$

  and $\phi_x(.) := \phi(x, .)$.
- Under appropriate condition on λ, the Markov chain on $\mathbb{R}^+$ is geometrically ergodic. (It is however not reversible.)

Some references

Bertrand Cloez. Arxiv. 2012.

Bardet, Christen, Guillin, Malrieu, and Zitt. Electron. J. Probab. 2013.

Bouguet. ESAIM: PS. 2015.

Identifying λ through the invariant measure

- Under some assumptions, we have existence (and uniqueness) of an invariant measure on $\mathbb{R}^+$, *i.e.* such that $\nu_B \mathcal{P}_B = \nu_B$.
- More precisely, we have a contraction property

$$\sup_{|g| \leq V} \left| \mathcal{P}_\lambda^k g(\boldsymbol{x}) - \int g(\boldsymbol{z}) \nu_\lambda(d\boldsymbol{z}) \right| \leq RV(\boldsymbol{x}) \gamma^k$$

uniformly in $\lambda \in \mathcal{E}$, for an appropriate Lyapunov function V.

Identifying λ through the invariant measure

$$\begin{aligned}\nu_\lambda(y) &= \int_E \nu_\lambda(x)\mathcal{P}_\lambda(x,y)\mathbb{1}_{\{f(x)\leq y\}}dx \\ &= \int_E \nu_\lambda(x)\lambda(f^{-1}(y))e^{-\int_{f(x)}^{y}\lambda(f^{-1}(s))g_x(s)ds}g_x(y)\mathbb{1}_{\{f(x)\leq y\}}dx\end{aligned}$$

thank to "Survival analysis trick"

$$e^{-\int_{f(x)}^{y}\lambda(f^{-1}(s))g_x(s)ds} = \int_y^\infty \lambda(f^{-1}(s))g_x(s)e^{-\int_{f(x)}^{s}\lambda(f^{-1}(s'))g_x(s')ds'}ds$$

and as we recognize $\mathcal{P}_\lambda$... We obtain

$$\nu_\lambda(y) = \lambda(f^{-1}(y))\int_E \nu_\lambda(x)g_x(y)\mathbb{1}_{\{f(x)\leq y\}}\int_y^\infty \mathbb{1}_{\{s\geq y\}}\mathcal{P}_\lambda(x,s)dsdx$$

Thus

$$\nu_\lambda(y) = \lambda(f^{-1}(y))\mathbb{E}_{\nu_\lambda}[g_{Z_0}(y)\mathbb{1}_{\{f(Z_0)\leq y\}}\mathbb{1}_{\{Z_1\geq y\}}]$$

Key representation

We conclude

$$\lambda(y) = \frac{\nu_\lambda(f(y))}{\mathbb{E}_{\nu_\lambda}[g_{Z_0}(f(y))\mathbb{1}_{\{f(Z_0)\leq f(y)\}}\mathbb{1}_{\{Z_1\geq f(y)\}}]},$$

We consider an orthonormal basis (φ_l) of S_m. Let us set

$$a_l =< \varphi_l, \nu_\lambda >= \int_{\mathcal{A}} \varphi_l(x)\nu_\lambda(x)dx \quad \text{and} \quad \nu_m(x) = \sum_{l=1}^{D_m} a_l \varphi_l(x).$$

The function ν_m is the orthogonal projection of ν_λ on $L^2(\mathcal{A})$. We consider the estimator

$$\hat{\nu}_m(x) = \sum_{l=1}^{D_m} \hat{a}_l \varphi_l(x) \quad \text{with} \quad \hat{a}_l = \frac{1}{n}\sum_{k=1}^{n} \varphi_l(Z_k).$$

Proposition

If $D_m^2 \leq n$, under some assumptions, for any $\lambda \in \mathcal{F}(\mathfrak{c}, b)$,

$$\mathbb{E}\left(\|\hat{\nu}_m - \nu_\lambda\|^2_{L^2(\mathcal{A})}\right) \leq \|\nu_m - \nu_\lambda\|^2_{L^2(\mathcal{A})} + C_{\mathfrak{c},b}\frac{D_m}{n} + \frac{c_{\mathfrak{c},b}}{n}$$

✏K., Schmisser. Bernoulli. 2021.

$$\hat{\mathbf{D}}_n(y) := \frac{1}{n}\sum_{k=1}^{n} g_{Z_{k-1}}(f(y))\mathbb{1}_{Z_k \geq f(y), y \geq Z_{k-1}}.$$

We can now consider the estimator

$$\hat{\lambda}_n(y) = \frac{\hat{\nu}_{\hat{m}}(f(y))}{\hat{\mathbf{D}}_n(y)}\mathbb{1}_{\hat{\nu}_{\hat{m}}(f(y)) \geq 0}\mathbb{1}_{\hat{\mathbf{D}}_n(y) \geq \ln(n)^{-1}}. \tag{1}$$

Theorem

Under some assumptions as soon as $\ln(n)^{-1} \leq D_0/2$*, for any* $\lambda \in \mathcal{E}(\bar{\mathfrak{c}}, b)$*,*

$$\mathbb{E}\left(\left\|\hat{\lambda}_n - \lambda\right\|^2_{L^2(\mathcal{I})}\right) \leq C_{\mathfrak{c},b}\ln^2(n)\left(\mathbb{E}\left(\|\hat{\nu}_\lambda - \nu_\lambda\|^2_{L^2(f(I))}\right) + \frac{1}{n}\right).$$

$$\sup_{\lambda \in \mathcal{E}(\bar{\mathfrak{c}}, b)\cap H^\alpha(M_1,\mathcal{I})} \mathbb{E}\left(\left\|\hat{\lambda}_n - \lambda\right\|^2_{L^2(\mathcal{I})}\right) \lesssim \ln^2(n) n^{-2\alpha/(2\alpha+1)}.$$

✏K., Schmisser. Bernoulli. 2021.

Theorem (Minimax bound)

Under some assumptions, we get

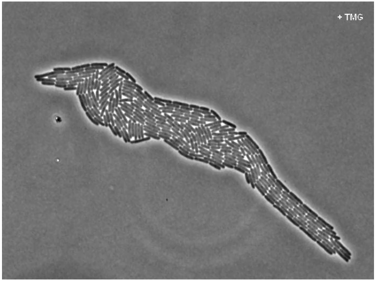
$$\inf_{\hat{\lambda}_n} \sup_{\lambda \in \mathcal{E}(\bar{\mathfrak{c}}, b) \cap H^{\alpha}(\mathcal{I}, M_1)} \mathbb{E}\left(\left\| \hat{\lambda}_n - \lambda \right\|^2_{L^2(\mathcal{I})} \right) \geq C n^{-2\alpha/(2\alpha+1)}.$$

where the infimum is taken among all estimators.

✏K., Schmisser. Bernoulli. 2021.

Table of contents

The data set of Stewart (2005) is the evolution of 88 microcolonies of *E. Coli* bacteria cultures.



Direct observations

The exponential growth for Bacteria is now, after much debate, commonly admitted:

$$x_t = x_0 e^{\tau t}.$$

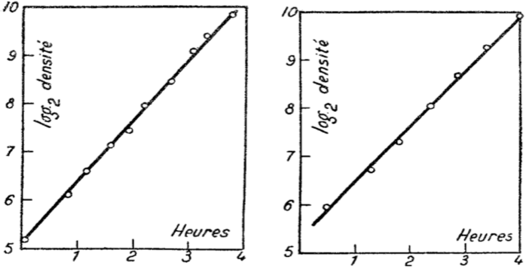


Fig. 10. — Phase exponentielle de la croissance d'une culture de *B. coli* en milieu synthétique, avec 300 mgr. par l. de glucose. Coordonnées semi-logarithmiques.

Fig. 11. — Phase exponentielle de la croissance d'une culture de *B. subtilis* en milieu synthétique, avec 500 mgr. par l. de saccharose. Coordonnées semi-logarithmiques.

Figure: Monod's 1942 thesis on *B. Coli* culture cells.

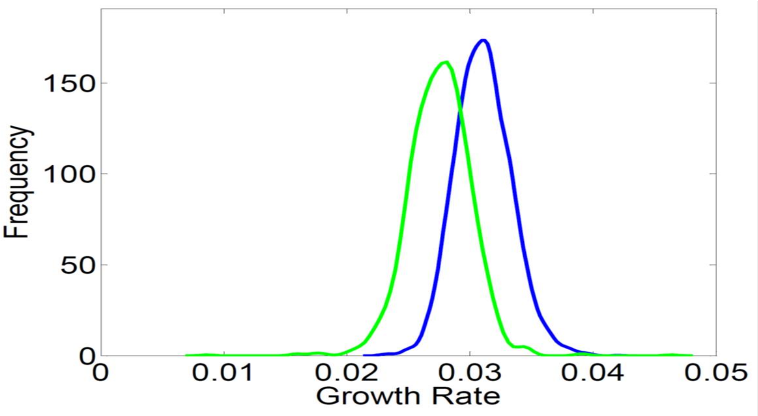
Models assumption:

The division rate B depends on

- size
- age (A. Olivier and M. Hoffmann. SPA. 2016.)
- nothing
- the increment of size (Adder model)
- and/or previous elements and/or something else...

✏Doumic, Hoffmann, K., Robert, Aymerich et Robert. BMC Biology. 2014.

Variability among exponential growth rates



In a first approach, we ignore variability and assume a constant τ for all cells.

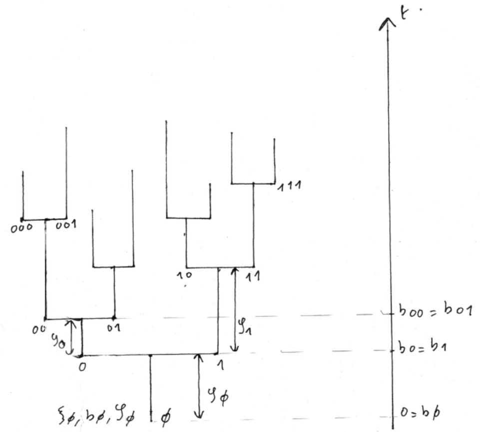
✏Delyon, de Saporta, K., Robert. CSBIGS. 2018.

Table of contents

The microscopic approach: constant growth rate

- Initially a singe cell of size x_0.
- Exponential growth $x_t = x_0 e^{\tau t}$.
- Two offsprings, at a rate $B(x_t)$. Division occurs at time T.
- The two offsprings have initial size $x_T/2$.
- And so on...

Figure: Random marked tree

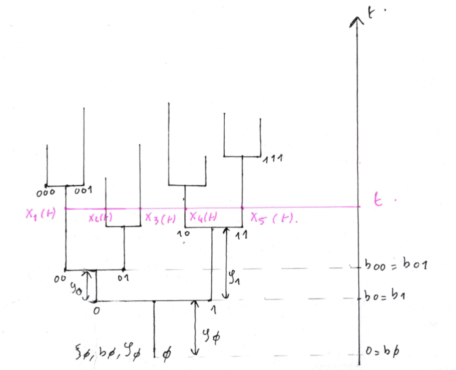


ξ_u the birth size $\quad$ b_u the birth time $\quad$ ζ_u the life time

$$u \in \{\emptyset, 0, 1, 00, 01, 10, 11, 000, \ldots\} \ .$$

The microscopic approach (cont.)

$X(t) = \big(X_1(t), X_2(t), \dots\big)$ process of the sizes of the population at time t.



$X_1(t) = \xi_{00} e^{\tau(t-b_{00})}$ ... $X_5(t) = \xi_{11} e^{\tau(t-b_{11})}$ ξ_u the birth size b_u the birth time ζ_u the life time

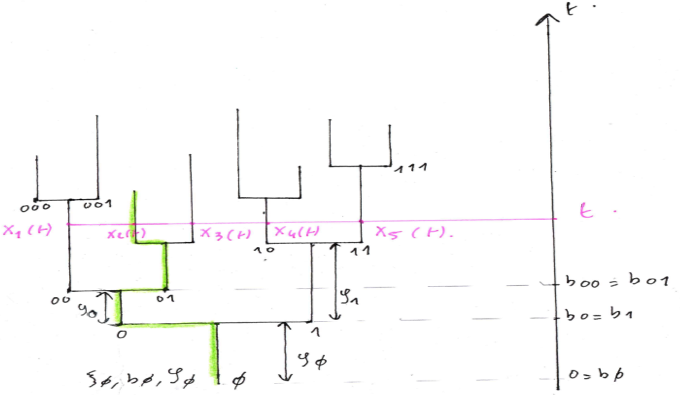
Main probabilistic tools

- Branching property
- Mass (size) conservation:

$$\sum_i X_i(t) = x_0 e^{\tau t}.$$

The tagged fragment approach

Pick a cell at random at each division and follow its size $\chi(t)$ through time. Inspired from fragmentation processes techniques (Bertoin, Haas, among others).



The tagged fragment approach

- $$\chi(t) = x_0 \frac{e^{\tau t}}{2^{N_t}}$$
  where N_t is the number of divisions of the tagged fragment up to time t.
- **$\chi(t)$ is a PDMP**
- This enables to obtain a many-to-one formula.

A many-to-one formula

- Exists in other contexts for Branching Markov processes in a general setting (*e.g.* Bansaye *et al.*, 2009, Cloez, 2011).
- We have,

$$\mathbb{E}\Big[f\big(\chi(t)\big)\Big] = \mathbb{E}\Big[\sum_i X_i(t)\frac{e^{-\tau t}}{x_0} f\big(X_i(t)\big)\Big]$$

from which we obtain

$$\mathbb{E}\Big[\frac{f\big(\chi(t)\big)}{\chi(t)} x_0 e^{\tau t}\Big] = \mathbb{E}\Big[\sum_i f\big(X_i(t)\big)\Big].$$

Transport-fragmentation equation

The mean empirical distribution

$$\boxed{\partial_t n_t(x) + \partial_x\big(\tau x n_t(x)\big) + B(x)n_t(x) = 4B(2x)n_t(2x)}$$

with $\langle n_t, f\rangle := \mathbb{E}\big[\sum_{i=1}^{\infty} f\big(X_i(t)\big)\big]$.

Main results of the global approach

In Doumic, Hoffmann, Rivoirard and Reynaud-Bouret SIAM J. Numer. Anal. 2012, if $B \in \mathcal{H}^s$, we have

$$\left(\mathbb{E}\left[\|\widehat{B}_n - B\|^2_{L^2(\mathcal{D})}\right]\right)^{1/2} \lesssim n^{-s/(2s+3)}.$$

This rate is provably min-max optimal.

Incorporating variability

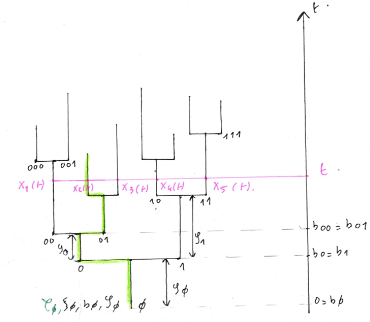
- To each cell labeled by u, we associate a random growth rate

$$\tau_u \in [e_{\min}, e_{\max}].$$

- Conditional on τ_{u-}, the variability is distributed according to a (nice) Markov kernel

$$\rho(\tau_{u-}, d\tau_u).$$

Figure: Random marked tree



ξ_u the size b_u the birth time ζ_u the life time τ_u the growth rate $X_1(t) = \xi_{00} e^{\tau_{00}(t-b_{00})}$ $Z_1(t) = \tau_{00}$

The corresponding many-to-one formula

- $\mathcal{G}_t$: the cumulate growth rate of the tagged-fragment.
- The many-to-one formula becomes

$$\mathbb{E}\Big[\frac{f\big(\chi(t),\tilde{Z}(t)\big)}{\chi(t)}x_0 e^{\mathcal{G}_t}\Big] = \mathbb{E}\Big[\sum_{i=1}^{\infty} f\big(X_i(t), Z_i(t)\big)\Big].$$

  where $\tilde{Z}(t)$ is the instantaneous growth rate of the tagged fragment.
- **$(\chi(t), \tilde{Z}(t))$ is a PDMP**

What of the transport-fragmentation PDE?

The mean empirical distribution

$$\partial_t n_t(x, a) + a\,\partial_x\big(x n_t(x, a)\big) + B(x) n_t(x, a)$$
$$= 4 \int_{\mathbb{R}_+} \rho(a', a) n_t(2x, a') da'.$$

with $\langle n_t, f(\cdot,\cdot)\rangle := \mathbb{E}\Big[\sum_{i=1}^{\infty} f\big(X_i(t), Z_i(t)\big)\Big].$

Table of contents

Statistical estimation

- The dynamic is determined by the division rate $B(x)$ and the variability kernel $\rho(a, da')$ (and an initial condition $(\xi_\emptyset, \tau_\emptyset)$.)
- Observation scheme

$$\boxed{\big\{(\xi_u, \zeta_u, \tau_u),\ \ u \in \mathcal{U}_n\big\}}$$

with

$$\boxed{\sharp\, \mathcal{U}_n = n}$$

- Asymptotics taken as $n \to \infty$.
- We want to estimate nonparametrically $x \rightsquigarrow B(x)$.

Key representation

- We get

$$\boxed{B(y) = \frac{y}{2}\frac{\nu_B(y/2)}{\mathbb{E}_{\nu_B}\Big[\frac{1}{\tau_{u^-}}\mathbf{1}_{\{\xi_{u^-}\leq y,\, \xi_u\geq y/2\}}\Big]}.$$

- Final estimator

$$\widehat{B}_n(y) = \frac{y}{2}\frac{n^{-1}\sum_{u\in\mathcal{U}_n} K_{h_n}(\xi_u - y/2)}{n^{-1}\sum_{u\in\mathcal{U}_n}\frac{1}{\tau_{u^-}}\mathbf{1}_{\{\xi_{u^-}\leq y, \xi_u\geq y/2\}}\bigvee\varpi_n},$$

is specified by a kernel function K, the bandwidth h_n and the threshold ϖ_n.

Proposition

Work under the previous assumptions. Specify

$$h_n = c_0 n^{1/(2s+1)}, \;\; \varpi_n = (\ln(n))^{-1}.$$

We have

$$\boxed{\mathbb{E}_\mu\Big[\|\widehat{B}_n - B\|^2_{L^2(\mathcal{D})}\Big]^{1/2} \lesssim (\ln(n))n^{-s/(1+2s)}}$$

uniformly in $B \in \mathcal{F} \cap \mathcal{H}^s(\mathcal{D})$ *.*

✏Doumic, Hoffmann, K., Robert. Bernoulli. 2015.

Numerical implementation

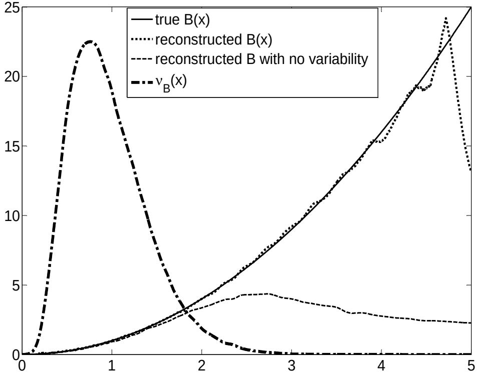


Figure: 100 Monte-Carlo estimations, dense tree case. Target function $B(x) = x$, $\tau = 1$. Reconstruction for $n = 2^{17}$ and $\varphi = n^{1/2}$.

Table of contents

The goal is to generalize what precedes to stick even more to the reality

- take into account the difference between "young" and "old" poles
- look at the Adder models
- allow that division does not give 2 bacteria of the same size

This is a work in progress with Bertrand Cloez, Benoîte de Saporta and Tristan Roget.

Two types.

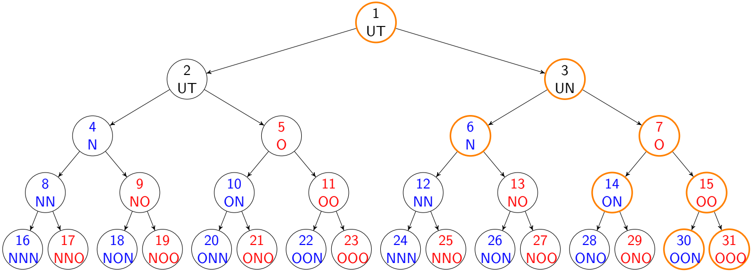
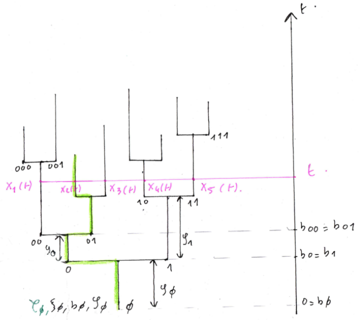


Figure: Cell division binary tree with the type of each cell

Figure: Random marked tree



ξ_u the size $\quad$ b_u the birth time $\quad$ ζ_u the life time $\quad$ τ_u the growth rate $\quad$ θ_u the proportion of the mother size

$$X_1(t) = \xi_{00} e^{\tau_{00}(t-b_{00})} \qquad Z_1(t) = \tau_0 \qquad \xi_{00} = \theta_0 \xi_0 e^{\tau_0 \zeta_0}$$

The corresponding many-to-one formula

- The many-to-one formula becomes $\mathbb{E}\left[\frac{f\left(\chi(t),\tilde{Z}(t),P(t)\right)}{\chi(t)}x_0 e^{\overline{\mathcal{V}}(t)}\right] = \mathbb{E}\left[\sum_{i=1}^{\infty} f\left(X_i(t), Z_i(t), P_i(t)\right)\right]$. where $\tilde{Z}(t)$ is the instantaneous growth rate, $\overline{\mathcal{V}}(t)$ accumulated growth rate and $P(t)$ type of the tagged bacterium.
- **$(\chi(t), \tilde{Z}(t), P(t))$ is a PDMP**
- We then have the representation

$$\chi(t) = xe^{\overline{\mathcal{V}}(t)}\theta_0^{C_t^o}\theta_1^{C_t^1} \tag{2}$$

with C_t^o the number of divisions resulting in a bacterium with a old pole and C_t^1 the one with a new pole.

What of the transport-fragmentation PDE?

The mean empirical distribution

$$\begin{cases} \partial_t n(t,x,v,i) + v\,\partial_x\big(xn(t,x,v,i)\big) + B(x)n(t,x,v,i) \\ = \int_{\mathcal{E}} \frac{\phi(x,v',0)}{\theta_0^2}\rho_0(v,dv')B(x/\theta_0)n(t,x/\theta_0,dv',i) \\ + \int_{\mathcal{E}} \frac{\phi(x,v',1)}{\theta_1^2}\rho_1(v,dv')B(x/\theta_1)n(t,x/\theta_1,dv',i), \\ n(0,x,v,i) = n^{(0)}(x,v,i), x \geq 0. \end{cases} \tag{3}$$

with

$$\langle n(t,\cdot),\phi\rangle = \mathbb{E}_\mu\Big[\sum_{i=1}^{\infty}\phi\big(X_i(t),Z_i(t),P_i(t)\big)\Big] \text{ for every } \phi \in \mathcal{C}_0^1(\mathcal{S})$$

and $n_i(t,x,v)$ the density of $n_i(t,dx,dv)$.

✏K., Proceedings of IWBPA24

Numerical implementation

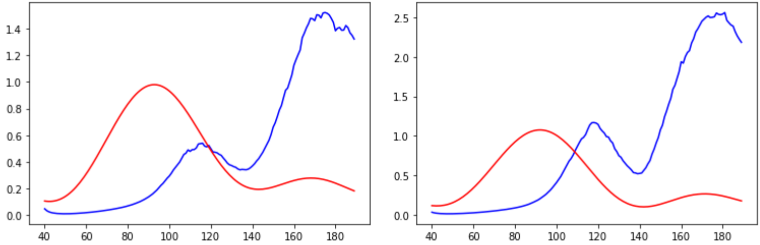


Figure: In red the estimated invariant probability and in blue the estimated division rate. On the left for the old cell and on the right for the young.

- Doumic, M., Hoffmann.,M., K., N. and Robert, L. (2015) *Statistical inference across scales for size-strutured models under growth variability*. *Bernoulli, 21, 1760–1799.*
- K., N., and Schmisser E. (2021) *Nonparametric estimation of jump rates for a specific class of piecewise deterministic Markov processes. Bernoulli, 27(4):2362–2388,*
- N. K. *Statistical estimation of the jump rate of a special class of PDMPs. ESAIM: PS 20 (2016) 196–216*
- B. Cloez, B. de Saporta, N. K. and T. Roget. *Model estimation and selection for cell division data.* Work in progress.
- N. K. *Branching processes and bacterial growth* To appear at Proceedings of IWBPA24.